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CADTH Reimbursement Recommendation

Ravulizumab (Ultomiris)

Indication: For the treatment of adult patients with anti–aquaporin 4 (AQP4) antibody–positive neuromyelitis optica spectrum disorder (NMOSD)
Sponsor: Alexion Pharma GmbH
Recommendation: Reimburse with conditions

Summary

What Is the CADTH Reimbursement Recommendation for Ultomiris?

CADTH recommends that Ultomiris be reimbursed by public drug plans for the treatment of neuromyelitis optica spectrum disorder (NMOSD) if certain conditions are met.

Which Patients Are Eligible for Coverage?

Ultomiris should only be covered to treat adult patients with anti–aquaporin 4 (AQP4) antibody–positive NMOSD. Patients must have had at least 1 relapse (also known as an "attack") of NMOSD in the 12 months before initiation. Patients must have an Expanded Disability Status Scale score of 7 points or less.

What Are the Conditions for Reimbursement?

Ultomiris should only be reimbursed if prescribed by a neurologist with expertise in treating NMOSD and if the price is reduced by at least 73%. Ultomiris should not be initiated during an NMOSD relapse episode or when used in combination with rituximab, satralizumab, eculizumab, or inebilizumab.

Why Did CADTH Make This Recommendation?

- Evidence from a clinical trial demonstrated that Ultomiris reduced the likelihood of having an NMOSD relapse compared to placebo, resulting in a meaningful improvement for patients. Ultomiris also reduced the probability of loss of function compared to placebo.
- Ultomiris meets patients' unmet needs by reducing the risk of future relapses, maintaining the current level of physical ability, and slowing disease progression.
- Based on CADTH's assessment of the health economic evidence, Ultomiris does not represent good value to the health care system at the public list price. A price reduction is therefore required.
- Based on public list prices, Ultomiris is estimated to cost the public drug plans approximately $72.8 million over the next 3 years.

Additional Information

What Is NMOSD?

NMOSD is a severe, chronic, and progressive disease of the central nervous system that causes inflammation in the optic nerve and spinal cord. NMOSD relapses are unpredictable and cause permanent neurological damage, leading to increasing amounts of irreversible impairment of vision

Summary

and/or mobility and sometimes death due to respiratory failure. Over time, patients may experience progressively increasing disability, pain, and loss of independence due to the cumulative effect of repeat relapses. NMOSD is rare and disproportionately affects females. Systemic reviews based on data from several countries have estimated that the prevalence ranges from 0.51 per 100,000 people to 4.4 per 100,000 people, but there are no Canadian-specific estimates.

Unmet Needs in NMOSD

Patients with NMOSD expressed a need for accessible treatments that are effective in the prevention of NMOSD relapses because reducing or avoiding relapses may delay the progression of disability and increase patients' ability to maintain independence and health-related quality of life.

How Much Does Ultomiris Cost?

Treatment with Ultomiris is expected to cost approximately $567,618 for the first year of treatment and $522,104 in subsequent years.

Recommendation

The Canadian Drug Expert Committee (CDEC) recommends that ravulizumab be reimbursed for the treatment of adult patients with anti–aquaporin 4 (AQP4) antibody–positive neuromyelitis optica spectrum disorder (NMOSD) only if the conditions listed in Table 1 are met.

Rationale for the Recommendation

One open-label, single-arm, phase III, multicentre, external placebo-controlled trial (CHAMPION-NMOSD; N = 58) in adult patients with AQP4 antibody–positive NMOSD who had at least 1 relapse within the prior 12 months demonstrated that treatment with ravulizumab resulted in a clinically important reduction in the probability of having an NMOSD relapse compared to placebo; the use of ravulizumab was associated with a hazard ratio (HR) of 0.014 (95% confidence interval [CI], 0.000 to 0.103) versus placebo. The median analysis follow-up time was 73.50 weeks (range, 11.00 to 117.71 weeks) for the ravulizumab group and 36.00 weeks (range, 1.86 to 117.71 weeks) for the placebo arm. Throughout the study follow-up, no patients in the ravulizumab group reported a primary outcome event of adjudicated on-trial relapse compared with 20 patients (42.6%) in the placebo group, yielding a relative relapse risk reduction of 98.6% (95% CI, 89.7% to 100.0%). Treatment with ravulizumab likely results in a clinically important reduction in the proportion of patients who have worsening scores from baseline on the Hauser Ambulation Index (HAI) compared to placebo (odds ratio [OR] = 0.155; 95% CI, 0.031 to 0.771). The use of ravulizumab may also result in a clinically important reduction in the proportion of patients who have worsening scores from baseline on the Expanded Disability Status Scale (EDSS) compared to placebo; however, the evidence has very low certainty.

Patients expressed a need to have access to therapy options that can reduce the risk of future relapses, maintain the current level of physical ability, and slow disease progression. CDEC concluded that ravulizumab met some important patient needs by reducing the risk of future relapses as well as slow disease progression.

Using the sponsor-submitted price for ravulizumab and publicly listed prices for all other drug costs, the incremental cost-effectiveness ratio (ICER) for ravulizumab was $2,386,625 per quality-adjusted life-year (QALY) gained compared with satralizumab. At this ICER, ravulizumab is not cost-effective at a willingness to pay (WTP) threshold of $50,000 per QALY for adult patients with NMOSD. A price reduction is required for ravulizumab to be considered cost-effective at a WTP threshold of $50,000 per QALY gained.

Table 1: Reimbursement Conditions and Reasons

Reimbursement condition	Reason	Implementation guidance
Initiation		
1. The patient must have had at least 1 “attack” or relapse of NMOSD in the previous 12 months.	The CHAMPION-NMOSD study showed a benefit of ravulizumab in patients with NMOSD who had at least 1 relapse episode within the prior 12 months.	CDEC noted that “attack” and “relapse” are used interchangeably in NMOSD clinical practice.

