



CADTH 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: Do not reimburse



Summary

What Is the CADTH Reimbursement Recommendation for Ultomiris?

CADTH recommends that Ultomiris should not be reimbursed by public drug plans for the treatment of adult patients with anti-acetylcholine receptor (AChR) antibody-positive generalized myasthenia gravis (gMG).

Why Did CADTH Make This Recommendation?

- Although evidence from a clinical trial (CHAMPION) suggested that Ultomiris contributed to improvement in activities of daily living and gMG disease severity after 26 weeks, it is uncertain if immunosuppressive therapy (IST) was optimized at the time of study enrolment. Patients in both Ultomiris and placebo groups of the CHAMPION trial received stable doses of IST; however, it was unclear if IST was optimized in both groups. The eligibility criteria for duration of IST treatment and duration of stable IST dosing in the CHAMPION trial were below the estimated range of time to maximal response according to the clinical experts consulted by CADTH. Although some evidence (mean time frame since MG diagnosis, mean corticosteroid treatment durations) was available, without dose information, it is unclear if corticosteroid was optimized for patients at the time of study enrolment.
- Feedback from patient and clinician groups identified an unmet need for patients with gMG who have symptoms but are not considered refractory to IST. Although some evidence from the CHAMPION trial was presented for [REDACTED]
[REDACTED]
[REDACTED].
There is an unmet need for effective therapy for patients with refractory gMG, but the CHAMPION trial did not require patients to be refractory. Therefore, it is unknown how many patients in the CHAMPION trial were refractory and if the results observed in the trial would be the same in these patients. As a result, the ability of Ultomiris to fill the unmet need for patients who are refractory to IST is limited by the CHAMPION trial design, which used Ultomiris earlier in the treatment paradigm for gMG and did not require participants to be refractory to IST.
- The CHAMPION trial did not provide evidence on the efficacy or harms of Ultomiris compared with other therapies used in clinical practice, such as rituximab, IV immunoglobulin, and plasma exchange. Therefore, the potential therapeutic benefit is unknown compared to what is used in clinical practice.



Summary

- Other forms of evidence (indirect treatment comparisons and observational study) [REDACTED].

Additional Information

What Is Generalized Myasthenia Gravis?

MG is a condition that causes muscle weakness. In some patients, symptoms remain exclusively to the eyes (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.

Unmet Needs in Generalized Myasthenia Gravis

Symptom control can be achieved with standard treatment for most patients with gMG; however, for some patients, symptom control cannot be achieved with any standard treatment. For these patients, fewer 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 \$569,140 and \$685,887 in year 1 and between \$474,284 and \$569,140 in subsequent years.

Recommendation

The CADTH Canadian Drug Expert Committee (CDEC) recommends that ravulizumab not be reimbursed for the treatment of adult patients with anti-acetylcholine receptor (AChR) antibody–positive generalized myasthenia gravis (gMG).

Rationale for the Recommendation

Evidence from 1 phase III, multicentre, double-blind, randomized, placebo-controlled trial (CHAMPION) suggested that administration of ravulizumab in adult patients with anti-AChR antibody–positive MG contributed to statistically significant and potentially clinically meaningful improvement compared with placebo in activities of daily living and gMG disease severity after 26 weeks of treatment. Patients in both groups of the CHAMPION trial received stable doses of immunosuppressive therapy (IST); however, it was uncertain if IST was optimized in both groups. The CHAMPION trial also did not provide evidence on the efficacy or harms of ravulizumab compared with relevant comparators (e.g., rituximab, IV immunoglobulin [IVIg], plasma exchange). Treatment adjustments were discouraged in the CHAMPION trial, [REDACTED], and, without dose information, it is unclear if this was indicative of optimized dosing. There is an unmet need for effective therapy for patients with refractory gMG; however, the CHAMPION trial did not require participants to be refractory, so the proportion of the study population with refractory gMG is unknown. An unmet need may also exist in patients who remain symptomatic and are not considered refractory to IST; however, an evidence gap remains with respect to how ravulizumab compares with optimized IST regarding efficacy, effect durability, or harms in this patient population. [REDACTED]

Patients identified a need for new treatments that can decrease the intensity of gMG exacerbations, help maintain their independence, and prevent hospitalization as well as a desire for treatments with minimal side effects and convenient administration (e.g., once-daily oral administration, easy to swallow, fast onset, long duration of action). Ravulizumab may offer more convenience in terms of longer period between infusions in a subpopulation (e.g., potentially compared to some IVIg regimens); however, the desire for an oral treatment that is easy to swallow and other identified patient needs were not met by ravulizumab. The impact of ravulizumab on hospitalization is unclear due to the exploratory nature of the outcome assessed.

