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Reimbursement Recommendation

Ravulizumab (Ultomiris)

Indication: For the treatment of adult patients with anti-acetylcholine receptor antibody-positive generalized Myasthenia Gravis

Sponsor: Alexion Pharma GmbH

Final recommendation: Reimburse with conditions

Summary

What Is the Reimbursement Recommendation for Ultomiris?

Canada's Drug Agency (CDA-AMC) recommends that Ultomiris be reimbursed by public drug plans for the treatment of adults with generalized myasthenia gravis (gMG) if certain conditions are met.

Which Patients Are Eligible for Coverage?

Ultomiris should only be covered to treat those who meet the Myasthenia Gravis Foundation of America (MGFA) classification (which categorizes clinical features by increasing severity) of II (i.e., mild weakness affecting body muscles and may also include weakness in the eye muscles) to IV (i.e., severe weakness affecting body muscles and may also include weakness in the eye muscles), test positive for anti–acetylcholine receptor (AChR) antibodies, and have a Myasthenia Gravis Activities of Daily Living (MG-ADL) score (which estimates patients' ability to perform activities of daily living) of at least 6 (scores range from 0 to 24, with higher scores indicating more impairment). Ultomiris should only be covered to treat patients if their symptoms persist despite a stable dose of standard of care acetylcholinesterase inhibitors (AChEIs), corticosteroids (CSs), and/or nonsteroidal immunosuppressants (NSISTs). Ultomiris should only be covered to treat those who have received prior vaccination against meningococcal infections.

What Are the Conditions for Reimbursement?

Ultomiris should not be reimbursed when given during a gMG exacerbation (i.e., a moment when the patient experiences weakness in some or all muscles, without needing assistance to breath) or crisis (i.e., a moment when respiratory muscles are too weak, limiting air flow in and out of lungs, and as a result the patient is unable to breathe), or within 12 months of thymectomy (i.e., surgical removal of thymus gland). Ultomiris should only be reimbursed if prescribed by or in consultation with a neurologist with expertise in managing patients with gMG and the cost of Ultomiris is reduced. Ultomiris should not be used concomitantly with rituximab, efgartigimod alfa, or complement inhibitors, such as eculizumab.

Why Did CDA-AMC Make This Recommendation?

- Evidence from a clinical trial (CHAMPION-MG) demonstrated that, compared with placebo, treatment with Ultomiris was associated with a meaningful improvement in gMG daily activity and reduction in disease severity for patients in whom symptoms persisted despite a stable standard of care dose.

Summary

- Ultomiris met some of the identified patient needs as it improves activities of daily living and gMG disease severity and may offer more convenience in terms of longer periods between infusions (e.g., potentially compared to some IV immunoglobulin [IVIg] regimens).
- Based on the CDA-AMC 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 $138 million over the next 3 years. However, the actual budget impact is uncertain.

Additional Information

What Is gMG?

Myasthenia gravis (MG) is a condition that causes muscle weakness. In some patients, symptoms remain exclusively to the eyes (i.e., ocular MG); however, most patients either are diagnosed with or progress within a few years to gMG, which affects the head and neck, and other muscles. Symptoms of gMG include eyelid drooping and double vision, altered facial expression, difficulty chewing and swallowing food, difficulty speaking, and, in patients with more severe disease, problems with limb movement and breathing. In Canada, the incidence of MG is estimated at approximately 23 cases per 1 million population annually.

Unmet Needs in gMG

For patients with refractory gMG and in those whose symptoms persist despite adequate treatment with standard of care, symptoms are difficult to control and few treatment options exist.

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. Ultomiris costs between $495,186 and $597,136 in year 1 and between $473,340 and $568,008 in subsequent years.

Recommendation

The Canadian Drug Expert Committee (CDEC) recommends that ravulizumab be reimbursed for the treatment of adults with AChR antibody-positive gMG only if the conditions listed in Table 1 are met.

Rationale for the Recommendation

As outlined in the 2023 CDEC final recommendation for the original review of ravulizumab, 1 phase III, randomized, double-blind, placebo-controlled trial (CHAMPION-MG; N = 175) demonstrated that, compared with placebo, treatment with ravulizumab resulted in statistically significant improvements in activities of daily living and gMG disease severity after 26 weeks of treatment as measured by MG-ADL scores, Quantitative Myasthenia Gravis (QMG) total scores, and 5-point QMG response. CDEC recognized an unmet need for an effective therapy in patients with refractory gMG and those with nonrefractory disease who remain symptomatic despite adequate treatment with conventional therapies. The committee concluded in its first review that a lack of information on immunosuppressive therapy (IST) dosage at study entry and insufficient data on patients with refractory and nonrefractory but symptomatic gMG precluded CDEC from determining whether ravulizumab provided clinically meaningful value compared to optimized IST. Moreover, the initial recommendation stated that the CHAMPION-MG trial did not provide evidence on the efficacy or harms of ravulizumab compared to relevant comparators (e.g., rituximab, IVIg, plasma exchange).

As part of the evidence base for the resubmission, CDEC considered 2 post hoc cohorts in the CHAMPION-MG trial, longer-term data from the open-label extension (OLE) period of the CHAMPION-MG trial, and updated sponsor-submitted indirect treatment comparisons (ITCs). CDEC agreed that the patient populations included in the 2 cohorts reflected patients with unmet needs in clinical practice in Canada and the dose and durations of conventional IST at study entry were sufficient to achieve maximal responses in patients at the time of enrolment. The post hoc results in the 2 cohorts were consistent with the results in the overall trial population across primary and secondary outcomes — change from baseline in MG-ADL score and QMG total scores at week 26 and the proportion of patients achieving a 5-point QMG and a 3-point MG-ADL response at week 26 — suggesting ravulizumab was favoured over placebo. The findings on long-term efficacy and safety based on the OLE set appeared consistent with the randomized controlled period and suggested ongoing benefit of ravulizumab. Due to limitations in the sponsor-submitted ITCs, CDEC was unable to draw definitive conclusions on the relative efficacy of ravulizumab compared to efgartigimod alfa, IVIgs, rituximab, and eculizumab.

Patients identified a need for effective treatment options that maintain patients' independence in daily activities, have fewer side effects, provide improved administration (e.g., method, frequency, setting of delivery), decrease the frequency and intensity of exacerbations, and offer fewer and shorter hospital admissions. Based on the evidence reviewed, CDEC concluded that ravulizumab met some of the identified needs. The efficacy results in the 2 post hoc cohorts in the CHAMPION-MG trial suggested a meaningful benefit in activities of daily living and gMG disease severity compared to placebo; although the impact of ravulizumab relative to other comparators remains uncertain. Ravulizumab may offer more convenience in

terms of longer periods between infusions (e.g., potentially compared to some IVIg regimens). CDEC noted that a conclusion regarding the impact of ravulizumab on quality of life could not be drawn based on the available evidence. The impact of ravulizumab on MG exacerbation and hospitalization remains unclear due to the exploratory nature of the analyses and small number of events.

Using the sponsor-submitted price for ravulizumab and publicly listed prices for all other drug costs, the incremental cost-effectiveness ratio for ravulizumab plus usual care was $2,996,852 per quality-adjusted life-year gained compared with rituximab plus usual care. At this incremental cost-effectiveness ratio, ravulizumab plus usual care is not cost-effective at a $50,000 per quality-adjusted life-year willingness-to-pay threshold for adults with AChR antibody-positive gMG whose symptoms persist despite adequate treatment with AChEIs, CSs, and/or NSISTs. A reduction in price is therefore required.