Reimbursement condition	Reason	Implementation guidance
2. Patients must have an EDSS score of 7 points or less.	Patients enrolled in CHAMPION-NMOSD were required to have an EDSS score of 7 points or less at baseline.	—
3. The maximum duration of initial authorization is 12 months.	Authorization of funding for 12 months provides flexibility to accommodate the practical challenges of assessing clinical response after treatment initiation given the natural history of NMOSD.	—
Renewal		
4. The physician should measure and provide EDSS scores every 12 months after the initial authorization to determine if the continuation of ravulizumab reimbursement should occur.	Annual assessments will help ensure the treatment is used for those benefiting from the therapy and would reduce the risk of unnecessary treatment. In addition, annual assessment is reasonable for stable patients based on input from the clinical experts.	—
Discontinuation		
5. Reimbursement of ravulizumab treatment should be discontinued if the patient's EDSS score is greater than 8 points.	CHAMPION-NMOSD study did not apply defined study treatment discontinuation criteria. Given the natural history of NMOSD, CDEC concluded that preventive treatment for relapse is likely of limited clinical benefit when patients are severely disabled, corresponding to an EDSS score greater than 8 points.	—
Prescribing		
6. The prescribing of ravulizumab for the treatment of NMOSD should be restricted to neurologists with expertise in treating NMOSD.	Accurate diagnosis of NMOSD is important to ensure that ravulizumab is prescribed to the appropriate patients. In addition, several treatment options must be considered when selecting the most appropriate therapy for patients who have NMOSD.	—
7. Ravulizumab should not be initiated during an NMOSD relapse episode.	Ravulizumab acts to prevent — not treat — relapses of NMOSD. There is no evidence to support starting treatment with ravulizumab during an NMOSD relapse episode.	—
8. Ravulizumab should not be reimbursed when used in combination with rituximab, satralizumab, eculizumab, or inebilizumab.	There is no evidence to support the use of ravulizumab in combination with rituximab, satralizumab, eculizumab, or inebilizumab.	—
Pricing		
9. A reduction in price	The ICER for ravulizumab is $2,386,625 compared with satralizumab. A price reduction of at least 73% would be required for ravulizumab to achieve an ICER of $50,000 per QALY compared to satralizumab.	—

CDEC = Canadian Drug Expert Committee; EDSS = Expanded Disability Status Scale; ICER = incremental cost-effectiveness ratio; NMOSD = neuromyelitis optica spectrum disorder.

Discussion Points

- Patient group input identified a need for accessible therapies to reduce the frequency and severity of NMOSD relapses and the associated progression of disability, loss of health-related quality of life (HRQoL), and loss of independence. Ravulizumab could address some of these unmet needs. Based on the Grading of Recommendations, Assessment, Development, and Evaluations (GRADE) assessment of selected outcomes from the CHAMPION-NMOSD trial, it was concluded with high certainty that, after a median follow-up of 73.50 weeks, treatment with ravulizumab results in a higher probability of not having a relapse compared to placebo. Moderately certain evidence suggested that ravulizumab likely results in a clinically important reduction in the proportion of patients who have worsening scores from baseline on the HAI, and very low certainty that ravulizumab may result in a clinically important reduction in the proportion of patients who have worsening scores from baseline on the EDSS. The EDSS outcome was associated with very low certainty as per the GRADE assessment because of serious imprecision.
- CDEC discussed that the use of a single-arm treatment design, utilizing the placebo group from the PREVENT study as an external placebo comparator, may have introduced a risk of bias leading to uncertainty surrounding the estimates. However, overall assessment suggests that the 2 trials likely feature sufficient similarity to ensure a valid comparison and that differences observed in patient populations might not meaningfully impact the risk of relapse according to the clinical experts. It was also noted that concern over this uncertainty was mitigated by the magnitude of relapse risk reduction with ravulizumab treatment observed in the CHAMPION-NMOSD trial.
- CDEC discussed that ravulizumab may have a clinically significant impact on function and HRQoL; however, there is some uncertainty in the evidence due to the limitations of the study design and the fact that statistical significance was not consistently reached or formally evaluated for all end points. The clinical expert noted to CDEC that maintaining function and HRQoL is very important to patients, but it may be more difficult to observe changes in these outcomes in the context of a clinical trial because loss of function and quality of life is cumulative over time and related to the severity of the relapse.
- Patients were excluded from the CHAMPION-NMOSD trial if they had used rituximab 3 months before screening, and they were not permitted to use rituximab during the study. The clinical experts noted to CDEC that rituximab is potentially used as a first-line therapy for the prevention of relapses in NMOSD. Therefore, the generalizability of results of the CHAMPION-NMOSD trial among patients with a recent history of use of rituximab is uncertain.
- CDEC discussed the fact that results from the network meta-analysis (NMA) suggest that ravulizumab performs better in some contexts compared with other monoclonal antibodies, but the quantification of benefit over the comparators is not clear due to the limitations of the NMA and the wide credible intervals (CrIs) around the estimates.
- The clinical experts noted to CDEC that discontinuation based on disability score should be a medical decision rather than a coverage decision due to the complexities of measuring disability in NMOSD

and the lack of a validated scale for this population of patients. The EDSS is not validated in NMOSD and has limitations for assessing disability outside of ambulatory disability in this population (e.g., visual acuity, other forms of paralysis). CDEC heard that although the EDSS is not validated in NMOSD, it is used in clinical practice and is presently the best available tool to assess response.

- CDEC discussed that there is no evidence to define the order of use among rituximab, inebilizumab, satralizumab, eculizumab, and ravulizumab nor is there evidence for switching from 1 treatment to another; therefore, the place of ravulizumab in therapy is uncertain. In addition, there was no evidence presented to conclude the most cost-effective sequence of treatments.

Background

NMOSD is a rare, inflammatory disease that affects the central nervous system, specifically the optic nerves and spinal cord, often leading to permanent blindness and paralysis. It is distinct from multiple sclerosis (MS) by its association with serum AQP4 immunoglobulin G (IgG) antibodies (AQP4-IgG). Patients with NMOSD experience acute unpredictable relapses that can last days to weeks and cause worsening symptoms. These relapses are recurrent; they occur among 80% to 90% of patients, leading to permanent disabilities. The most common manifestation of an acute relapse involves the inflammation of optic nerves (optic neuritis), which leads to eye pain and vision loss in 1 eye or both eyes. The clinical presentation also involves inflammation of the spinal cord (transverse myelitis), resulting in weakness or paralysis of arms and legs, bladder or bowel control problems, sensory loss, and painful muscle spasms. NMOSD may involve brainstem syndromes, such as intractable nausea, vomiting, hiccups, facial nerve palsy, oculomotor dysfunction, or vertigo. Disease symptoms and cumulative damage associated with NMOSD are associated with poor HRQoL. At its worst, NMOSD can lead to fatal respiratory failure. Clinical deterioration in patients with NMOSD accumulates in a stepwise fashion after each relapse and is often irreversible. Therefore, prevention of relapse is the key goal of therapy in the overall management of patients with NMOSD to minimize the amount of irreversible damage.

NMOSD disproportionately affects females with a reported female:male ratio of 9:1 to 12:1 in patients with AQP4 antibody–positive NMOSD. The disease presents at a reported mean age at onset of 40 years. Prevalence data of NMOSD within Canada is not available. Based on data from various countries in previous systematic reviews, NMOSD prevalence ranges from 0.50 per 100,000 people to 4.00 per 100,000 people and its incidence ranges from 0.053 per 100,000 people to 0.40 per 100,000 people. Regarding mortality, recent studies reported NMOSD mortality rates from 3.3% to 7%. Other studies estimated worldwide mortality rates in NMOSD to range from 9% to 32%, depending on age, relapse rate, and recovery from relapses.