Discussion Points

- The sponsor requested a reconsideration of the initial draft recommendation to not reimburse ravulizumab for the treatment of adult patients with anti-AChR antibody–positive gMG. CDEC discussed each of the issues identified by the sponsor in their request for reconsideration.

- CDEC discussed the current treatment paradigm and standard of care and noted that gMG is initially treated symptomatically with acetylcholinesterase inhibitors (AChEIs) followed by corticosteroids and IST if AChEIs provide insufficient symptom relief. According to clinical experts, maximal responses to IST are typically delayed by 2 to 6 months, after which slow tapering of corticosteroids begins (optimized IST). CDEC noted that while the CHAMPION trial allowed concomitant medications, such as AChEIs, IST agents (corticosteroids, azathioprine, mycophenolate mofetil, methotrexate, tacrolimus, cyclosporine, cyclophosphamide), and rescue therapy (e.g., high-dose corticosteroid, IVIg, plasma exchange or plasmapheresis), patients who entered the study receiving corticosteroids or IST were mandated by protocol to maintain the dose and schedule. CDEC acknowledged that some exceptions to changes to dose and schedules were permitted (e.g., change in the dosing regimen due to known toxicity or side effects associated with IST drug).
- During the reconsideration meeting, CDEC noted that in the CHAMPION trial, [REDACTED]. Without dose information, it is unclear if this indicated patients were not receiving optimized dosing before study entry or it was reflective of standard of care.
- During the reconsideration meeting, CDEC also discussed the feedback from the sponsor, clinician groups, and clinical experts regarding stabilized dosing at study entry. CDEC noted that the eligibility criteria for duration of IST treatment and duration of stable IST dosing in the CHAMPION trial were below the estimated range of time to maximal response according to the clinical experts consulted by CADTH. CDEC noted the mean time frame since MG diagnosis and mean corticosteroid treatment durations. However, without dose information, it remains unclear whether corticosteroid treatment was optimized for patients at the time of study enrolment. CDEC also highlighted that within the treatment history recorded for the CHAMPION trial (2 years before screening), 5% of patients did not use any IST, almost one-quarter of patients did not receive corticosteroids, almost one-third of patients received only 1 IST, while nearly two-thirds received 2 or more ISTs. At the first dose of study drug, 10% of patients were not using any IST, almost one-third of patients were not receiving corticosteroids, just over two-fifths of patients were receiving only 1 IST, while almost half were receiving 2 ISTs.
- CDEC discussed the rarity of this condition and noted that, despite its low incidence, treatment options are available for patients (e.g., azathioprine, mycophenolate mofetil, cyclophosphamide, cyclosporine, tacrolimus, methotrexate, prednisone). CDEC acknowledged that not all treatment options may be available to every patient in every jurisdiction. However, CDEC noted that currently available standard treatments are generally effective in most patients according to the clinical experts.
- CDEC deliberated on the approved Health Canada indication which encompasses a broad population, including both IST-naïve patients and patients who had received ISTs as well as patients along a continuum of gMG severity. CDEC acknowledged that despite the available treatment options for patients, there is an unmet need for effective therapy for patients with refractory gMG (e.g., patients

whose symptoms persist despite treatment with adequate corticosteroid doses, other ISTs, and/or chronic IVIg, plasma exchange, or plasmapheresis, or whom the doses or frequencies of these therapies cannot be reduced). CDEC noted that the inclusion criteria for the CHAMPION trial did not require participants to be refractory, and the proportion of the study population with refractory gMG was unknown. Therefore, the results of the CHAMPION trial cannot be directly generalized to patients with refractory gMG and the magnitude of clinical benefit of ravulizumab in this population is unknown.