Table 1: Reimbursement Conditions and Reasons

Reimbursement condition	Reason	Implementation guidance
Initiation		
1. Adults with gMG who have all of the following: 1.1. positive serologic test for anti-AChR antibodies 1.2. MG-ADL score at baseline of ≥ 6 1.3. MGFA class II to IV disease 1.4. persistent symptoms, despite a stable dose of standard of care AChEIs, CSs, and/or NSISTs 1.5. vaccination against meningococcal infections.	Two post hoc cohorts in the CHAMPION-MG trial (reflecting 75% of patients in the overall trial population), demonstrated that compared to placebo, treatment with ravulizumab resulted in clinical benefit in patients with refractory and nonrefractory gMG whose symptoms persisted despite adequate treatment with AChEIs, CS, and/or NSISTs. The inclusion criteria for the 2 post hoc cohorts in the CHAMPION-MG trial aligned with the overall trial population and included adult patients (age ≥ 18 years) with gMG who tested positive for anti-AChR antibodies, had an MG-ADL score ≥ 6, an MGFA class of II to IV, vaccination against meningococcal infections, and persistent symptoms despite a stable dose of standard of care AChEIs, CSs, and/or NSISTs at baseline.	Stable dose may be defined as an adequate trial (as determined by the treating physician) of at least 1 AChEI, CS, and/or NSIST (such as azathioprine, mycophenolate mofetil, cyclosporine, tacrolimus, methotrexate, and cyclophosphamide) in the previous 12 months. CDEC noted that rituximab may be available in some jurisdictions; however, CDEC heard from the clinical experts that access to rituximab remains a barrier for some patients.
2. Ravulizumab should not be initiated: 2.1. during a gMG exacerbation or crisis 2.2. within 12 months of thymectomy.	Patients who had thymectomy within 12 months before screening and had MG crisis or exacerbation at the time of screening or randomization were excluded from the CHAMPION-MG trial. The efficacy and harms of ravulizumab in such patients are unknown.	—
3. An MG-ADL score must be measured and provided by the physician at baseline.	A baseline MG-ADL score was measured in the CHAMPION-MG trial and was used to determine response to treatment.	—

Reimbursement condition	Reason	Implementation guidance
4. The maximum duration of initial authorization is 6 months.	According to the clinical experts, approval for 6 months initially would be reasonable to assess response to treatment. The treatment phase in the CHAMPION-MG trial was a 26-week treatment period.	—
Renewal		
5. Reimbursement of ravulizumab treatment should be continued if, after the initial 6 months of treatment, there is a documented MG-ADL score improvement of 2 points or more.	Although no MID has been estimated, an improvement of approximately 2 points in the total MG-ADL score is a recommended response threshold that indicates clinical improvement for patients with MG. The clinical experts propose a 2-point reduction in MG-ADL score as a minimal clinically meaningful measure of response to treatment.	Based on clinical expert opinion, after the first initial 6 months of ravulizumab, if a patient has responded, treatment would be given as long as the patient continues to have a clinically meaningful response. In terms of maximum duration of treatment, treatment with ravulizumab would probably be given as long as ravulizumab continued to be effective or until the disease spontaneously remitted.
6. For subsequent renewal, the treating clinician must provide proof that the initial MG-ADL score response achieved after the first 6 months of therapy with ravulizumab has been maintained. Reassessment for renewal should occur every 6 months.	This is meant to ensure that a patient's disease is maintaining its response to treatment with ravulizumab.	Based on clinical expert opinion, there is the possibility of ravulizumab being used for 1 or more years. A patient whose disease had initially responded to ravulizumab (after the initial 6 months) and was stable for a year, but worsened afterward (while the patient was no longer receiving ravulizumab), could reinitiate therapy, as long as the initiation criteria are met. The patient would not be expected to try standard care (AChEIs, CSs, and/or NSISTs) again.
Prescribing		
7. Ravulizumab should be prescribed by or in consultation with a neurologist with expertise in managing patients with gMG.	Accurate diagnosis and follow-up of patients with gMG is important to ensure that ravulizumab is prescribed to appropriate patients.	—
8. Ravulizumab should not be used concomitantly with rituximab, efgartigimod alfa, and/or complement inhibitors such as eculizumab.	The efficacy and safety of ravulizumab in combination with rituximab, efgartigimod alfa, and/or eculizumab is unknown.	—
Pricing		
9. A reduction in price.	The ICER for ravulizumab plus usual care is $2,996,852 per QALY gained when compared with rituximab plus usual care. A price reduction of 97% would be required for ravulizumab to achieve an ICER of $50,000 per QALY gained compared to usual care alone. Cost-effectiveness relative to other advanced treatments (i.e., efgartigimod	—

Reimbursement condition	Reason	Implementation guidance
	alfa, rituximab, and IVIg) for AChR antibody-positive gMG is uncertain given the lack of direct head-to-head evidence and limitations with the indirect comparisons. To ensure cost-effectiveness, ravulizumab should also be priced no higher than the lowest-cost advanced treatment reimbursed for AChR antibody-positive gMG.	
Feasibility of adoption		
10. The economic feasibility of adoption of ravulizumab plus usual care must be addressed.	At the submitted price, the incremental budget impact of ravulizumab is expected to be greater than $40 million in year 1, 2, and 3.	—

AChEI = acetylcholinesterase inhibitor; AChR = acetylcholine receptor; CS = corticosteroid; gMG = generalized myasthenia gravis; ICER = incremental cost-effectiveness ratio; IVIg = IV immunoglobulin; MG = myasthenia gravis; MG-ADL = Myasthenia Gravis Activities of Daily Living; MGFA = Myasthenia Gravis Foundation of America; MID = minimal important difference; NSIST = nonsteroidal immunosuppressant therapy; QALY = quality-adjusted life-year; RCT = randomized controlled trial.

Discussion Points

- **Resubmission of the ravulizumab initial submission:** The sponsor filed a resubmission of the ravulizumab initial submission that received a negative final CADTH recommendation in 2023. CDEC highlighted in its initial review a lack of information on IST dosage at study entry in the CHAMPION-MG trial, insufficient data on patients with refractory gMG and those with nonrefractory disease but who remain symptomatic, and absence of comparative evidence of ravulizumab versus relevant comparators (i.e., rituximab, IVIg, plasma exchange). The sponsor sought to address these deficiencies with additional information provided in the resubmission: 2 post hoc cohorts of patients in the CHAMPION-MG trial (i.e., the concomitant IST optimized cohort with 132 patients [75%] and the refractory concomitant IST optimized cohort with 88 patients [50%]), longer-term data from the OLE period of the CHAMPION-MG trial, and updated sponsor-submitted ITCs.
- **Unmet need:** CDEC discussed the rarity of gMG and noted that despite its low incidence, treatment options are available for patients (e.g., azathioprine, mycophenolate mofetil, cyclophosphamide, cyclosporine, tacrolimus, methotrexate, prednisone). However, CDEC acknowledged that not all treatment options may be available to every patient in all jurisdictions. Furthermore, CDEC recognized that there is an unmet need for effective therapy in patients with refractory gMG and patients with nonrefractory disease who remain symptomatic despite an adequate trial of conventional therapies (e.g., AChEIs, CSs, and/or NSISTs). CDEC members discussed the evidence base for the resubmission and agreed with the clinical expert that the patient selection criteria used in the 2 post hoc cohorts were reasonably aligned with the unmet needs in patients with refractory gMG and in those whose symptoms persist despite adequate treatment with conventional therapies. CDEC heard from the clinical expert that in clinical practice there are no standard definitions for the terms

refractory disease and *inadequate symptom control*, though there is significant overlap between these 2 groups of patients.

- **Efficacy:** CDEC considered that the CHAMPION-MG trial did not conduct a calculation to determine the sample size needed to detect statistically significant differences in effect estimates in the 2 post hoc cohorts of patients, which were the focus of the resubmission. However, the committee members discussed that the consistent effects of ravulizumab observed in the cohorts compared with the overall trial population across the primary outcome (i.e., MG-ADL total score) and secondary outcomes (i.e., QMG total score, QMG 5-point response, MG-ADL 3-point response) indicated the likelihood that ravulizumab has a beneficial clinical effect in patients with AChR antibody-positive gMG compared to optimized IST at study baseline (during the study, dose and schedule changes to baseline IST required sponsor approval). However, CDEC noted that the confidence in the between-group differences for efficacy in the 2 cohorts was limited due to imprecision (i.e., associated confidence intervals [CIs] included effects close to the null or crossed the null; the CI crossed the null for QMG total score in the refractory concomitant IST optimized cohort). The committee discussed that a conclusion regarding the impact of ravulizumab on health-related quality of life (HRQoL), measured by the Myasthenia Gravis Quality of Life 15-item Scale (MG-QoL15r) and Neuro-QoL Fatigue score, could not be drawn based on the small sample sizes and wide CIs.
- **IST dosing at study entry**: CDEC discussed the information provided in the resubmission on IST dosage at study entry in the 2 post hoc cohorts of the CHAMPION-MG trial. CDEC agreed with the clinical expert that the dose and durations of IST received by patients at enrolment were sufficient to achieve maximal responses in patients (i.e., the mean and median duration of prior corticosteroid treatment and NSIST exceeded 2 to 6 months for corticosteroids and 9 to 18 months for NSISTs) and were reflective of an adequate trial of IST.
- **Long-term extension study:** CDEC considered the data from the long-term extension study of the CHAMPION-MG trial included in the resubmission, which suggested sustained benefit to up to 3.5 years and a long-term adverse effects profile in patients receiving ravulizumab that was consistent with the CHAMPION-MG trial. However, interpretation of the long-term results was limited by the open-label and descriptive nature of the extension study and was considered as supportive evidence by CDEC.
- **Adverse effects**: CDEC discussed patients' desire for treatments with fewer adverse effects. While the CHAMPION-MG trial did not provide direct comparative evidence on the adverse effects of ravulizumab versus other advanced gMG therapies (e.g., eculizumab, efgartigimod alfa, IVIg), CDEC noted that overall treatment-emergent adverse events (TEAEs) appeared more frequently in patients treated with ravulizumab compared to placebo. The most common TEAEs included headache, diarrhea, and infections in the ravulizumab group. CDEC noted that serious infections were higher in the ravulizumab group, which was acknowledged in the Health Canada product monograph. CDEC noted that 2 deaths were reported in the ravulizumab group and no deaths were reported for the placebo group; the deaths were not considered by the study investigator to be treatment related. No meningococcal infections were reported in the trial. The incidence of TEAEs and serious adverse

events (AEs) in the 2 post hoc cohorts of patients in the CHAMPION-MG trial were overall consistent with the harms results in the overall trial population.