In Canada, NMOSD is diagnosed by a neurologist or specialized physician in demyelinating disorders. Diagnostic criteria follow the 2015 consensus-based criteria developed by the International Panel for NMO Diagnosis. Diagnosis is based on clinical characteristics, and AQP4 antibody testing.

Ravulizumab is a monoclonal antibody and a terminal complement inhibitor that binds to the complement protein C5 with high affinity and specificity, thereby inhibiting its cleavage to C5a (a proinflammatory

anaphylatoxin) and C5b (the initiating subunit of the membrane attack complex [MAC or C5b-9]), and thus preventing the generation of MAC. Ravulizumab has been approved by Health Canada for the treatment of adult patients with AQP4 antibody–positive NMOSD. Ravulizumab is supplied as a 10 mg/mL or 100 mg/mL concentrate. The recommended ravulizumab IV maintenance dose in adult patients (≥ 18 years) with NMOSD with a body weight greater than or equal to 40 kg is based on the patient's body weight. Maintenance doses are administered every 8 weeks, starting 2 weeks after the loading dose. Ravulizumab should be administered by a qualified health care professional.

Sources of Information Used by the Committee

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

- a review of 1 external placebo-controlled, open-label, phase III, multicentre clinical study with NMOSD
- patients perspectives gathered by 2 patient groups, MS Canada and The Sumaira Foundation (TSF)
- input from public drug plans that participate in the CADTH review process
- 2 clinical specialists with expertise diagnosing and treating patients with NMOSD
- input from 1 clinician group, the Canadian Network of Multiple Sclerosis Clinics (CNMSC)
- a review of the pharmacoeconomic model and report submitted by the sponsor.

Stakeholder Perspectives

Patient Input

Two patient groups, MS Canada and TSF, responded to CADTH's call for patient input for the current review of ravulizumab.

MS Canada gathered information for this submission via a survey launched in 2023 targeting people in Canada living with NMOSD and their caregivers, which included 13 respondents. TSF gathered information through various surveys of patients and caregivers, patient narratives, focus groups, roundtables, discussions with key opinion leaders, ambassadors, TSF's global medical advisory board, advisors, peer-reviewed medical literature, and TSF's experience working in the NMOSD community.

The 2 patient groups indicated that NMOSD is more prevalent among women and that the disease is initiated with a severe episode and continues with subsequent devastating relapses that have a negative impact on vision, mobility, function, mental health, and quality of life of patients. The disease has a tremendous impact on all aspects of patients' lives, including a negative effect on independence, their family and caregivers, employment, and social life.

The patient inputs stated that treatment for NMOSD involves IV steroids, IV immunoglobulin or plasmapheresis or plasma exchange, mofetil mycophenolate, as well as the use of off-label immunosuppressants to help prevent further relapses. These have varying levels of therapeutic benefit.

Many patients suffer significant additional relapses and additional disability while cycling through off-label therapies, and others indicated these therapies partially managed their disease due to worsening symptoms and/or challenging side effects. There are some efficacious Health Canada–approved medications, such as eculizumab and satralizumab; however, access to these medications is very limited. Eculizumab is also administered by infusion every 2 weeks, which can be onerous and disruptive to the lives of individuals living with NMOSD. According to the patient inputs, patients need to have access to more treatment options that are able to prevent any further relapses with less frequent infusion dosing and fewer side effects.

Ravulizumab is simply a more stable analogue of eculizumab and requires much less frequent dosing after initiation (every 8 weeks), which can improve treatment adherence.

Clinician Input

Input From Clinical Experts Consulted by CADTH

NMOSD is a rare and severe disease with a generally poor natural trajectory and inherently high risk of relapse. Currently available therapies are often associated with an unacceptable harms profile and only provide suboptimal relapse prevention, resulting in accumulation of irreversible neurological disability, including paralysis and blindness. The clinical experts highlighted the unmet need of access to an effective treatment, which would make a great difference in the lives of patients and their caregivers.

There are no formal treatment guidelines in Canada that specify which interventions should be used as first- or second-line therapies. The clinical experts indicated that treatment of individuals with NMOSD differs by the province or territory based on differential access to drugs. The treatment goal of NMOSD is to prevent relapses, which is of upmost importance in prevention of neurological disability (including, but not limited to, paralysis and loss or impairment of vision) and mortality. There are many downstream desirable effects of early prevention and controlling the disease: maintaining neurological function will have a positive impact on the patients' quality of life, decrease risk of complications related to neurological dysfunction, and, in turn, maintain independence, increase ability to maintain employment, and reduce burden on caregivers.

Oral glucocorticoids, azathioprine, mycophenolate mofetil, and rituximab are frequently used to prevent relapses in NMOSD; however, many individuals with NMOSD still have ongoing disease activity while receiving these treatments. As their efficacy is viewed as suboptimal, corticosteroids are often used as adjunct therapy, adding to the harms profile. Although approved in Canada, satralizumab and eculizumab are rarely attainable for persons living with NMOSD.

Access to ravulizumab is likely to cause a shift in the current treatment paradigm because it addresses the underlying disease process of NMOSD with high efficacy. All individuals with AQP4 antibody–positive NMOSD should be considered eligible to receive ravulizumab. The clinical experts emphasized that it would be inappropriate to recommend that patients try other treatments before initiating treatment with ravulizumab because it is paramount to control NMOSD's irreversible progression as early as possible.

The appropriate settings for initiating and monitoring treatment with ravulizumab are neurology clinics with adequate expertise in NMOSD, including neurologists with expertise or subspecialty in MS or autoimmune

neurology, and occasionally neuro-ophthalmology. Meningococcal vaccination should be mandatory in the patients planning to receive this therapy.

Although the absence of relapse would be ideal, this may not be realistic. The severity of a relapse, as well as accumulation of disability, are important factors to consider when determining response to therapy. Once stability is established, treatment response may be assessed every year. Patients may need to discontinue a treatment if they experience a severe relapse (e.g., requiring intubation and support on a ventilator), 2 or more relapses within 2 years (assessed on case-by-case basis depending on severity), or severe adverse events (SAEs) while on treatment.

Clinician Group Input

One clinician group, the CNMSC (authored by 1 clinician), responded to CADTH's call for clinician group input. Clinician perspectives from the CNMSC were obtained through clinical experience, knowledge of the medical literature, and from clinicians across the country who specialize in this therapeutic area.

According to the clinician group, there are a variety of treatments available in Canada that are not specifically indicated for NMOSD as well as other more efficacious therapies, such as monoclonal antibodies; however, access to these therapies is extremely limited due to their stringent funding coverage criteria. Failure of treatment, with even just 1 relapse, can lead to a profound, permanent disability, including blindness and paralysis.