- During the reconsideration meeting, CDEC discussed that the ability of ravulizumab to fill the same therapeutic space as eculizumab in patients who are refractory to IST was limited by the CHAMPION trial design, which used ravulizumab earlier in the treatment paradigm for gMG and did not require participants to be refractory to IST. Therefore, CDEC concluded that the efficacy of ravulizumab to fill the unmet need in patients who are refractory is unknown.
- During the reconsideration meeting, the ability of ravulizumab to fulfill an unmet need in a population who remain symptomatic but are not necessarily considered refractory was discussed. [REDACTED]
[REDACTED]
[REDACTED]. Therefore, there remains an evidence gap with respect to how ravulizumab compares to optimized IST for efficacy, effect durability, or harms in this patient population.
- CDEC discussed patient needs and, in particular, their desire for convenient administration (e.g., once-daily oral administration, easy to swallow, fast onset, long duration of action). CDEC noted that although ravulizumab is administered less frequently than eculizumab (every 8 weeks compared to every 2 weeks), this potential advantage in dosing of ravulizumab is difficult to appreciate because eculizumab is not currently listed for reimbursement by jurisdictions for adult patients with anti-AChR antibody-positive gMG. Moreover, ravulizumab is administered intravenously and not orally. However, CDEC acknowledged that ravulizumab has a longer period between infusions in a subset of patients compared with some IVIg regimens.
- CDEC discussed that patients would value improvements in health-related quality of life (HRQoL). CDEC noted that change from baseline in revised 15-item Myasthenia Gravis Quality of Life (MG-QoL15r) score at week 26 was not statistically significant; change from baseline in Neurological Quality of Life (Neuro-QoL) Fatigue score at week 26 was tested after a prior nonsignificant result in the statistical hierarchy, leading to an increased risk of type I error. EQ-5D score was an exploratory outcome and lacked formal statistical testing.

Background

MG is an autoimmune disease in which antibodies against AChRs or functionally associated molecules in the neuromuscular junction disrupt nerve impulse conduction, resulting in localized or generalized skeletal muscle weakness. In a minority of patients, symptoms remain restricted exclusively to the eyes (ocular MG), whereas most patients either are diagnosed with or progress within a few years to gMG, which affects

the bulbar 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. Together, these symptoms negatively impact HRQoL. The disease has a fluctuating natural history: MG exacerbation (an increase in symptoms in patients who were previously asymptomatic or minimally symptomatic) and myasthenic crisis (muscle weakness causing life-threatening difficulties with breathing and swallowing and requiring ventilator support) can occur gradually or without warning. In Canada, the incidence of MG is approximately 23 cases per 1 million population annually, and its prevalence is approximately 263 to 320 cases per 1 million population. According to the clinical experts consulted by CADTH for this review, the prevalence worldwide, based on an average of epidemiological studies, may be slightly lower (approximately 100 to 200 cases per 1 million population).

According to the clinical experts consulted by CADTH for this review, gMG is initially treated symptomatically with AChEIs (usually pyridostigmine). If symptom relief is insufficient, IST with corticosteroids is administered. Maximal responses typically occur 2 to 6 months later, after which slow tapering of corticosteroids begins. In patients who do not respond to corticosteroids, who have significant comorbidities so that long-term corticosteroid treatment is contraindicated, or for whom doses of corticosteroids cannot be tapered, treatment with a steroid-sparing immunosuppressant and/or immunomodulatory agents, including rituximab, may be initiated. However, access to steroid-sparing ISTs and rituximab varies by jurisdiction. Patients with severe gMG are often started on all 3 of pyridostigmine, corticosteroids, and a steroid-sparing drug simultaneously. In patients with moderate to severe gMG, IVIg, plasma exchange, or plasmapheresis may be administered, either at the time of IST initiation or to treat MG exacerbation or myasthenic crisis. Critical care, including intensive care unit admission and ventilator support, may also be required for patients experiencing myasthenic crisis. Surgery (thymectomy) may also be considered for some patients. As MG symptoms improve, doses of AChEIs, corticosteroids, and then other ISTs are reduced and the frequency of IVIg, plasma exchange, or plasmapheresis is reduced until the minimal maintenance therapy required for remission is identified; patients whose symptoms persist despite treatment with adequate doses of corticosteroids, other ISTs, and/or chronic IVIg, plasma exchange, or plasmapheresis, or cannot reduce the doses or frequencies of these therapies are considered to have refractory gMG (10% to 15% of patients).

According to the clinical experts, the goal of treatment in most patients with gMG is to reduce disease symptoms and adverse effects of MG therapy and to allow the patient to function and work normally with good HRQoL. Other goals of treatment include avoiding MG exacerbations and myasthenic crisis, minimizing hospitalizations and intensive care unit admissions, and reducing the numbers and doses of therapies required for symptom control. The clinical experts consulted by CADTH for this review stated that most patients with gMG (more than 80%) will respond well to currently available treatments. Although these treatments cannot cure the disease, excellent symptom control is achieved in most patients and prognosis is generally good in terms of muscle strength and function as well as HRQoL. However, many patients with MG who respond well to currently available treatments for their MG symptoms still suffer from treatment-related side effects, which may be severe.