- **Indirect evidence:** CDEC members discussed the uncertainty of the comparative efficacy and safety of ravulizumab due to the absence of direct comparative evidence. CDEC considered 1 sponsor-submitted network meta-analysis (NMA) assessing ravulizumab relative to efgartigimod alfa, IVIg, rituximab, and eculizumab, and 1 matching-adjusted indirect comparison (MAIC) comparing ravulizumab with efgartigimod alfa. Numerous limitations in the analyses (e.g., limited number of studies, heterogeneity across study designs and populations, and wide credible intervals or CIs) meant that there was insufficient evidence for CDEC to draw conclusions on the efficacy and safety of ravulizumab versus comparator therapies.
- **Treatment administration:** CDEC discussed patients' desire for improved treatment administration (e.g., method, frequency, setting of delivery). CDEC noted that ravulizumab may offer more convenience in terms of longer periods between infusions (e.g., potentially compared to some IVIg regimens). While ravulizumab is administered less frequently than eculizumab (every 8 weeks compared to every 2 weeks), the committee noted that eculizumab is not currently listed for reimbursement by jurisdictions for adult patients with AChR antibody-positive gMG. Ravulizumab is administered intravenously in specialized care centres.
- **Relevant comparators:** According to feedback from public drug plans, coverage of advanced treatments included in the pharmacoeconomic analysis is variable across jurisdictions. As such, CDEC noted that relevant comparators to ravulizumab are likely to vary by public drug plan.

Background

MG is a chronic autoimmune disease that affects how nerve signals reach muscles, leading to muscle weakness. The immune system mistakenly produces antibodies that target and block or destroy acetylcholine receptors on muscle cells, leading to poor or incomplete muscle contraction. Approximately 85% to 90% of patients with MG either are diagnosed with or progress within a few years to gMG, and their symptoms include eyelid drooping and double vision, altered facial expression, difficulty chewing and swallowing food, difficulty speaking, and, in patients with more severe disease, problems with limb movement and breathing. Collectively, symptoms of MG negatively impact patients' HRQoL. In Canada, the prevalence of MG is approximately 263 to 320 cases per 1 million population and its incidence is approximately 23 cases per 1 million population annually. The initial symptomatic treatment for most patients with gMG is an AChEI such as pyridostigmine. Many patients need treatment with CSs and/or NSISTs when they do not reach their treatment goals with AChEIs. Other treatment options include immunomodulating therapies, plasma exchange (PLEX), and IV immunoglobulin (IVIg). Novel biologic treatments include efgartigimod alfa, eculizumab, and rituximab.

Ravulizumab has been approved by Health Canada for the treatment of adults with AChR antibody-positive gMG. It is a terminal complement inhibitor that specifically binds to the complement protein C5 with high

affinity, thereby inhibiting its cleavage to C5a and C5b and thus preventing the generation of membrane attack complex. Ravulizumab is available as a 10 mg/mL or 100 mg/mL concentrate for IV infusion. The recommended ravulizumab maintenance dose for adults with gMG is based on the patient's body weight, with maintenance doses administered every 8 weeks, starting 2 weeks after the loading dose. Patients must be vaccinated against meningococcal infections before, or at the time of, initiating ravulizumab, unless the risks of delaying ravulizumab therapy outweigh the risks of developing a meningococcal infection.

Sources of Information Used by the Committee

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

- a review of the efficacy and harms of ravulizumab in 1 phase III randomized controlled trial (RCT) (CHAMPION-MG, N = 175) and 2 post hoc cohorts in the CHAMPION-MG trial (the concomitant IST optimized cohort, N = 132, and the refractory concomitant IST optimized cohort, N = 88); an OLE of the CHAMPION-MG trial (with follow-up data up to 3.5 years); and 2 ITCs submitted by the sponsor
- patients' perspectives gathered by 1 patient group, Muscular Dystrophy Canada (MDC)
- input from the public drug plans and cancer agencies that participate in the CDA-AMC review process
- 1 clinical specialist with expertise diagnosing and treating patients with AChR antibody-positive gMG
- input from 1 clinician group, the Neuromuscular Disease Network for Canada (NMD4C)
- a review of the pharmacoeconomic model and report submitted by the sponsor.

Perspectives of Patients, Clinicians, and Drug Programs

The information in this section is a summary of input provided by the patient and clinician groups that responded to CDA-AMC's call for input and from the clinical expert consulted by CDA-AMC for the purpose of this review. The full patient and clinician group submissions received by CDA-AMC are available in the consolidated patient and clinician group input document for this review on the project website.

Patient Input

CDA-AMC received 1 patient group submission from MDC, which is a health charity that supports people affected by muscular dystrophies and related muscle diseases in Canada. MDC collected information from 215 patients impacted by MG through a health care experience survey and semistructured phone or virtual interviews. These patients consisted of 83 males and 132 females aged between 22 and 78 years from all provinces in Canada. MDC also conducted an MG Canadian Journey Mapping project among patients living with MG via completing virtual interviews, round table sessions, surveys, and HRQoL measures. Respondents indicated that MG has a significant impact on productivity; fatigue, energy levels, and quality of sleep; respiratory health; mobility and strength; independence; relationships and social participation; eyes, vision, speech, and swallowing; mental health; quality of life; and the well-being of respondents' families.

MDC added that, according to the respondents, while supportive treatments have had positive health outcomes, there are concerns about the long-term and sustained benefits of these treatments.

MDC noted that patients with gMG seek better control over their condition to minimize the impact of symptoms, side effects, and disease exacerbations on their lives; allowing them to maintain their independence and avoid serious hospital admissions. MDC added that patients stated that they would be willing to deal with side effects of medications if these aspects of MG were better controlled. According to MDC, respondents indicated that currently available therapies may decrease MG exacerbations but not their overall HRQoL.

Based on the patient group input, the important factors in evaluating different treatments include treatment administration, potential side effects, duration and frequency of treatments, convenience (e.g., travel time and parking for clinic visits), and financial impact (costs).

MDC explained that patients value new treatments that offer improved disease control and disease symptoms and extend dosing intervals.

In terms of diagnostic testing, MDC stated that 85% of respondents reported significant difficulty getting diagnosed. The vast majority of patients found the test to be cost-effective but noted the overall lengthy process with many missed opportunities (e.g., delays, misdiagnoses, and costs incurred). A diagnosis received as part of hospitalization was reported as a seamless experience.

MDC believed that there is a pressing need for improved treatment options to address the ongoing challenges faced by patients with MG and ravulizumab provides a new treatment option for patients with MG that has demonstrated efficacy, safety, and improved dosing convenience compared to other treatment options.

Clinician Input

Input From the Clinical Expert Consulted by the Review Team for This Resubmission

The clinical expert identified the following unmet needs associated with the currently available treatments for patients with gMG whose symptoms persist even if they have been treated with conventional medications for this disease (such as AChEIs, CSs, and/or NSISTs). The first is, although multiple treatment options are available to patients with gMG, some patient's disease does not have adequate response to the existing treatments, and 15% to 20% of patients have refractory disease and require alternative therapeutic options; the second is that patients may become intolerant to ISTs; and the third is that some exiting treatments are only suitable for select patients. Because of its unique mechanism of action, ravulizumab, a complement C5 inhibitor, could be another treatment option for patients in Canada with gMG whose disease has an inadequate response to or fails to respond conventional ISTs, or who cannot tolerate conventional ISTs.

The clinical expert indicated that patients in Canada with significant symptoms of gMG whose disease fails to respond to conventional ISTs, or who cannot tolerate them, would be eligible to receive treatment with ravulizumab. Initiation of ravulizumab therapy could be considered when the patients are experiencing significant symptoms of gMG, are resistant to conventional therapies, requiring multiple concomitant

ISTs (which include CSs and NSISTs), or when patients cannot tolerate the significant side effects of conventional ISTs.

The expert noted that in clinical practice, regular follow-up visits with a neuromuscular specialist or a neurologist are required to monitor the patient's response to treatment, using certain MG-specific scales (e.g., MD-ADL), as well as the treating physicians' clinical examination.