As per the CNMSC, there is a large unmet need in Canada for high-efficacy, well-tolerated therapies for NMOSD that have a significant impact on preventing and/or reducing relapses. Use of some of the off-label therapies is limited because of many side effects and lack of efficacy. Also, eculizumab is given by an IV infusion every 2 weeks which is too onerous for some patients to tolerate. According to the clinician group, the best approach for patients is to use efficacious, safe, and tolerable therapy as soon as possible after the first episode to avoid any relapses, reduce the severity of relapses and the cumulative disability associated with them, and minimize adverse events (AEs) related to therapies. Ravulizumab would be the first therapy for patients diagnosed with a confirmed diagnosis of NMOSD, with a positive serum test for the AQP4 antibody after their first relapse and for those who have severe AEs on first-line therapy.

According to the CNMSC, avoidance of a new relapse, which includes vision loss, weakness, sensory impairment, or bladder/bowel dysfunction, is the outcome used to determine whether a patient is responding to treatment. The clinician group indicated that discontinuation of therapy should be considered in patients who have a new relapse on this therapy.

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:

- relevant comparators
- considerations for initiation of therapy

- considerations for continuation or renewal of therapy
- considerations for discontinuation of therapy
- considerations for prescribing of therapy.

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

Table 2: Responses to Questions From the Drug Programs

Implementation issues	Response
Relevant comparators	
Would any of the off-label preventive therapies for NMOSD (such as rituximab, azathioprine, mycophenolate, tacrolimus, cyclophosphamide, methotrexate, and corticosteroids) be considered an appropriate comparator?	The clinical experts noted to CDEC that azathioprine, mycophenolate, tacrolimus, cyclophosphamide, methotrexate, and corticosteroids should not be considered as appropriate comparators, mainly because they have different mechanisms of action and very limited effectiveness. Of the potential comparators listed, rituximab would be the closest to ravulizumab according to the clinical experts; however, rituximab has limited efficacy in preventing NMOSD relapses.
Considerations for initiation of therapy	
How should "relapse" be defined? Should the initial attack which leads to the diagnosis of NMOSD be considered a "relapse" for the purpose of the initiation criteria?	The clinical experts noted to CDEC that in clinical practice, definition and assessment of relapses are based on a combination of patient reported symptoms, clinical exam, clinical tools, and patient history. The clinical experts indicated that the initial episode that leads to the diagnosis of NMOSD should be considered a relapse for the purpose of the initiation criteria. CDEC noted that "attack" and "relapse" are used interchangeably in clinical practice.
Should patients be required to try (or rule out) off-label preventive therapies before accessing ravulizumab for NMOSD?	The clinical experts noted to CDEC that patients should not be required to try an off-label, less effective therapy before being allowed to use an approved drug with high efficacy at preventing relapses. Any relapse could be a disabling relapse, even early in the disease trajectory; therefore, preventing all relapses is very important. CDEC noted that there is no evidence to define order of use among rituximab, inebilizumab, satralizumab, eculizumab, or ravulizumab, nor is there evidence for switching from 1 treatment to another.
What is the appropriate treatment sequence for satralizumab and ravulizumab? Should 1 be trialled in advance of the other?	The clinical experts noted to CDEC that currently there is no evidence to answer this question. CDEC noted that there is no evidence to define order of use among rituximab, inebilizumab, satralizumab, eculizumab, or ravulizumab, nor is there evidence for switching from 1 treatment to another.
Eculizumab is not funded publicly. Given the lack of availability, how should it be considered in the treatment algorithm? If eculizumab fails for a patient, would it be reasonable to try ravulizumab? Should there be consideration of switching from eculizumab to ravulizumab for patients whose disease responds to therapy with eculizumab?	The clinical experts noted to CDEC that they do not use eculizumab and satralizumab due to very limited and difficult access. The clinical experts also noted that if there is evidence of a suboptimal response while on eculizumab, these patients would likely be switched to a drug with a different mechanism of action. However, patients whose NMOSD shows a good response on eculizumab may be switched to ravulizumab for convenience of administration. Here *suboptimal response* is defined as ongoing clinical disease activity in

Implementation issues	Response
	the form of new symptoms or findings on neurological examination: new relapse, poor tolerance, or adverse events. CDEC noted that there is no evidence to define order of use among rituximab, inebilizumab, satralizumab, eculizumab, or ravulizumab, nor is there evidence for switching from 1 treatment to another.
Is there evidence to support use of ravulizumab in patients whose NMOSD does not respond to treatment with eculizumab and/or satralizumab?	The clinical experts noted to CDEC that currently there is no evidence in this patient population.
The initiation criteria in the CDEC reimbursement recommendation for eculizumab for NMOSD is as follows: 1. The patient must have had at least 2 relapses of NMOSD in the previous 12 months or 3 relapses in the previous 24 months, with at least 1 relapse in the past 12 months before the initiation of treatment 1.1. despite an adequate trial of other accessible preventive treatments for NMOSD 1.2. the patient cannot tolerate other preventive treatments for NMOSD. 2. Patients must have an EDSS score of 7 points or less. 3. Eculizumab should not be initiated during an NMOSD relapse episode. 4. The maximum duration of initial authorization is 12 months. Although eculizumab is not publicly reimbursed for NMOSD, and an alignment in initiation criteria might not be necessary, is there evidence to align the initiation criteria of ravulizumab with that of eculizumab for NMOSD?	The initiation criteria in the CDEC reimbursement recommendation for eculizumab are based on data from eculizumab trial(s). The clinical experts suggested that the initiation criteria in the CDEC reimbursement recommendation for ravulizumab should be based on data from CHAMPION-NMOSD. CDEC recommended that ravulizumab be reimbursed in patients who have had at least 1 relapse of NMOSD in the previous 12 months and an EDSS score of 7 points or less, with a maximum duration of initial authorization of 12 months.
Considerations for continuation or renewal of therapy	
How often are EDSS scores measured in clinical practice, and how frequently are these patients monitored?	The clinical experts indicated that EDSS scores are widely used in clinical practice and routinely assessed in patients on a yearly basis. The clinical experts mentioned that, for reimbursement purposes, it would be best to allow for more than 12 months to allow for the delays that can occur in yearly appointments. CDEC recommended that physicians should measure and provide EDSS scores every 12 months after the initial authorization to determine if the continuation of ravulizumab reimbursement should occur.
Is the EDSS score the appropriate tool to assess response to therapy?	The clinical experts highlighted that, although there are some limitations to the EDSS, it remains a part of the global evaluation of response to treatment. CDEC recommended that reimbursement of ravulizumab treatment should be discontinued if the patient's EDSS score is greater than 8 points.