Ravulizumab is a monoclonal antibody and terminal complement inhibitor that is supplied as a 10 mg/mL or 100 mg/mL concentrate and administered at a maintenance dose of 3,000 mg to 3,600 mg by IV infusion every 8 weeks. The drug underwent standard review at Health Canada and received a Notice of Compliance on January 6, 2023. The Health Canada indication is “for the treatment of adult patients with anti-acetylcholine receptor (AChR) antibody–positive generalized myasthenia gravis (gMG).” The sponsor’s reimbursement request aligns with the Health Canada indication.

Sources of Information Used by the Committee

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

- a review of 1 phase III, double-blind, placebo-controlled randomized controlled trial with an open-label extension in complement-inhibitor–naïve adult patients with gMG
- patients’ perspectives gathered by 1 patient group, Muscular Dystrophy Canada
- input from public drug plans that participate in the CADTH review process
- 2 clinical specialists with expertise diagnosing and treating patients with anti-AChR antibody–positive gMG
- input from 1 clinician group, including the Neuromuscular Disease Network for Canada
- a review of the pharmacoeconomic model and report, and indirect treatment comparison report submitted by the sponsor
- information submitted as part of the Request for Reconsideration (described subsequently)
- stakeholder feedback on the draft recommendation.

Stakeholder Perspectives

The information in this section is a summary of input provided by the patient groups who responded to CADTH’s call for patient input, clinician groups who responded to CADTH’s call for clinician input, and from clinical experts consulted by CADTH for the purpose of this review.

Patient Input

One patient group, Muscular Dystrophy Canada, provided input for this review. Information was collected from 149 individuals impacted by MG through a health care experience survey and semistructured phone or virtual interviews (92 [61.7%] women and 57 [38.3%] men from all provinces of Canada, including 9 respondents from Quebec; 29 patients with a confirmed diagnosis of anti-AChR antibody–positive gMG; age range, 23 to 75 years). Half (50%) of patients recounted difficulties with MG diagnosis, including delays, misdiagnoses, and costs incurred. The patient group input highlighted the negative effects of MG on daily activities and HRQoL, including fatigue and sleep disruptions, lack of strength and mobility, decreased independence and social participation, eyesight problems, difficulties with speech and swallowing, loss

of employment and financial hardships, and mental health burdens for family members. The input also highlighted the potential benefits and side effects of currently available treatments, including prednisone (depression, weight gain, diabetes), pyridostigmine (diarrhea, nausea, “jumpy legs”), thymectomy (painful recovery), and IVIg (inconvenience of hospital administration). Respondents indicated that currently available therapies may decrease MG exacerbations but not their overall impact on HRQoL. Only 1 respondent had experience with ravulizumab and felt it had been helpful in improving their symptoms. Respondents identified an unmet need for new treatments that can decrease the intensity of MG exacerbations, maintain independence, and prevent hospitalization. Patients also desired treatments with minimal side effects and convenient administration (e.g., once-daily oral administration, easy to swallow, fast onset, long duration of action, low cost), however, they indicated they would be willing to accept the side effects of new therapies that better control the consequences of MG.

Clinician Input

Input From Clinical Experts Consulted by CADTH

Input was provided by 2 clinical specialists with expertise in the diagnosis and management of patients with anti-AChR antibody–positive gMG. According to the clinical experts consulted by CADTH for this review, mild to moderate gMG (Myasthenia Gravis Foundation of America [MGFA] class II or IIIa) is initially treated symptomatically with AChEIs (usually pyridostigmine) and the onset of benefit occurs in hours to days. If this provides insufficient symptom relief, IST with corticosteroids (usually prednisone) is administered. Maximal responses typically occur 2 to 6 months later, after which slow tapering of corticosteroids begins. In patients who do not respond to corticosteroids, who have significant comorbidities so that long-term corticosteroid treatment is contraindicated, or for whom doses of corticosteroids cannot be tapered, treatment with a steroid-sparing immunosuppressant (e.g., azathioprine, mycophenolate mofetil, cyclophosphamide, cyclosporine, tacrolimus, methotrexate) and/or immunomodulatory agents, including rituximab, may be initiated. The clinical experts explained that the onset of benefit from steroid-sparing agents occurs in months to years (9 to 18 months for azathioprine and mycophenolate). According to the clinical experts, patients with moderate to severe gMG (MGFA class IIIb, IV, or V) are often started on all 3 of pyridostigmine, prednisone, and a steroid-sparing drug simultaneously.