The expert also noted that treatment with ravulizumab should be discontinued when a patient's disease does not respond well to the treatment or when the patient experiences significant treatment side effects, such as meningococcal infections, or by patient preference. In addition, if the patient shows long-term stability of neurologic status and is perceived to have achieved remission, the clinician may suggest holding the treatment under observation.

The expert indicated that initiation of treatment with ravulizumab and the follow-up assessments could be provided by a neurologist with expertise in MG management.

Clinician Group Input

One input was received from NMD4C, a new pan-Canadian network that brings together clinical, scientific, technical, and patient expertise to improve care, research, and collaboration in neuromuscular diseases. The mission of NMD4C is to improve the care, research, and treatment of neuromuscular disorders for all people living in Canada. The information presented in this submission was gathered from 8 clinicians with experience treating gMG.

NMD4C noted that the goals of therapy are to minimize morbidity and mortality from MG, keep patients out of hospital, improve quality of life, prevent repeated attacks, and prevent prolonged, untreated, or partially treated MG. According to the clinician input, the current mainstay of therapies for MG includes supportive therapies, symptomatic treatments, and disease-modifying strategies. NMD4C provided opinions consistent with the clinical expert consulted for this review regarding the unmet needs with currently available treatments: limited available options for active and refractory disease, limited response to the traditional ISTs, slow onset of treatment action, and serious side effects.

NMD4C believes ravulizumab inhibits the immune-mediated damage to the neuromuscular junction rather than being a symptomatic treatment. Place in therapy for ravulizumab would likely be in patients with inadequate MG response after treatment with pyridostigmine and after treatment with either steroids and/or other immunosuppressive therapies, including steroid-sparing immunosuppressive drugs. Ravulizumab is likely to affect the treatment paradigm of patients with refractory and nonrefractory MG whose disease does not respond to the first- and second-line therapies or those who require chronic IVIg infusions or PLEX. It may also be considered in patients who are intolerant to other immunomodulatory treatments.

NMD4C stated that patients with MG should try other treatments before initiating ravulizumab, which requires periodic IV infusions over an extended period, is unlikely to induce long-term disease remission, is likely to be expensive, will likely not be available in smaller cities or nonspecialized centres, and requires extensive expertise.

Based on the clinician group input, adults who are seropositive for AChR antibodies and have gMG would be best suited for treatment with ravulizumab, while there is no data on efficacy of ravulizumab for a minority population of MG patients, including those younger than aged 18 years, those who had thymectomy within a year, those with thymic carcinoma, those who are pregnant or breastfeeding, those with anti-muscle specific tyrosine kinase (MuSK) or anti-low density lipoprotein receptor-related protein 4 (LRP4) antibodies, or those who are seronegative. Patients with MG who are AChR antibody positive who have not responded to pyridostigmine and steroids and/or oral ISTs or are additionally dependent on periodic PLEX or chronic IVIg therapy are most in need.

NMD4C noted that the diagnosis must have been confirmed clinically and supported by confirmatory laboratory tests before treatment with ravulizumab.

NMD4C explained that the outcomes used to determine whether a patient is responding to treatment in clinical practice include increased survival, avoidance of emergency department visits or hospital or intensive care unit admissions, need for rescue therapy as well as maintenance therapy with IVIg and plasmapheresis, reduction in the dose and/or duration of concomitant steroids, level of fatigable weakness, and activities of daily living and quality of life.

Based on the NMD4C input, the factors that should be considered when deciding to discontinue treatment include the amount of clinical improvement or response, the duration of time spent in clinically stable state, the AEs associated with the treatments, and the inconvenience associated with the therapy.

NMD4C added that an appropriate setting for treatment includes a clinical team with general knowledge of MG, appropriate nursing experience in managing IV medications, familiarity with venous access issues, and managing potential adverse effects. It is recommended that ravulizumab be prescribed by neurology specialists with expertise in the diagnosis, assessment, monitoring, and management of MG.

Drug Program Input

Input was obtained from the drug programs that participate in the CDA-AMC reimbursement review process. The clinical expert consulted by CDA-AMC provided advice on the potential implementation issues raised by the drug programs (refer to Table 2 for details).

Table 2: Responses to Questions From the Drug Programs

Implementation issues	Response
Relevant comparators	
The efficacy and safety of ravulizumab for gMG were previously reviewed by CADTH, based on the evidence from a phase III, multicentre, double-blind, placebo-controlled RCT (CHAMPION-MG). This drug received a CDEC recommendation of “do not reimbursed.” In this resubmission, the sponsor is requesting different reimbursement criteria and provided new clinical evidence, including post hoc analyses in the concomitant IST optimized cohort and refractory concomitant IST optimized	The clinical expert noted that there is currently no robust direct or indirect evidence of ravulizumab compared to other advanced treatments (e.g., efgartigimod alfa, IVIg, rituximab, eculizumab) in patients with gMG whose symptoms persist despite adequate treatment with AChEIs, CSs, and/or NSISTs. CDEC agreed with the clinical expert that the evidence provided by the sponsor-submitted ITCs was insufficient to conclude whether

Implementation issues	Response
cohort, new open-label extension study data up to 3.5 years of treatment with ravulizumab, and a new ITC, in which the relative efficacy of ravulizumab vs. efgartigimod alfa, rituximab, IVIg, and eculizumab were evaluated in the concomitant IST optimized cohort. The sponsor noted that, based on the results of the ITC, ravulizumab was, at minimum, comparable to other active treatments at the time points considered. Is this indirect comparison analysis sufficient to demonstrate that ravulizumab is comparable to other active treatments in patients with gMG whose symptoms persist despite adequate treatment with AChEIs, CSs, and/or NSISTs?	ravulizumab is comparable to other advanced treatments for patients with gMG.
In many jurisdictions, rituximab is listed with relatively accessible criteria, though it is used off-label for patients with gMG and has not been reviewed by CDEC. Eculizumab (Soliris) has received a positive recommendation for patients with gMG from CDEC; however, it did not reach a successful PLA between the drug plans and the sponsor; therefore, it is not listed in any jurisdictions in Canada. Efgartigimod alfa has recently received a positive recommendation from CDEC for patients with gMG who are AChR antibody positive. It is currently undergoing PLA negotiations.	This is a comment from the drug programs to inform CDEC deliberations.
Considerations for initiation of therapy	
In accordance with the requested reimbursement criteria, how are patients identified as having “persistent symptoms” despite adequate treatment? Do all standard and/or conventional therapies need to be maximized first? How should an adequate trial on these drugs be defined? The sponsor has noted that ravulizumab would be used as an add-on therapy for patients who continue to experience debilitating symptoms despite adequate conventional therapies. This is different from the eculizumab review, in which eculizumab was used for patients with refractory disease. Is there a clear definition of “refractory disease” for the population with gMG? Can ravulizumab also be used for patients with refractory disease?	The expert suggested that patient’s gMG symptoms can be identified using MG-related scales (e.g., MG-ADL). The number of symptoms that the patient experienced will be recorded — the higher the number, the more symptomatic the patient is. The expert indicated that in clinical practice, it is not realistic for patients to maximize all standard or conventional therapies before receiving ravulizumab, as not every patient is a good candidate for all standard and/or conventional treatments; in addition, it also depends on how conservative the treatment plan would be. However, the expert anticipated that most clinicians would likely attempt to maximize at least 1 IST before ravulizumab. The expert also noted that different drugs have different requirements for being considered maximized. For example, patients who receive steroids, IVIgs, or other therapies need to receive these treatments for approximately 6 to 9 months before they can be considered received for sufficiently long and deemed effective for the patients or not. In clinical trials of gMG, the treatment effects of the investigated medications can be determined using certain scales (e.g., the MG-ADL) to capture the changes in symptoms. In this scale, higher scores indicate more severely impacted daily activities for the patients. The expert noted that in practice, there is no standard definition