Implementation issues	Response
The renewal criteria in the CDEC reimbursement recommendation for eculizumab for NMOSD is that the physician should measure and provide EDSS scores every 6 months after the initial authorization to determine if the continuation of eculizumab reimbursement should occur. Should consideration be given to aligning the renewal criteria of ravulizumab with those recommended for eculizumab?	The clinical experts highlighted that assessment is performed yearly in clinical practice, and an every 6 months requirement would add substantial and unnecessary burden to patients, clinicians, and to the health care system. The clinical experts strongly suggest yearly assessments. CDEC recommended that the maximum duration of initial authorization is 12 months and that the physician should measure and provide EDSS scores every 12 months after the initial authorization to determine if the continuation of ravulizumab reimbursement should occur.
Considerations for discontinuation of therapy	
The discontinuation criteria in the CDEC reimbursement recommendation for eculizumab for NMOSD is that reimbursement of eculizumab treatment should be discontinued if the patient's EDSS score is 8 points or greater. Should consideration be given to aligning the discontinuation criteria of ravulizumab with those recommended for eculizumab?	The clinical experts suggested that the discontinuation criteria in the CDEC reimbursement recommendation for ravulizumab should be based on data from CHAMPION-NMOSD and experience from clinical practice. As such, patients enrolled in CHAMPION-NMOSD had EDSS scores ≤ 7. However, in clinical practice, some patients with an EDSS score > 7 are still considered to have some preservable function that could be lost by the next relapse. Given that the EDSS has limitations in the assessment of function in patients with NMOSD, more flexibility would be required if using this tool for discontinuation purposes. Therefore, the clinical experts suggested that ravulizumab treatment should be maintained as long as a patient's EDSS score is ≤ 9 points. CDEC recommended that reimbursement of ravulizumab treatment should be discontinued if the patient's EDSS score is greater than 8 points.
Should relapse rate also be a consideration for discontinuation of therapy?	The clinical experts emphasized that a relapse in itself should not result in treatment discontinuation. Relapses are not all equal. Severity of the relapse and recovery from the relapse will have a significant impact on the decision of escalating or switching therapy. Whether or not there are alternative options may also impact the decision to discontinue a particular treatment. CDEC recommended that reimbursement of ravulizumab treatment should be discontinued if the patient's EDSS score is greater than 8 points.
Considerations for prescribing of therapy	
Would ravulizumab be used in combination with satralizumab? Is there evidence to support other therapies in combination with ravulizumab (i.e., rituximab or inebilizumab)?	The clinical experts indicated that ravulizumab should be used as monotherapy, with the exception of concomitant use of corticosteroids and/or other symptomatic therapies. There is no evidence regarding combination therapies with ravulizumab and other drugs, such as rituximab or inebilizumab. CDEC recommended that, due to lack of evidence, ravulizumab should not be reimbursed when used in combination with rituximab, satralizumab, eculizumab, or inebilizumab.
As an accurate diagnosis of NMOSD is important to ensure appropriate prescribing, who should prescribe ravulizumab? Is it a neurologist, ophthalmologist, or others?	The clinical experts noted to CDEC that treatment should be supervised by a neurologist with expertise in this area (which may include autoimmune neurology and occasionally neuro-ophthalmology). Although NMOSD and MS are not the same disease, the populations and medications are similar and persons with NMOSD are often

Implementation issues	Response
How do patients living in remote areas access such specialties?	cared for in an MS clinic. Thus, the diagnosis could be confirmed by a neurologist associated with an MS clinic, and treatment could be initiated and monitored by a neurologist associated with an MS clinic or similar subspecialty clinic with expertise in NMOSD.

CDEC = Canadian Drug Expert Committee; EDSS = Expanded Disability Status Scale; MS = multiple sclerosis; NMOSD = neuromyelitis optica spectrum disorder.

Clinical Evidence

Systematic Review

Description of Studies

One study was reviewed, CHAMPION-NMOSD (n = 58), which was an external placebo-controlled, open-label, phase III, multicentre trial designed to evaluate the efficacy and safety of ravulizumab in adult patients with AQP4 antibody–positive NMOSD who had at least 1 relapse within the prior 12 months. The study had a single-arm treatment design, utilizing the placebo group from the PREVENT study as an external placebo comparator. PREVENT is a recent study that evaluated the efficacy and safety of eculizumab in preventing relapses in patients with AQP4 antibody–positive NMOSD who had at least 2 relapses within the prior 12 months or 3 relapses within the prior 24 months, at least 1 of which occurring within the prior 12 months. Patients were randomly assigned in a 2:1 ratio to receive either eculizumab (n = 96) or a matching-administration placebo (n = 47) every 2 weeks.

The primary outcome in the study was time to first adjudicated on-trial relapse, which was defined as a new onset of neurological symptoms or worsening of existing neurological symptoms, with an objective change on neurological examination that persists for more than 24 hours as confirmed by the treating physician. Neurological signs and symptoms had to be attributed to NMOSD (e.g., not caused by other identifiable causes such as an infection). On-trial relapses were independently reviewed by the relapse adjudication committee, which consisted of physicians with expertise in NMOSD who conduct independent reviews of all on-trial relapses.

Secondary outcomes in the study included function, as measured by the HAI, which is a rating scale developed to assess mobility by evaluating the time and effort used by the patient to walk 8 m. The scale ranges from 0 to 9, with 0 being the best score (asymptomatic; fully ambulatory with no assistance) and 9 being the worst (complete lack of independent mobility). Function was also assessed using the EDSS score, an ordinal clinical rating scale that ranges from 0 (normal neurological examination) to 10 (death) in half-point increments. The EDSS quantifies disability in the 7 Kurtzke functional systems (pyramidal, cerebellar, brainstem, sensory, bowel and bladder, visual, and cerebral). In conjunction with ambulation, they are rated in the context of a standard neurological examination, then these ratings are used together with observations and information concerning the patient's mobility, gait, and use of assistive devices to assign a score.

Secondary outcomes in the study included HRQoL, which was assessed using the EQ-5D, a generic preference-based HRQoL instrument, consisting of a visual analogue scale (VAS), and a composite index

score of 5 dimensions: mobility, self-care, usual activities, pain and discomfort, and anxiety and depression. HRQoL was also assessed as an exploratory outcome using the Short Form (36) Health Survey (SF-36), a patient self-administered questionnaire designed to assess generic HRQoL in adult populations with and without disease. The SF-36 consists of 36 items organized into the 8 scales (physical function, social function, role limitations [physical and emotional], bodily pain, general medical health, mental health, vitality, and health transition). The questionnaire also yields 2 summary measures of physical health and mental health derived from scale aggregates. Higher global scores are associated with better quality of life.

Finally, visual acuity was assessed as an exploratory outcome using the Optic-Spinal Impairment Scale (OSIS), a generic instrument assessing visual acuity and motor, sensory, and urinary sphincter functions. Scores are assessed for each individual domain and range from 0 to 8 for visual acuity and from 0 to 5 for the other domains; a lower score indicates better functioning.