The clinical experts explained that, in some patients with gMG, symptom control can only be achieved by chronic administration of IVIg every 1 to 4 weeks or cannot be achieved with any standard treatment (refractory gMG). In these patients, there are very few remaining options, including complement inhibitors. Some patients also experience side effects of currently available treatments that necessitate permanent discontinuation of the drug. The clinical experts stated that additional treatments are needed with more rapid onset of action, longer-lasting benefits, improved efficacy in patients with refractory gMG, and fewer side effects. According to the clinical experts, ravulizumab has a similar mechanism of action as eculizumab, which is rarely used and used only in patients with refractory gMG. Because of their distinct mechanism of action, ravulizumab and eculizumab may be used in combination with standard treatments. The clinical experts felt that there might also be a rationale for use of either ravulizumab or eculizumab early in the disease course in patients with more severe disease in addition to or instead of other options (e.g., AChEIs,

IST, IVIg, or plasma exchange or plasmapheresis) but acknowledged that currently there are limited data to justify this approach. The clinical experts stated that because currently available standard treatments are generally effective in most patients, it would be difficult to recommend early use of ravulizumab unless it was clearly more effective and/or pharmacoeconomically favourable compared with other options.

According to the clinical experts, candidates for ravulizumab (primarily patients with refractory gMG and potentially those with severe but nonrefractory gMG) would be identified through the judgment of an expert neurologist based on clinical evaluation following serologic testing for AChR antibodies and, potentially, following chest CT to rule out thymoma and thymic carcinoma. The clinical experts stated that although patients with thymoma were excluded from the trials of complement inhibitors, there is no reason to expect that these patients would not benefit from these drugs. Response to ravulizumab would be assessed by monitoring patient symptoms and/or signs on clinical examination (e.g., the Myasthenia Gravis Activities of Daily Living [MG-ADL] assessment and/or Quantitative Myasthenia Gravis [QMG] score every 1 to 3 months) and via reduction of other MG therapies (especially chronic IVIg). Clinically meaningful responses to ravulizumab would be reflected by improvements in disease symptoms (decreases of approximately 2 points for MG-ADL [total score range 0 to 24, with higher scores indicating greater severity of symptoms and a more significant impact on daily living] and approximately 3 points for QMG [total score range 0 to 39, with higher scores indicating greater disease severity based on impairments of body functions and structures]), as well as by reduction of other treatments (e.g., chronic IVIg, plasma exchange or plasmapheresis, and rituximab) and hospitalizations. The drug would be discontinued in patients who do not achieve clinical improvement or are unable to reduce the numbers and doses of other MG therapies, in patients who experience worsening of MG symptoms requiring additional interventions, in patients who experience serious toxicities such as meningococcal infections, or by patient preference. However, the clinical experts also noted that, in some patients, treatment with complement inhibitors, including ravulizumab, could be lifelong if this is required to achieve sustained clinical benefit. Ravulizumab would be prescribed by a neurologist with expertise in managing patients with MG and administered in a hospital setting or at an infusion clinic.

Clinician Group Input

One clinician group, the Neuromuscular Disease Network for Canada (NMD4C), provided input for this review that reflected the views of 4 neurologists with experience in the management of patients with gMG. No major contrary views from those provided by the clinical experts consulted by CADTH for this review were presented. The clinician group reiterated that standard treatments for gMG are often transiently effective, may require relatively long treatment periods for benefits to be observed, may have side effects, and may not be effective in all patients. NMD4C indicated that ravulizumab would be unlikely to cause a shift in the standard treatment paradigm for gMG and would be used as an add-on third-line therapy in patients with anti-AChR antibody-positive gMG who are not responsive to AChEIs and IST and require chronic IVIg or plasma exchange or plasmapheresis. The clinician group noted the more convenient administration of ravulizumab (every 8 weeks) compared with eculizumab (every 2 weeks).

Drug Program Input

Input was obtained from the drug programs that participate in the CADTH reimbursement review process. The following were identified as key factors that could potentially affect the implementation of a CADTH recommendation for 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
- care provision issues
- system and economic issues.

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

Clinical Evidence

Pivotal Studies and Protocol-Selected Studies

Description of Studies

The CHAMPION trial (ALXN1210-MG-306; N = 175) was a phase III, double-blind, multicentre, placebo-controlled, randomized controlled trial with an open-label (OL) extension period of up to 4 years. The primary objective of the CHAMPION trial was to evaluate the safety and efficacy of ravulizumab compared with placebo in complement inhibitor-naïve adult patients with gMG. Following screening, adult patients with anti-AChR antibody-positive gMG (MGFA class II to IV, MG-ADL total score ≥ 6 , non-thymomatous; no requirements for prior treatment experience or its outcome) were enrolled at 85 centres in 13 countries (5 sites in Canada) and randomized 1:1 to receive either a weight-based dose of ravulizumab (n = 86) or a matching placebo (n = 89) for 26 weeks. The primary outcome of the study was change from baseline in MG-ADL total score at week 26 of the randomized controlled period, while secondary outcomes included change from baseline in QMG total score at week 26, proportion of patients with improvements of 5 points or more in QMG total score at week 26, change from baseline in MG-QoL15r score at week 26, change from baseline in Neuro-QoL Fatigue score at week 26, and proportion of patients with improvements of 3 points or more in MG-ADL total score at week 26.