Implementation issues	Response
	for patients with refractory disease. Usually, if the patients have persistent symptoms despite adequate conventional therapies, and the scores of certain scales (e.g., MG-ADL) are higher than predefined values, the patients are considered to have refractory disease. Other approaches for defining refractory disease include the history of treatments for gMG. For example, if patients do not respond well to multiple ISTs, or require chronic IVIg therapy or plasma exchange, they are considered to have refractory disease. The expert noted that ravulizumab can be used in patients with refractory gMG. CDEC acknowledged and agreed with the responses from the clinical expert.
Should patients who have experienced other drug treatments in this area (i.e., eculizumab, efgartigimod alfa, or rituximab) be eligible for treatment with ravulizumab?	The expert agreed that patients are still eligible for treatment with ravulizumab if they received previous gMG medications, such as eculizumab, efgartigimod alfa, or rituximab. CDEC agreed with the clinical expert that this would be reasonable.
FWG noted that consistency with the initiation criteria associated with other drugs in the same therapeutic space, specifically efgartigimod alfa, should be considered. This drug has been reviewed by CADTH in the same population, and a positive CDEC recommendation was issued in December 2023. Is there a specific place in therapy before or after efgartigimod alfa and eculizumab that will be considered for ravulizumab?	The expert indicated that ravulizumab should be included as a treatment option for patients with gMG, along with efgartigimod alfa and eculizumab. Even though these patients may have received multiple therapies for MG, they may still experience significant symptoms. CDEC acknowledged and agreed with the feedback from the clinical expert.
Considerations for continuation or renewal of therapy	
FWG noted that consistency with the continuation or renewal criteria associated with other drugs in the same therapeutic space, specifically efgartigimod alfa, should be considered. This drug has been reviewed by CADTH in the same population, and a positive CDEC recommendation was issued in December 2023.	This is a comment from the drug programs to inform CDEC deliberations.
Considerations for discontinuation of therapy	
What are the differences between “refractory disease” and “inadequate response to conventional therapy”? Can these 2 terms be clearly defined?	The expert indicated that these 2 terms overlap significantly, although there are no accepted definitions available for them. Based on the expert’s opinion, when compared to “inadequate response to conventional therapy,” “refractory disease” implies poorer response to treatment and a disease that is harder to treat. Patients with refractory disease can be identified if they have persistent symptoms despite adequate conventional therapies, which implies inadequate response to those treatments. Patients’ responses can be measured using scales specific for gMG; for example, in MG-ADL, higher scores indicate greater severity of symptoms. Other approaches for defining refractory disease include a patient’s history of gMG treatments. CDEC acknowledged the clinical expert’s response.

Implementation issues	Response
Are there guidelines for switching from eculizumab or efgartigimod alfa to ravulizumab and vice versa?	The expert noted that, currently, there are no guidelines for switching from eculizumab or efgartigimod alfa to ravulizumab and vice versa. CDEC acknowledged the clinical expert's response.
Considerations for prescribing of therapy	
Life-threatening meningococcal infections and/or sepsis have been reported in patients treated with ravulizumab. Therefore, patients are required to be vaccinated against meningococcal infections before or at the time of initiating ravulizumab and be monitored for early signs of meningococcal infections so they can be treated immediately if infection is suspected.	This is a comment from the drug programs to inform CDEC deliberations.
Please indicate if there are any concerns with adding ravulizumab to a regimen already containing 1 of the other ISTs (e.g., eculizumab, efgartigimod alfa) in patients with gMG.	The expert indicated that when combining multiple ISTs in patients with gMG, there is always a risk of potential superimposed infections due to patients' compromised immune systems. This is not unique to ravulizumab but applies to all ISTs. As meningococcal vaccination is mandatory before initiating treatment with ravulizumab, the expert did not have additional concerns for this type of infection. CDEC noted that there is currently insufficient evidence for ravulizumab in combination with rituximab, eculizumab, and/or efgartigimod alfa to guide a decision on combining ravulizumab with these advanced treatments.
FWG noted that consistency with the prescribing criteria associated with other drugs in the same therapeutic space, specifically efgartigimod alfa, should be considered.	This is a comment from the drug programs to inform CDEC deliberations.
Generalizability	
Patients who are currently receiving an active comparator treatment to ravulizumab may have a time-limited opportunity to switch to ravulizumab, if ravulizumab is a preferred treatment option. Would there be any concerns with this approach?	The expert did not have concerns for the time-limited opportunity to switch to ravulizumab if the patients are currently receiving another comparator treatment, such as eculizumab, efgartigimod alfa, or rituximab. CDEC acknowledged the input by the clinical expert but noted that there is currently insufficient evidence to guide a decision on switching to ravulizumab in patients who currently receive another comparator treatment, such as eculizumab, efgartigimod alfa, or rituximab.
Care provision issues	
FWG noted that meningococcal vaccination is required before treatment with ravulizumab, and patients receiving ravulizumab should be monitored for early signs of meningococcal infections.	This is a comment from the drug programs to inform CDEC deliberations.
System and economic issues	
FWG noted that the provision of ravulizumab may have a substantial budget impact due to the easier dosing regimen of this drug.	This is a comment from the drug programs to inform CDEC deliberations.

Implementation issues	Response
Efgartigimod alfa, 1 of the comparators for ravulizumab, is currently undergoing price negotiations for the same indication.	This is a comment from the drug programs to inform CDEC deliberations.

AChEI = acetylcholinesterase inhibitor; AChR = anti–acetylcholine receptor; CDEC = Canadian Drug Expert Committee; CS = corticosteroid; FWG = Formulary Working Group; gMG = generalized myasthenia gravis; IST = immunosuppressive therapy; ITC = indirect treatment comparison; IVIg = IV immunoglobulin; MG = myasthenia gravis; MG-ADL = Myasthenia Gravis Activities of Daily Living; NSIST = nonsteroidal immunosuppressants therapy; PLA = product listing agreement; RCT = randomized controlled trial; vs. = versus.

Clinical Evidence

Systematic Review

Description of Studies

The CHAMPION-MG trial (N = 175) was a phase III, double-blind, multicentre, placebo-controlled RCT with an OLE period of up to 4 years. The primary objective of the CHAMPION-MG trial was to evaluate the safety and efficacy of ravulizumab compared with placebo in adults with gMG who are complement inhibitor naive. The randomized controlled portion of the trial is complete (data cut-off May 11, 2021; database locked on June 30, 2021) and the OLE concluded on May 25, 2023 (last patient's last visit).

In this resubmission, the sponsor provided new clinical evidence to support their revised reimbursement request: ravulizumab as add-on therapy for adults with AChR antibody-positive gMG whose symptoms persist despite adequate treatment with AChEIs, CSs, and/or NSISTs. Post hoc analyses were performed in the concomitant IST optimized cohort ([redacted]) and the refractory concomitant IST optimized cohort ([redacted]), which were the focus of this clinical review report. The purpose of the post hoc analyses was to evaluate the efficacy and safety of 26-week treatment with ravulizumab or placebo in patients with AChR antibody-positive gMG. Therefore, the inclusion criteria of the previous ADAPT trial (efgartigimod alfa versus placebo) and the REGAIN trial (eculizumab versus placebo) were adopted to select patients who would be considered to have IST optimization and IST optimization with refractory disease (i.e., patients who do not achieve symptom control after 12 months of treatment with ≥ 2 ISTs OR ≥ 1 IST and chronic IVIg or PLEX based on the REGAIN pivotal trial criteria for eculizumab) at the time of study enrolment from the CHAMPION-MG trial, respectively. The primary efficacy end point (change from baseline in MG-ADL at week 26) was the same as that in the primary analysis in the full population. Other outcomes in these analyses included change from baseline in QMG total score, improvement of at least 5 points in QMG total score from baseline, change from baseline in the MG-QoL15r score, change from baseline in the Neuro-QoL Fatigue score, improvement of at least 3 points in the MG-ADL total score from baseline, incidence of clinical deterioration and/or MG crisis, and safety. In the subgroup population of patients who received optimized IST or those who were refractory despite optimized IST, all outcomes analyzed were exploratory. Baseline demographic and disease characteristics of the concomitant IST optimized cohort and refractory concomitant IST optimized cohort were consistent with the full CHAMPION-MG population in terms of distribution of MGFA classification, baseline MG-ADL score ([redacted]), baseline QMG score ([redacted]), and age at diagnosis.

Efficacy Results

The evidence examined in this review was informed by 2 post hoc cohorts: the concomitant IST optimized cohort (patients receiving concomitant optimized IST, with or without refractory disease), and refractory concomitant IT optimized cohort (patients receiving concomitant optimized IST, with refractory disease).

MG-ADL Total Score

The MG-ADL total score ranges from 0 to 24, and higher scores indicate greater severity of symptoms and a more significant impact on a patient's daily living. Although no minimal important difference (MID) has been estimated, an improvement of approximately 2 points in the total MG-ADL score is a recommended response threshold that indicates clinical improvement at the level of individual patients with MG. In the concomitant IST optimized cohort, during the randomized controlled period (RCP), the least square (LS) mean change from baseline to week 26 in MG-ADL total score was [redacted] in the ravulizumab group compared to [redacted] in the placebo group. The LS mean treatment difference was [redacted]. In the refractory concomitant IST optimized cohort, the LS mean change from baseline to week 26 in MG-ADL total score was [redacted] in the ravulizumab group compared to [redacted] in the placebo group. The LS mean treatment difference was [redacted].