Efficacy Results

NMOSD Relapse

The outcome of relapse was considered the preferred and most reliable end point by clinical experts. In patients with AQP4 antibody–positive NMOSD, the use of ravulizumab was associated with a HR of 0.014 (95% CI, 0.000 to 0.103) versus placebo. The log-rank test yielded a P value less than 0.0001. The median analysis follow-up time was 73.50 weeks (range, 11.00 to 117.71 weeks) for the ravulizumab group and 36.00 weeks (range, 1.86 to 117.71 weeks) for the placebo group. Throughout the study follow-up, no patients in the ravulizumab group reported a primary outcome event of adjudicated on-trial relapse compared with 20 patients (42.6%) in the placebo group from the PREVENT study, yielding a relative relapse risk reduction of 98.6% (95% CI, 89.7% to 100.0%). Therefore, treatment with ravulizumab resulted in a clinically important reduction in the probability of having an NMOSD relapse compared to placebo.

Results from sensitivity analyses, which aimed to assess whether any imbalances in observed baseline characteristics due to trial design could be sufficient to confound the observed treatment effect, were similar with those from the primary analysis. Results were also consistent across prespecified and post hoc subgroups.

Function

Treatment with ravulizumab likely results in a clinically important reduction in the proportion of patients with worsening from baseline in HAI score at the primary data cut-off compared to placebo (OR = 0.155; 95% CI, 0.031 to 0.771). The proportions of patients with clinically important worsening from baseline through the end of the study period in HAI score were 3.4% (2 patients of 58) in the ravulizumab arm and 23.4% (11 patients of 47) in the placebo arm.

The use of ravulizumab may result in a clinically important reduction in the proportion of patients with worsening from baseline in EDSS score at the primary data cut-off compared to placebo; however, the evidence is very uncertain because the CI for the difference between groups includes the possibility of no difference. The proportions of patients with clinically important worsening from baseline through the end of

study period in EDSS score were 10.3% (6 patients of 58) in the ravulizumab arm and 23.4% (11 patients of 47) in the placebo arm, yielding an OR of 0.332 (95% CI, 0.106 to 1.042).

Health-Related Quality of Life

Treatment with ravulizumab may result in a clinically important difference in HRQoL at the primary data cut-off compared to placebo, as measured by the EQ-5D index score, the EQ-5D VAS score, and [redacted]; however, the evidence is very uncertain because the CI for difference between groups includes the possibility of no difference. The mean change from baseline through the end of the study period in the EQ-5D index score was 0.01 (SD = 0.15) in the ravulizumab arm and −0.04 (SD = 0.21) in the placebo arm, yielding a difference in least square (LS) means of ranks of 11.15 (95% CI, −0.32 to 22.62). For the EQ-5D VAS score, the mean change from baseline to end of study period was 2.6 (SD = 14.1) in the ravulizumab arm and 0.6 (SD 16.4) in the placebo arm; the difference in LS means of ranks was 13.38 (95% CI, 1.35 to 25.41). Finally, for the [redacted].

[redacted].

The evidence [redacted].

[redacted].

Harms Results

A total of 93% of patients receiving ravulizumab reported at least 1 AE and 19% of patients reported at least 1 SAE, of which the most frequently reported involved infections and infestations. However, treatment with ravulizumab appeared to be well tolerated because only 1 patient discontinued due to AEs; the reason for withdrawal from the study drug was infection. No deaths were reported in the study. Meningococcal infection was an AE of special interest. Two patients experienced meningococcal infection during the primary treatment period. No new meningococcal infections were reported during the long-term extension period.

The clinical experts indicated that the overall harms profile of ravulizumab in CHAMPION-NMOSD did not raise any particular safety signal, with the exception of meningococcal infections. As such, all patients should receive meningococcal vaccination before the start of ravulizumab therapy, as per the product monograph.

Critical Appraisal

The CHAMPION-NMOSD trial had a single-arm treatment design, utilizing the placebo group from the PREVENT study as an external placebo comparator; this may have introduced a risk of bias leading to uncertainty surrounding the estimates. However, the overall assessment suggests that the 2 trials likely feature sufficient similarity to ensure a valid comparison, and that differences observed in patient populations might not substantially affect results for the primary outcome of relapse prevention. According to the clinical experts consulted by CADTH, the differences observed in the number of historical relapses between groups is not expected to have a substantial impact on the risk of future relapses; in addition, the annualized relapse rate within the prior 12 months and 24 months between treatment groups were consistent with the assumption that both groups actually had a relatively similar evolution in terms of relapse frequency. Some level of uncertainty could be mitigated by the magnitude of relapse risk reduction with ravulizumab treatment observed in the CHAMPION-NMOSD trial. In addition, results from sensitivity analyses of the primary outcome suggest that the findings are robust and statistically infer that imbalances in patient populations were not likely to have a meaningful impact on the estimates.

Secondary efficacy and exploratory outcomes of function, HRQoL and visual acuity were assessed adequately using appropriate tools; however, no studies assessed their validity or reliability in NMOSD specifically. Minimal clinically important differences were established through clinical expert input because none could be identified in the literature for this patient population. The thresholds used in the study for dichotomous outcome assessment (HAI and EDSS) were considered appropriate and consistent with clinical practice according to the clinical experts. The clinical experts indicated that loss of function and quality of life is cumulative over time, and that the magnitude of worsening depends on the severity of the relapse; therefore, measurement of these outcomes may be less sensitive to changes in the context of a clinical trial. The goal for patients receiving active treatment would be to maintain a stable status; patients in the placebo group would be expected to have a worsening status based on natural disease trajectory. Because follow-up only went until the first on-trial relapse for ethical reasons (median follow-up time in CHAMPION-NMOSD was 73.50 weeks for the ravulizumab group and 36.00 weeks for the placebo group), assessment of these outcomes may lead to an underestimation of active treatment effect over time.

Findings from the CHAMPION-NMOSD trial can be considered generalizable to patients with NMOSD in Canada because the study population was considered representative of patients in clinical practice; disability was consistent with what is expected within an NMOSD population. The primary outcome of relapse prevention is consistent with the treatment goals of NMOSD in clinical practice according to the clinical experts. Relapse assessment in the trial was performed in a similar manner as in clinical practice. The clinical experts confirmed that follow-up duration was long enough for the trial to adequately capture relapses, considering the inherently high risk of relapse in patients with AQP4 antibody–positive NMOSD.