The eligibility criteria for duration of IST treatment on azathioprine was 180 days or more; on other steroid-sparing agents, such as mycophenolate mofetil, cyclophosphamide, cyclosporine, tacrolimus, and methotrexate, it was 90 days or more. The eligibility criteria for duration of stable IST dosing on oral corticosteroids was 28 days or more; on azathioprine was 60 days or more; and on other steroid-sparing agents, such as mycophenolate mofetil, cyclophosphamide, cyclosporine, tacrolimus, and methotrexate, it

was 30 days or more. The mean time frame since MG diagnosis was 9.9 years and the mean corticosteroid treatment duration was 816.9 days in the ravulizumab arm and 643.6 days in the placebo arm.

Patients' baseline demographic and disease characteristics were generally well-balanced across treatment arms, although there were minor imbalances by race or ethnicity, age at MG diagnosis, age at first study drug infusion, MG type at diagnosis (ocular versus generalized), time to gMG from diagnosis among patients whose first presentation was ocular MG, MGFA clinical classification, and prior corticosteroid use. The mean age at first infusion in the overall study population was 55.6 years (standard deviation = 15.2 years) and most patients were from North America (45.7%) or Europe (36.6%). Before screening, 55.7% of patients had experienced moderate to severe MG (MGFA class IIIb, IV, or V), 60.0% had experienced MG exacerbations, 24.4% had experienced MG crises, and 17.1% had required ventilator support. At study baseline, 23.4% of patients had moderate to severe MG; at first dose of study drug, 83 patients (47.4%) were receiving 2 or more ISTs, 74 patients (42.3%) were receiving 1 IST, and 18 patients (10.3%) were not receiving IST.

Efficacy Results

Key efficacy results during the randomized controlled period of the CHAMPION trial are summarized subsequently.

Activities of Daily Living

At week 26, the least square mean (LSM) change in MG-ADL total score in the placebo arm was -1.4 (95% confidence interval [CI], -2.1 to -0.7) versus -3.1 (95% CI, -3.8 to -2.3) in the ravulizumab arm. The LSM difference in MG-ADL total score between the ravulizumab and placebo arms was -1.6 (95% CI, -2.6 to -0.7; $P = 0.0009$). The adjusted percentage of patients with improvements of at least 3 points in MG-ADL total score at week 26 was 56.7% (95% CI, 44.3% to 68.3%) in the ravulizumab arm and 34.1% (95% CI, 23.8% to 46.1%) in the placebo arm (≥ 3 points improvement: odds ratio [OR] = 2.526; 95% CI, 1.330 to 4.799). The adjusted percentage of patients with improvements of at least 2 points in MG-ADL total score (a recognized response threshold that indicates clinical improvement) at week 26 was 63.9% (95% CI, 51.7% to 74.6%) in the ravulizumab arm and 53.0% (95% CI, 41.1% to 64.6%) in the placebo arm (≥ 2 points improvement: OR = 1.569; 95% CI, 0.833 to 2.955).

Disease Severity

At week 26, the LSM change in QMG total score in the placebo arm was -0.8 (95% CI, -1.7 to 0.1) versus -2.8 (95% CI, -3.7 to -1.9) in the ravulizumab arm. The LSM difference in QMG total score between the ravulizumab and placebo arms was -2.0 (95% CI, -3.2 to -0.8; $P = 0.0009$). The adjusted percentage of patients with improvements of at least 5 points in MG-ADL total score at week 26 was 30.0% (95% CI, 19.2% to 43.5%) in the ravulizumab arm and 11.3% (95% CI, 5.6% to 21.5%) in the placebo arm (≥ 5 points improvement: OR = 3.350; 95% CI 1.443 to 7.777; $P = 0.0052$). The adjusted percentage of patients with improvements of at least 3 points in QMG total score (the estimated minimal important difference) at week 26 was 44.8% (95% CI, 32.3% to 58.0%) in the ravulizumab arm and 24.2% (95% CI, 15.3% to 36.2%) in the placebo arm (≥ 3 points improvement: OR = 2.544; 95% CI, 1.283 to 5.044).