QMG Total Score

The total QMG score ranges from 0 to 39, where higher scores indicate greater disease severity. A definite MID for the QMG scale has not been established, although a threshold ranging between 2 and 3 points, depending on disease severity, has been suggested for patients with MG, which represents the minimal clinically important difference for the QMG scale. In the concomitant IST optimized cohort, the LS mean (standard error of the mean) change from baseline to week 26 in QMG total score was [redacted] in the ravulizumab group and [redacted] in the placebo group. The LS mean treatment difference was [redacted]. In the concomitant IST optimized refractory cohort, the LS mean (standard error of the mean) change from baseline to week 26 in QMG total score was [redacted] in the ravulizumab group and [redacted] in the placebo group during the RCP. The LS mean treatment difference was [redacted].

QMG 5-Point Response

Clinical responders was defined as patients who achieved a greater than 5-point improvement in QMG total score. In the concomitant IST optimized cohort, [redacted] of patients in the ravulizumab group compared to [redacted] in the placebo group achieved at least 5-point improvement. The between-group difference was [redacted] and the odds ratio (OR) was [redacted]. In the refractory concomitant IST optimized cohort, the proportion of patients meeting the clinical responder definition for QMG improvement was [redacted] in the ravulizumab

group versus [redacted] in the placebo group, with a between-group difference of [redacted] and an OR of [redacted]. The results in the 2 cohorts aligned with those in the primary analysis population.

MG-ADL 3-Point Response

Patients who achieved at least a 3-point improvement in MG-ADL total score were considered responders. In the full analysis set (FAS) of the CHAMPION-MG trial, this outcome was tested after a prior nonsignificant result of the hierarchical testing procedure and therefore is at increased risk of type I error (i.e., falsely rejecting the null hypothesis). In the concomitant IST optimized cohort, the proportion of patients who met the clinical responder definition for an MG-ADL improvement of at least 3 points was [redacted] in the ravulizumab group compared to [redacted] in the placebo group, with a between-group difference of [redacted] and an OR of [redacted]. In the refractory concomitant IST optimized cohort, the proportion of patients meeting the clinical responder definition for MG-ADL improvement was [redacted] in the ravulizumab group compared to [redacted] in the placebo group, with a between-group difference of [redacted] and an OR of [redacted]. The results in the 2 cohorts were aligned with the primary analysis set.

MG-QoL15r Total Score and Neuro-QoL Fatigue Score

HRQoL and fatigue were assessed based on LS mean change from baseline in MG-QoL15r total score and Neuro-QoL Fatigue score. An MID for MG-QoL15r or Neuro-QoL Fatigue in patients with MG has not been estimated. As the MG-QoL15r outcome did not reach statistical significance in the overall trial population, the P values for the subsequent secondary end points included in the prespecified hierarchical testing order, including Neuro-QoL Fatigue score, were considered nominal. [redacted] In the concomitant IST optimized cohort, the LS mean change from baseline to week 26 in the MG-QoL15r total score was [redacted] in the ravulizumab group and [redacted] in the placebo group during the RCP. The LS mean treatment difference was [redacted]. In the refractory concomitant IST optimized cohort, the LS mean change from baseline to week 26 in the MG-QoL15r total score was [redacted] in the ravulizumab group and [redacted] in the placebo group during the RCP. The LS mean treatment difference was [redacted]. In the concomitant IST optimized cohort, the LS mean change from baseline to week 26 in the Neuro-QoL Fatigue score was [redacted] in the ravulizumab group and [redacted] in the placebo group during the RCP. The LS mean treatment difference was [redacted]. In the refractory concomitant IST optimized cohort, the LS mean change from baseline to week 26 in the Neuro-QoL Fatigue score was [redacted] in the ravulizumab group and [redacted] in the placebo group during the RCP. The LS mean treatment difference was [redacted]. The results in the 2 cohorts aligned with those in the primary analysis population.

Incidence of Clinical Deterioration and MG Crisis

During the RCP, in the concomitant IST optimized cohort, [redacted] in the ravulizumab group and [redacted] in the placebo group reported clinical deterioration. In the refractory concomitant IST optimized cohort, [redacted] in the ravulizumab group and [redacted] in the placebo group reported clinical deterioration. [redacted] MG crisis was reported by [redacted]. [redacted] reported MG crisis.

Harms Results

Generally, the results for harms in the 2 cohorts were similar to the full population in the CHAMPION-MG trial.

The percentage of patients with any AEs was [redacted] of patients treated with placebo and [redacted] of patients treated with ravulizumab in the concomitant IST optimized cohort and [redacted] of patients treated with placebo and [redacted] of patients treated with ravulizumab in the concomitant IST optimized refractory cohort. Most commonly reported AEs in these 2 cohorts included [redacted] (concomitant IST optimized cohort = [redacted] in the ravulizumab group versus [redacted] in the placebo group; refractory concomitant IST optimized cohort = [redacted] in the ravulizumab group versus [redacted] in the placebo group) and [redacted] (concomitant IST optimized cohort = [redacted] in the ravulizumab group versus [redacted] in the placebo group; refractory concomitant IST optimized cohort = [redacted] in the ravulizumab group versus [redacted] in the placebo group). [redacted].

In the concomitant IST optimized cohort, the percentage of patients with serious AEs was [redacted] in the ravulizumab group ([redacted]) compared to the placebo group ([redacted]). In the refractory concomitant IST optimized cohort, [redacted] of patients treated with ravulizumab and [redacted] of patients in the placebo group experienced at least 1 serious AE. [redacted].

[redacted], and no death was reported for the placebo group. Meningococcal infection was considered a notable harm for treatment with ravulizumab. No events of meningococcal infection were reported during the RCP in the entire study population.

Critical Appraisal

This is a resubmission of the initial ravulizumab review. In the previous review of ravulizumab in 2023, CDEC issued a negative reimbursement recommendation based on the evidence submitted to CADTH. The current review focuses on 2 post hoc cohorts that were identified from the FAS in the CHAMPION-MG trial: the concomitant IST optimized cohort and the refractory concomitant IST optimized cohort. The criteria and definitions used for patient selection for these 2 cohorts were considered reasonable and acceptable in clinical practice, according to the clinical expert consulted for this review. Based on the patient

characteristics at baseline (which were similar to those reported in the full population) and their previous IST history, the selected cohorts of patients represented a heavily pretreated population of those who, despite lengthy duration of IST, continued to experience significant gMG symptoms. Theoretically, post hoc analyses that are not prespecified in a trial's analysis plan can be at risk of bias due to selective reporting; however, the sponsor provided clear justification for the selected subpopulations using criteria informed by the other gMG trials to provide directly relevant information related to a previous negative reimbursement recommendation. Additionally, the same prespecified analysis methods of the CHAMPION-MG trial were used to analyze the subgroup data, and the results for all relevant end points were presented. As a result, any concern for selective reporting is minimized. In these 2 subgroups, patients' baseline demographic and disease characteristics were generally well balanced between treatment groups and were similar to the FAS population. Also similar to the FAS, minor imbalances were observed for MG type at initial diagnosis (more patients in the placebo group first presented with ocular MG, while more patients in the ravulizumab group first presented with gMG) and MGFA clinical classification. The imbalances in the FAS could be due to the small sample size, which would have been exacerbated in the smaller subgroups. The clinical expert consulted by the review team noted that these may not have a significant impact on results interpretation. Tests for subgroup differences between the subgroup populations and the rest of the FAS were performed for MG-ADL score and QMG score; however, these analyses were post hoc and the CHAMPION-MG trial was not powered to find a difference between the groups. Otherwise, results from these post hoc subgroups can be interpreted for consistency with the main analyses of the CHAMPION-MG trial and share the same limitations of those analyses. In addition, it should be considered that the small sample size in these 2 subgroups [redacted] could have resulted in insufficient power to detect true between-group differences, and multiplicity was not controlled using hierarchical testing; therefore, there was an increasing risk of type I error (i.e., falsely rejecting the null hypothesis) for the investigated outcomes that achieved statistical significance at a conventional alpha of 0.05.

The reimbursement request also includes patients who have had an adequate trial of AChEIs and no ISTs; these patients are not included in the 2 post hoc cohorts but were studied in the FAS in the CHAMPION-MG trial. A similar proportion of patients who received AChEIs but did not have experience with ISTs were enrolled in the CHAMPION-MG and ADAPT trials (i.e., approximately 10% of the overall trial populations). The clinician group (NMD4C) and the clinical expert consulted for this review agreed that, while the place in therapy for ravulizumab would also include patients who had received AChEIs but not ISTs, it would be reasonable for patients with gMG to try other treatments before initiating ravulizumab, which requires periodic IV infusions over an extended period, is likely to be expensive, may not be available in smaller cities or nonspecialized centres, and requires extensive expertise.

The patient selection for these 2 subgroups was based on the inclusion criteria from other RCTs: ADAPT and REGAIN. According to the clinical expert consulted for this review, the definitions used to identify patients are reasonable and adequately reflect the patients who experience unmet needs in the treatment of gMG in clinical settings in Canada (i.e., patients with refractory gMG as well as those whose disease responded

inadequately to prior gMG treatment). Furthermore, based on the duration of prior ISTs and concomitant ISTs used in the 2 subgroups before enrolment into the CHAMPION-MG trial, the clinical expert consulted for this review considered patients in these subgroups to have entered the CHAMPION-MG trial on optimized ISTs.