GRADE Summary of Findings and Certainty of the Evidence

For nonrandomized comparative studies, such as a single-arm trial with an external control, CADTH followed the GRADE approach. The CADTH review team assessed study limitations (which refers to internal validity or risk of bias), inconsistency across studies, indirectness, imprecision of effects, and publication

bias to present these important considerations. Because of the inherent risk of bias from the absence of randomization and differences in patient populations, the certainty of evidence for single-arm trials started at low certainty, with opportunity for rating up.

When possible, certainty was rated in the context of the presence of an important (nontrivial) treatment effect; if this was not possible, certainty was rated in the context of the presence of any treatment effect (i.e., the clinical importance is unclear). In all cases, the target of the certainty of evidence assessment was based on the point estimate and where it was located relative to the threshold for a clinically important effect (when a threshold was available) or to the null.

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

- NMOSD relapse
- function
- HRQoL
- visual acuity
- health care resource utilization
- harms

Table 3: Summary of Findings for Ravulizumab Versus Placebo for Patients With AQP4 Antibody–Positive NMOSD in CHAMPION-NMOSD (PREVENT Placebo Group as External Control)

Outcome and follow-up	Patients (studies), N	Relative effect (95% CI)	Absolute effects			Certainty	What happens
			Placebo	Ravulizumab	Difference (95% CI)		
NMOSD event or relapse							
Patients with an adjudicated relapse during the primary treatment period Follow-up: Primary analysis data cut-off	Ravulizumab: N = 58 Placebo: N = 47 (1 RCT)	RRR = 98.6 (89.7 to 100.0)	426 per 1,000 patients	0 per 1,000 patients	426 fewer per 1,000 patients	High[a]	Ravulizumab results in a clinically important reduction in the probability of having an NMOSD relapse at the primary data cut-off compared to placebo.
Function							
Patients with clinically important worsening from baseline in HAI score Follow-up: Primary analysis data cut-off	Ravulizumab: N = 58 Placebo: N = 47 (1 RCT)	OR = 0.155 (0.031 to 0.771)	234 per 1,000 patients	34 per 1,000 patients	200 fewer per 1,000 patients	Moderate[b]	Ravulizumab likely results in a clinically important reduction in the proportion of patients who have worsening from baseline in HAI score at the primary data cut-off compared to placebo.
Patients with clinically important worsening from baseline in EDSS score Follow-up: Primary analysis data cut-off	Ravulizumab: N = 58 Placebo: N = 47 (1 RCT)	OR = 0.332 (0.106 to 1.042)	234 per 1,000 patients	103 per 1,000 patients	131 fewer per 1,000 patients	Very low[c]	Ravulizumab may result in a clinically important reduction in the proportion of patients who have worsening from baseline in EDSS score at the primary data cut-off compared to placebo. However, the evidence is very uncertain.
HRQoL							
Change from baseline in EQ-5D index score Follow-up: Primary analysis data cut-off	Ravulizumab: N = 58 Placebo: N = 47 (1 RCT)	NR	Observed mean = −0.043 (SD = 0.2115) LS mean =	Observed mean: 0.005 (SD = 0.1522)	LS mean difference of ranks = 11.15	Very low[c]	Ravulizumab may result in a clinically important difference in EQ-5D index score at the primary data cut-off compared to placebo.

Outcome and follow-up	Patients (studies), N	Relative effect (95% CI)	Absolute effects			Certainty	What happens
			Placebo	Ravulizumab	Difference (95% CI)		
			46.84 (SE = 4.229)	LS mean = 57.99 (SE = 3.793)	(−0.32 to 22.62)		However, the evidence is very uncertain.
Change from baseline in EQ-5D VAS score Follow-up: Primary analysis data cut-off	Ravulizumab: N = 58 Placebo: N = 47 (1 RCT)	NR	Observed mean = 0.6 (SD = 16.39) LS mean = 45.61 (SE = 4.343)	Observed mean = 2.6 (SD = 14.07) LS mean = 58.99 (SE = 3.874)	LS mean difference of ranks = 13.38 (1.35 to 25.41)	Very low[c]	Ravulizumab may result in a clinically important difference in EQ-5D VAS score at the primary data cut-off compared to placebo. However, the evidence is very uncertain.
[redacted]							
[redacted]							
Visual acuity							
[redacted]							
[redacted]							
[redacted]							

Outcome and follow-up	Patients (studies), N	Relative effect (95% CI)	Absolute effects			Certainty	What happens
			Placebo	Ravulizumab	Difference (95% CI)		
Health care resource utilization							
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Harms							
Patients with AEs Follow-up: 120-day safety follow-up	Ravulizumab: N = 58 Placebo: N = 47 (1 RCT)	NR	NR	931 per 1,000 patients	NA	Very low	In the absence of comparative data, the evidence is very uncertain about the effect of ravulizumab on AEs compared with any comparator.
Patients with SAEs Follow-up: 120-day safety follow-up	Ravulizumab: N = 58 Placebo: N = 47 (1 RCT)	NR	NR	190 per 1,000 patients	NA	Very low	In the absence of comparative data, the evidence is very uncertain about the effect of ravulizumab on SAEs compared with any comparator.

AE = adverse event; CI = confidence interval; EDSS = Expanded Disability Status Scale; HAI = Hauser Ambulation Index; HRQoL = health-related quality of life; LS = least square; NMOSD = neuromyelitis optica spectrum disorder; NA = not applicable; NR = not reported; OR = odds ratio; OSIS = Optic-Spinal Impairment Scale; RRR = relative risk reduction; SAE = serious adverse event; SD = standard deviation; SE = standard error.

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

[a]Rated up 2 levels due to the magnitude of relapse risk reduction with ravulizumab treatment observed in CHAMPION-NMOSD, which was large and constant over time.

[b]Rated up 1 level due to the magnitude of effect observed with ravulizumab in preventing clinically important worsening from baseline in HAI score.

[c]Rated down 1 level for serious imprecision because the CI for difference between groups includes the possibility of no difference. Minimal clinically important difference established through clinical expert input.

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

Indirect Comparisons

Description of the NMA

The sponsor submitted indirect evidence in the form of a [redacted] which objective was to obtain relative treatment effects between ravulizumab, [redacted] for the treatment of adult patients with AQP4 antibody–positive NMOSD. Analyses were performed for [redacted]. Outcomes of interest for evaluation included [redacted].

A total of [redacted] unique clinical trials were included into the evidence base for the NMA: [redacted] patients; however, patients who were [redacted] were excluded from analyses. All patients from [redacted] at enrolment.

The start date of the studies ranged from [redacted]. Treatment duration ranged from [redacted]. All studies had a [redacted] treatment group except for [redacted]. Sample size ranged from [redacted]. [redacted] was not required in any trial but was permitted in [redacted]. The mean age of patients ranged from [redacted] across the trials.

Efficacy Results

[redacted]

[redacted] were reported in [redacted] trials evaluating ravulizumab [redacted]. The relative treatment effect of [redacted] patients taking ravulizumab | [redacted].