[REDACTED]

Hospital Admission

A total of [REDACTED] patients ([REDACTED]) in the placebo arm and [REDACTED] patients ([REDACTED]) in the ravulizumab arm were hospitalized. Among these, [REDACTED] patients ([REDACTED]) in the placebo arm and [REDACTED] patients ([REDACTED]) in the ravulizumab arm were hospitalized due to MG. Only [REDACTED] ([REDACTED]) in the placebo arm and [REDACTED] patients ([REDACTED]) in the ravulizumab arm required ventilator support.

Number and Dose of Existing Medications

The number and dose of existing medications was not an efficacy outcome in the CHAMPION trial. Patients were to maintain stable doses of concomitant MG medications during the randomized controlled period unless there was a compelling medical need.

Need for Rescue Therapy

In the placebo arm, 14 patients (15.7%) required rescue therapy (IVIg: 12 patients; plasma exchange or plasmapheresis and high-dose corticosteroids: 1 patient each). In the ravulizumab arm, 8 patients (9.3%) required rescue therapy (IVIg: 5 patients; plasma exchange or plasmapheresis: 2 patients; high-dose corticosteroids: 1 patient).

Health-Related Quality of Life

At week 26, the LSM change in MG-QoL15r score in the placebo arm was -1.6 (95% CI, -3.0 to -0.3) versus -3.3 (95% CI, -4.7 to -1.9) in the ravulizumab arm. The LSM difference in MG-QoL15r score between the ravulizumab and placebo arms was -1.7 (95% CI, -3.4 to 0.1; P = 0.0636).

At week 26, the LSM change in Neuro-QoL Fatigue score in the placebo arm was -4.8 (95% CI, -8.1 to -1.1) versus -7.0 (95% CI, -10.7 to -3.2) in the ravulizumab arm. The LSM difference in Neuro-QoL Fatigue score between the ravulizumab and placebo arms was -2.2 (95% CI, -6.9 to 2.6).

Harms Results

Key harms results during the randomized controlled period of the CHAMPION trial are summarized subsequently.

Most patients (90.7% of patients treated with ravulizumab and 86.5% of patients treated with placebo) experienced adverse events. The most common adverse events were headache (ravulizumab 25.8%; placebo 18.6%), diarrhea (ravulizumab 12.4%; placebo 15.1%), and nausea (ravulizumab 10.1%; placebo 10.5%). A total of 23.3% of patients treated with ravulizumab and 15.7% of patients treated with placebo experienced serious adverse events. [REDACTED]

[REDACTED]

Critical Appraisal

There were no major internal validity concerns regarding the CHAMPION trial. Minor baseline imbalances between study arms were viewed as unlikely to be prognostic or to significantly affect the study results. Study discontinuations before completing the randomized controlled period were relatively infrequent (7% in the placebo arm and 8% in the ravulizumab arm) and missing data for reasons other than discontinuation were relatively rare (1 to 5 patients in each arm, depending on outcome). During the study, concomitant MG therapy was similar in both study arms, except for rescue therapy (IVIg), which was administered more frequently in the placebo arm. Important protocol deviations occurred similarly in both arms and unlikely to impact the study results. The instruments used to evaluate the primary and secondary efficacy outcomes (MG-ADL, QMG, MG-QoL15r, Neuro-QoL Fatigue) were appropriate and their psychometric properties have been investigated in patients with MG, although no minimal important differences have been estimated for the MG-QoL15r and Neuro-QoL Fatigue scores. Overall, statistical tests were appropriate, power was adequate for the primary analysis, and multiplicity was controlled using a hierarchical testing strategy. Statistical testing for a 3-point or more improvement in MG-ADL score and change from baseline in Neuro-QoL Fatigue score at 26 weeks occurred after a prior nonsignificant result in the statistical hierarchy, so there is an increased risk of type I error. Subgroup analyses that were identified of interest in the CADTH review protocol by MGFA clinical classification and IST at baseline were not adjusted for multiplicity nor were they specifically powered to detect differences among strata. Wide confidence intervals and small numbers of patients within strata reflected imprecision in effect estimates.