Because concomitant conventional therapy was required to remain stable during the randomized control period, except in the case of rescue therapy, ravulizumab was not compared to any individual or combination conventional therapy as it would typically be used in clinical practice (i.e., altering doses or adding additional medications to suit patients' current symptoms or other needs). Similar protocol requirements for concomitant ISTs are common across trials in patients with gMG to ensure consistency and to prevent confounding of trial results; notably in the ADAPT (efgartigimod alfa versus placebo) and REGAIN (eculizumab versus placebo) trials, a change in the type or dose of concomitant conventional care was not allowed unless deemed medically necessary.

The RCP of the CHAMPION-MG trial was 26 weeks. The longer-term treatment effects of ravulizumab can only be assessed in the OLE period of this study. Moreover, the CHAMPION-MG trial did not provide evidence for the comparisons between ravulizumab and other advanced treatments for gMG, such as efgartigimod alfa, IVIg, rituximab, and eculizumab.

Long-Term Extension Studies

Description of Studies

One long-term extension study is summarized here to provide evidence for the long-term efficacy and safety of ravulizumab in patients with gMG. In the current resubmission, OLE data from the pivotal study up to 3.5 years is available. At the end of the 26-week RCP, all patients were eligible to enter the OLE and receive open-label ravulizumab. Following the 26-week RCP, patients in the placebo group received a blinded loading dose of ravulizumab and patients in the ravulizumab group received a blinded ravulizumab dose of 900 mg. Starting at week 28, all patients began open-label ravulizumab maintenance doses every 8 weeks.

Efficacy Results

In the ravulizumab-ravulizumab group in the OLE set, the LS mean change from RCP baseline for the MG-ADL total score was −4.0 (95% CI, −5.3 to −2.8) at week 164 during the OLE period. In the placebo-ravulizumab group the LS mean change from RCP baseline was −3.6 (95% CI, −4.8 to −2.3) at week 164. In the ravulizumab-ravulizumab concomitant IST optimized cohort, LS mean change from the OLE baseline in the MG-ADL total score was [redacted]. In the placebo-ravulizumab concomitant IST optimized cohort, LS mean change from the OLE baseline was [redacted]. In the ravulizumab-ravulizumab concomitant IST optimized refractory cohort, LS mean change from the OLE baseline in the MG-ADL total score was [redacted]. In the placebo-ravulizumab concomitant IST optimized refractory cohort, LS mean change in the MG-ADL total score from the OLE baseline was [redacted]. In the ravulizumab-ravulizumab and placebo-ravulizumab

groups of the OLE set, the LS mean change from RCP baseline in QMG total score was [redacted]. In the ravulizumab-ravulizumab and placebo-ravulizumab groups of the concomitant IST optimized cohort, the LS mean change from the OLE baseline in QMG total score was [redacted].

In the ravulizumab-ravulizumab and placebo-ravulizumab groups of the concomitant IST optimized refractory cohort, the LS mean change from the OLE baseline in QMG total score was [redacted]. In the OLE set, based on a 5-point or greater improvement in QMG total score from the RCP baseline, the proportion of clinical responders in the ravulizumab-ravulizumab group and placebo-ravulizumab group was [redacted].

In the ravulizumab-ravulizumab and placebo-ravulizumab groups of the concomitant IST optimized cohort, the proportion of patients with a 5-point or greater improvement in QMG total score from the RCP baseline was [redacted].

In the ravulizumab-ravulizumab and placebo-ravulizumab groups of the concomitant IST optimized refractory cohort, the proportion of patients with a 5-point or greater improvement in QMG total score from the RCP baseline was [redacted].

In the ravulizumab-ravulizumab and placebo-ravulizumab groups in the OLE set, the LS mean change from RCP baseline in MG-QoL15r total score was [redacted].

In the ravulizumab-ravulizumab and placebo-ravulizumab groups in the OLE set, the LS mean change from RCP baseline in the Neuro-QoL Fatigue score was [redacted].

In the OLE set, based on a 3-point or greater improvement in MG-ADL total score from RCP baseline, the proportion of clinical responders in the ravulizumab-ravulizumab and placebo-ravulizumab groups was [redacted].

Harms Results

During ravulizumab treatment, 96.4% of patients experienced at least 1 AE. The most commonly reported AEs (≥ 10% of total patients) in the ravulizumab-treated set were COVID-19 (36.1%), headache (23.1%), diarrhea (17.2%), arthralgia (13.6%), back pain (13%), nausea (13%), urinary tract infection (12.4%), nasopharyngitis (11.8%), fatigue (10.7%), and dizziness (10.1%). The total number of patients with ravulizumab infusion interruption due to an AE was 8 (4.7%) and 74 (43.8%) patients reported potential infusion reactions during ravulizumab treatment. Serious AEs reported by 1 or more patients included

COVID-19 (6 patients), MG (5 patients), COVID-19 pneumonia (4 patients), cellulitis and pneumonia (3 patients each), and erysipelas, urinary tract infection, spinal compression fracture, intervertebral disc protrusion, transient ischemic attack, cardiac failure congestive, pyrexia, dyspnea, dysphagia, dehydration, and nephrolithiasis (2 patients each).

In the ravulizumab-treated set, there were 8 deaths throughout the entirety of the study period: 2 occurred during RCP (COVID-19 pneumonia and cerebral hemorrhage), 6 occurred during the OLE period due to COVID-19 (3 patients), toxicity due to various drugs (1 patient), dehydration (1 patient), and an unknown reason (1 patient).

[redacted] had AEs that were unrelated to the study drug and lead to discontinuation. There were no meningococcal infections reported during the study.

Critical Appraisal

The lack of control group precludes causal statements about benefit and harm compared with any comparator. The open-label nature of the study may increase the risk of bias in determining the magnitude of the safety outcomes and efficacy end points that include more subjective assessments, because the lack of blinding may affect patients' expectations of treatment. The direction and magnitude of these potential bias remain unclear. Patients in the OLE were those who did not drop out of the placebo-controlled study (92%), which puts the results at some risk of selection bias, likely to be favouring ravulizumab. Of the patients who started the placebo-controlled phase, 123 completed the OLE. There is therefore a risk of bias due to missing outcome data in both the placebo-ravulizumab and ravulizumab-ravulizumab arms, and the impact on direction of treatment effect over time is not clear. The limitations of the post hoc analyses of the subgroups mirror those discussed in the Systematic Review section; however, these concerns are minimized as the findings for these groups were generally consistent with the overall population.

Indirect Comparisons

Description of Studies

One sponsor-submitted NMA compared the efficacy and harms of ravulizumab to currently advanced treatments (i.e., efgartigimod alfa, eculizumab, IVIg, and rituximab) for the treatment of adults with AChR antibody-positive gMG in the concomitant IST optimized cohort as well as the refractory concomitant IST optimized cohort.[30] In total, 7 RCTs were included in the ITC. The sponsor also submitted a MAIC comparing ravulizumab to efgartigimod alfa at various time points, although for the overall trial populations rather than for specific subgroups.[31]

Efficacy Results

The comparative evidence of ravulizumab to other advanced treatments for gMG in the concomitant IST optimized cohort and refractory concomitant IST optimized cohort was available through sponsor-submitted NMAs. Based on the results of the NMAs, the evidence is insufficient to conclude whether ravulizumab differs from efgartigimod alfa, rituximab, or IVIg in terms of change from baseline in MG-ADL total score or QMG total score in the concomitant IST optimized cohort, or whether ravulizumab differs from

eculizumab in terms of change in MG-ADL total score or QMG total score in the refractory concomitant IST optimized cohort.

Evidence from the MAIC is insufficient to conclude whether ravulizumab differs from efgartigimod alfa in improvement in MG-ADL total score in patients with gMG who received a previous stable dose of IST.

Harms Results

The evidence from the NMA was not sufficient to conclude whether ravulizumab differs from the other advanced treatments in the risk of discontinuation of the study drug due to AEs in the overall patient population with gMG.

Critical Appraisal

One of the major concerns for NMAs is that the included trials could be highly heterogeneous in terms of study design and patient characteristics at baseline. Seven RCTs were included in the NMA: 6 for the analyses in the concomitant IST optimized cohort and 2 for the analyses in refractory concomitant IST optimized cohort. Heterogeneities were identified in the analysis populations, which included study design (i.e., phase of study, study time points, outcome measures in different ways) and patient characteristics at baseline (i.e., age, gender, or baseline MG-ADL scores).