[redacted] therapy were reported in [redacted] trials evaluating ravulizumab [redacted].

[redacted] were reported in [redacted] trials evaluating ravulizumab[redacted].

[redacted] were reported in [redacted] trials evaluating ravulizumab[redacted].

[redacted] were reported in [redacted] trials evaluating ravulizumab [redacted].

[redacted] were reported in [redacted] trials evaluating ravulizumab [redacted].

[redacted].

Harms Results

[redacted].

Critical Appraisal

The sponsor conducted an NMA using a [redacted] for all outcomes. This was a reasonable method to apply given the availability of [redacted] for only 2 of the included studies.

Comparisons in all NMA analyses were based on a [redacted] of trials and [redacted] of patients in each trial. The networks were linked to ravulizumab through a [redacted] that was not part of the [redacted] trial. The validity of the ravulizumab comparative results relies entirely on the putative comparability of the [redacted]. The possibility of residual confounding exists when 2 nonrandomized groups [redacted] are being compared.

The sponsor's decision to perform [redacted] NMA analyses based on the potential effect modifier of [redacted], was appropriate. The disadvantage of doing this was to create [redacted]. There were other sources of heterogeneity that were not explored in the NMA analyses, and it is not clear if the homogeneity assumption is correct. These sources include the following:

- The sponsor performed quality assessment of the individual trials, but the results were not provided and no information was provided on how they used the results of the quality assessment in the NMA.
- [redacted]. There could have been more residual effects from [redacted], compared to the other studies because [redacted] was not permitted within [redacted], whereas it was not permitted within [redacted] of study start in the other trials.
- The [redacted] differed between the trials and the handling of placebo usage also differed. The randomized period in the [redacted] ended at 197 days to limit exposure to placebo, whereas placebo was continued until end of study in [redacted]. The [redacted].

The sponsor used a [redacted] in their sensitivity analyses for the outcome of [redacted]. The factors selected by the sponsor for adjustment in the [redacted] were reasonable, but there was not enough information provided to assess the validity of the sensitivity analyses. Some analyses in the base case results that

favoured [redacted], no longer favoured [redacted] were performed for the [redacted]. These included comparisons to [redacted].

Summary of the NMA

Results of the sponsor's NMA favoured [redacted] but the results were [redacted].

Economic Evidence

Table 4: Cost and Cost-Effectiveness

Component	Description
Type of economic evaluation	Cost-utility analysis Markov model
Target population	Adult patients with anti–aquaporin 4 (anti-AQP4) antibody–positive neuromyelitis optica spectrum disorder (NMOSD)
Treatment	Ravulizumab
Dose regimen	Between 2,400 mg and 3,000 mg depending on patient's weight, followed by a maintenance dose between 3,000 mg and 3,600 mg every 8 weeks starting 2 weeks after the induction dose
Drug price	300 mg vial: $7,282.15 1,100 mg vial: $26,701.20
Treatment cost	Year 1: $567,618 Year ≥ 2: $522,104
Comparators	Eculizumab Satralizumab ISTs (steroidal and nonsteroidal)
Perspective	Canadian publicly funded health care payer
Outcomes	QALYs, life-years
Time horizon	Lifetime (53 years)
Key data source	CHAMPION-NMOSD study and the sponsor conducted an NMA to inform comparative clinical efficacy of eculizumab, satralizumab, and ISTs.
Key limitations	• The comparative effectiveness for ravulizumab, eculizumab, satralizumab, and ISTs is uncertain. CADTH's review of the sponsor's NMA concluded that ravulizumab may perform better in some contexts compared to other comparators, but the quantification of benefit over the comparators is not clear due to the limitations of the NMA and the wide confidence intervals around the estimates. • No patients treated with ravulizumab experienced an NMOSD-related relapse during the CHAMPION-NMOSD trial period used in the NMA analysis (median follow-up of 91 weeks in the ravulizumab group).

Component	Description
	This benefit was extrapolated throughout the entire 53-year time horizon of the model, resulting in an average of 0.2 relapses per patient over this time frame. However, the long-term benefit of ravulizumab is unknown, and the clinical expert feedback did not support the conclusion that ravulizumab would result in the indefinite prevention of relapse for a patient's entire lifetime. Thus, this approach likely overestimates the long-term benefit of ravulizumab. • The sponsor assumed that the decrease in the risk of experiencing an NMOSD relapse resulted in a decrease in the mortality rate of patients receiving ravulizumab, eculizumab, or satralizumab. Because NMOSD relapse rates were significantly lower for ravulizumab, this approach resulted in patients treated with ravulizumab having the same mortality rate as the general population, which lacks face validity based on feedback from the clinical experts consulted for this review. • The sponsor assumed that patients would remain on the same treatment for the entire time horizon, which lacks face validity based on feedback from the clinical experts consulted by CADTH and international treatment guidelines. This assumption leads to the overestimation of benefits and costs of all comparators.
CADTH reanalysis results	• Given the limitations identified, CADTH was unable to provide a more reliable estimate of the cost-effectiveness of ravulizumab. • Based on the sponsor's analysis, the ICER for ravulizumab vs. satralizumab was $2,386,625 per QALY gained (incremental costs: $11,261,849; incremental QALYs: 4.72). A price reduction of at least 73% would be required for ravulizumab to be cost-effective at a $50,000 per QALY gained threshold compared to satralizumab.

ICER = incremental cost-effectiveness ratio; IST = immunosuppressive therapy; NMA = network meta-analysis; NMOSD = neuromyelitis optica spectrum disorder; QALY = quality-adjusted life-year.

Budget Impact

CADTH reanalysis included updating the cost of rituximab to reflect current publicly available list prices and updating the market shares for satralizumab and rituximab in the reference scenario and updating the market shares for ravulizumab, rituximab, and satralizumab in the new drug scenario. With these changes, the CADTH reanalysis shows that the reimbursement of ravulizumab for the treatment of adult patients with anti-AQP4 positive NMOSD would be associated with a budgetary increase of $13,381,657 in year 1, $24,956,594 in year 2, $34,497,100 in year 3, with a 3-year total incremental cost of $72,835,350.

CDEC Information

Members of the Committee

Dr. James Silvius (Chair), Dr. Sally Bean, Mr. Dan Dunsky, Dr. Edward Xie, Mr. Bob Gagne, Dr. Ran Goldman, Dr. Peter Jamieson, Mr. Morris Joseph, Dr. Christine Leong, Dr. Kerry Mansell, Dr. Alicia McCallum, Dr. Srinivas Murthy, Dr. Trudy Huyghebaert, Dr. Danyaal Raza, and Dr. Peter Zed.

Meeting date: January 25, 2024

Regrets: One expert committee member did not attend.

Conflicts of interest: None

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