These differences would undermine the validity of the NMA, which relies on the transitivity assumption being upheld (i.e., that the trials are similar on all important effect modifiers). The limited number of included studies did not allow for meta-regression or other techniques to adjust for differences in effect modifiers across the studies within the NMA. The rarity of the population of interest limits the size and number of the clinical studies completed with potential comparators and adds to the practical challenges of ITCs.

Including post hoc subgroups in the analyses may raise concerns as these analyses are not prespecified and can be at risk of bias due to selective reporting (e.g., there is a risk that the presented results are selected from multiple analyses of the data based on their direction, magnitude, or statistical significance). However, the sponsor provided clear justification for the selected subpopulations using criteria informed by other MG trials. Additionally, various sensitivity analyses were conducted to examine the robustness of the results from the base-case analyses, and the results of the sensitivity analyses were consistent with the base-case analyses. As a result, any concern for selective reporting is minimized.

In the NMA, given the lack of closed loops in the networks, consistency in the ITC analyses could not be tested. All comparisons are therefore informed only by indirect evidence, which increases the level of uncertainty. Efficacy data were sparse in this NMA for the comparison of ravulizumab with other advanced treatments. Overall, the 95% credible intervals for the point estimates were wide for the efficacy and harm outcomes and spanned the null when compared with other regimens; therefore, confidence in the effect estimates for the study drugs' efficiency was limited due to imprecision indicated by the wide credible intervals for these outcomes and precludes any conclusions as to which treatment may be favoured.

In this NMA, 2 efficacy outcomes were analyzed (MG-ADL score and QMG score). Therefore, the relative treatment effect of ravulizumab versus relevant comparators on other important clinical outcomes, such as

patients' survival or HRQoL, remains unknown. Harms were only assessed in a full population instead of the IST optimized cohorts, which are the focus of this current review.

In the MAIC analysis, various patient characteristics at baseline were considered for inclusion in the adjusted analyses, including age, sex, MGFA class, disease duration, MG-ADL score, steroid use at study entry, and NSIST use at study entry. It was not clear whether other potential effect modifiers were missing; therefore, there remains a risk that the results are biased due to residual confounding. In this analysis, the effect sample size in the CHAMPION-MG trial after matching was substantially reduced by [redacted] for patients treated with ravulizumab, and [redacted] for those treated with placebo, suggesting that the results are heavily influenced by a subset of the sample in the trial who may not be representative of the full sample, nor generalizable to the original population represented by the CHAMPION-MG trial. In general, the 95% CIs for the point estimates often (except for at 4 weeks) crossed the null, and precluded definitive conclusions as to which treatment may be favoured. In this MAIC analysis, change in MG-ADL score was the only assessed outcome; therefore, other relevant outcomes were not assessed, such as HRQoL, symptom relief, or safety.

Economic Evidence

Cost and Cost-Effectiveness

Table 3: Summary of Economic Evaluation

Component	Description
Type of economic evaluation	Cost-utility analysis Markov model
Target population	Adults with AChR antibody-positive gMG whose symptoms persist despite adequate treatment with AChEIs, CSs, and/or NSISTs
Treatment	Ravulizumab plus usual care
Dose regimen	A single loading dose (2,400 mg, 2,700 mg and 3,000 mg for body weights of ≥ 40 kg to < 60, ≥ 60 to < 100, and ≥ 100 kg, respectively) followed by maintenance dosing (3,000 mg, 3,300 mg, and 3,600 mg for body weights of ≥ 40 kg to < 60, ≥ 60 to < 100, and ≥ 100 kg, respectively)
Submitted price	Ravulizumab, 300 mg vial (30 mL vial, 10 mg/mL) or (3 mL vial, 100 mg/mL): $7,282.15 Ravulizumab, 1,100 mg vial (11 mL vial, 100 mg/mL): $26,701.20
Submitted treatment cost	• ≥ 40 kg to < 60 kg: $495,186 in year 1 and $473,340 in subsequent years • ≥ 60 kg to < 100 kg: $546,161 in year 1 and $520,674 in subsequent years • ≥ 100 kg: $597,136 in year 1 and $568,008 in subsequent years
Comparators	• Efgartigimod alfa plus usual care • Rituximab plus usual care • Blood products (i.e., IVIg) plus usual care • Usual care alone — comprised of a basket of a cholinesterase inhibitor (e.g., pyridostigmine) and an IST (e.g., azathioprine, mycophenolate mofetil, cyclosporine, tacrolimus, methotrexate, cyclophosphamide, prednisone, methylprednisolone)

Component	Description
Perspective	Canadian publicly funded health care payer
Outcomes	QALYs, LYs
Time horizon	Lifetime (44 years)
Key data source	The CHAMPION-MG trial, a multicentre, double-blind, randomized, placebo-controlled trial (full analysis set and concomitant IST optimized cohort) and a sponsor-conducted NMA that assessed the relative efficacy of ravulizumab vs. usual care, efgartigimod alfa, IVIg, and rituximab
Key limitations	• The comparative efficacy and safety of ravulizumab relative to active treatments (i.e., efgartigimod alfa, rituximab, and IVIg) is uncertain due to the limitations of the sponsor-conducted NMA and MAIC. The clinical review noted that there is insufficient evidence to conclude whether ravulizumab differs from efgartigimod alfa, IVIg, or rituximab in terms of change in baseline MG-ADL total score and QMG total score. The sponsor's model did not predict any survival advantage for patients receiving ravulizumab compared with other active treatments and usual care, and the incremental QALYs were entirely driven by patients receiving ravulizumab achieving lower MG-ADL scores vs. those receiving comparators. As such, the incremental benefit predicted by the sponsor's model for ravulizumab compared with active treatments is highly uncertain. • The model structure, based on the MG-ADL score change categories, does not reflect the natural history of AChR antibody-positive gMG and does not represent homogenous health states. This modelling approach prevented CDA-AMC from fully validating the sponsor's model. As such, it is uncertain whether health benefits and costs have been adequately captured. • The sponsor assumed a deteriorating disease course (modelled by increasing a patient's MG-ADL score by 0.5 points annually) for all patients receiving usual care, which was not supported by the published literature or clinical expert feedback. This assumption directly impacted clinical event rates and biased the results in favour of ravulizumab.
CDA-AMC reanalysis results	• In the CDA-AMC reanalysis, CDA-AMC removed the assumption that all patients receiving usual care will experience health deterioration by assuming no annual increase in MG-ADL score. CDA-AMC was not able to address several key limitations, including uncertainty in the comparative efficacy of ravulizumab and active treatment comparators; structural limitations with the sponsor's model; and inappropriate assumptions about disease progression (i.e., the model was not sufficiently flexible to allow for changes that accurately reflected a fluctuating disease progression). • In the CDA-AMC base case, compared with rituximab plus usual care, ravulizumab plus usual care was associated with an ICER of $2,996,852 per QALY gained (incremental QALYs = 0.67; incremental costs = $2,020,771). • A price reduction of at least 97% (from $7,282.15 to $218.46 per 300 mg vial) would be needed for ravulizumab to be cost-effective at a WTP threshold of $50,000 per QALY gained.

AChEI = acetylcholinesterase inhibitor; AChR = anti–acetylcholine receptor; CDA-AMC = Canada's Drug Agency; CS = corticosteroid; gMG = generalized myasthenia gravis; ICER = incremental cost-effectiveness ratio; IST = immunosuppressive therapy; IVIg = IV immunoglobin; LY = life-year; MAIC = matching-adjusted indirect comparison; MG-ADL = Myasthenia Gravis Activities of Daily Living; NMA = network meta-analysis; NSIST = nonsteroidal immunosuppressant; QALY = quality-adjusted life-year; QMG = Quantitative Myasthenia Gravis; vs. = versus; WTP = willingness to pay.

Budget Impact

CDA-AMC identified several key limitations with the sponsor's analysis. The modelled distribution of patients across current treatments did not represent clinical practice and the market share of ravulizumab was uncertain. The sponsor's analyses were not conducted from a drug plan payer perspective because blood products and administration costs were included, which are not covered by drug plan programs. The public coverage rate was also uncertain. Finally, ravulizumab may be used in a broader population than modelled.

CDA-AMC revised the sponsor's base case by adopting a public coverage rate of 100% and removing the blood products (IVIg) and vaccination administration costs. CDA-AMC reanalyses suggest that the overall budget impact to the public drug plans of introducing ravulizumab for the treatment of symptomatic AChR antibody-positive gMG is $138,415,412 (year 1 = $40,405,866; year 2 = $46,573,094; year 3 = $51,436,451). The estimated budget impact is sensitive to assumptions regarding eligible population and market share. The budget impact increased to $1,071,326,718 over 3 years when the eligible population was not restricted by MGFA class and MG-ADL score.

CDEC Information

Members of the Committee

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

Meeting date: October 23, 2024

Regrets: Two expert committee members did not attend.

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

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