According to the clinical experts consulted by CADTH for this review, the demographic and disease characteristics and prior treatment history of patients enrolled in the CHAMPION trial were reflective of the Canadian population of adult patients with anti-AChR antibody-positive gMG seen in their clinical practice. Although patients with MGFA clinical classifications I and V, patients with MG-ADL scores less than 6, and patients with thymoma were excluded, the clinical experts stated that a subset of patients with these characteristics could benefit from treatment with ravulizumab, although the results of the trial cannot be generalized to these groups. In addition, changes in concomitant MG therapies would not be generalizable to clinical practice because changes to these medications were discouraged by the study protocol. [REDACTED]

[REDACTED] However, 2 important external validity issues must be considered in interpreting the results of the CHAMPION study. First, the study enrolled patients with various prior treatment experiences and co-interventions at baseline, including patients with no prior IST. There were no specific requirements about the outcome of prior therapies received, and the proportion of the study population with refractory gMG was unknown; however, the clinical experts consulted by CADTH stated that the CHAMPION trial almost certainly would have included some patients who are refractory, although no subgroup analysis was provided for patients who were and were not refractory. [REDACTED]

[REDACTED]. According to the clinical experts consulted by CADTH for this review, earlier lines of therapy for nonrefractory MG generally have higher response rates, and these patients would be more likely to respond to any therapy compared with patients later in the treatment course (e.g., refractory gMG). Therefore, the results of the CHAMPION



trial cannot be directly generalized to any specific line of therapy, including patients with refractory gMG or patients with severe but nonrefractory gMG. Second, the study was placebo-controlled despite the fact that many of the enrolled patients would have been eligible to receive IST with corticosteroids and steroid-sparing agents, as well as potentially eculizumab. The study provided no comparative evidence regarding the efficacy of ravulizumab and currently available therapies at various stages of the treatment paradigm for MG, and its results comparing ravulizumab to placebo provide no information regarding the drug's effectiveness compared with current standard of care.

Indirect Comparisons and Comparative Observational Evidence

Description of Studies

[Redacted text]

Efficacy Results

[Redacted text]

Harms Results

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

Critical Appraisal

[Redacted text]

Other Relevant Evidence

An OL extension study of the CHAMPION trial is currently ongoing, and 60-week data were available at the time this report was prepared. Overall, 91.0% of patients in the placebo arm and 89.5% of patients in the ravulizumab arm of the randomized controlled period received OL ravulizumab in the extension study. Patients randomized to the placebo arm during the randomized controlled periods who switched to OL ravulizumab during the extension period experienced [Redacted] in MG-ADL total score, QMG total score,

MG-QoL15r score, and Neuro-QoL Fatigue score that were sustained over the course of the OL extension period. No new safety signals were identified.

Critical Appraisal

Interpretation of the results from the OL extension period are limited by the absence of a randomized comparison group, which precludes causal conclusions. Patients and study personnel were aware of the treatment received during the extension period therefore, there is risk of bias in the measurement of subjective outcomes (MG-ADL, QMG, MG-QoL15r, Neuro-QoL Fatigue, and subjective harms). Long-term efficacy data were summarized descriptively; the absence of formal statistical analysis precluded definitive conclusions. Based on the number of patients in each treatment arm included in the efficacy analysis from the OL extension period baseline to week 60, the data were immature and there is a risk of bias due to missing outcome data at longer follow-up; the magnitude and direction of bias is unknown. However, the missing data are likely because not all patients had reached the week 60 visit by the data cut-off.

Economic Evidence

Table 1: Cost and Cost-Effectiveness

Component	Description
Type of economic evaluation	Cost-utility analysis Markov model
Target population	Adults aged 18 years and older diagnosed with anti-AChR antibody-positive gMG \geq 6 months before screening, classified as MGFA class II to IV at screening, and with a MG-ADL score of \geq 6
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 \geq 40 kg to < 60, \geq 60 to < 100, and \geq 100 kg, respectively), followed by a maintenance dose starting 2 weeks after (3,000 mg, 3,300 mg, and 3,600 mg for body weights of \geq 40 kg to < 60, \geq 60 to < 100, and \geq 100 kg, respectively), then administered every 8 weeks thereafter.
Submitted price	\$7,296.67 per 30 mL vial containing 300 mg of ravulizumab
Treatment cost	<ul style="list-style-type: none"> \geq 40 kg to < 60 kg: \$569,140 in year 1 and \$474,284 in subsequent years \geq 60 kg to < 100 kg: \$627,514 in year 1 and \$521,712 in subsequent years \geq 100 kg: \$685,887 in year 1 and \$569,140 in subsequent years
Comparators	Usual care comprised of cholinesterase inhibitor (pyridostigmine) and IST (azathioprine, mycophenolate mofetil, cyclosporine, tacrolimus, methotrexate, cyclophosphamide, prednisone, methylprednisolone)
Perspective	Canadian publicly funded health care payer
Outcome	QALYs, LYs
Time horizon	Lifetime (45 years)
Key data sources	CHAMPION trial, a multicentre, double-blind, randomized, placebo-controlled trial

Component	Description
Key limitations	<ul style="list-style-type: none"> The full Health Canada indication was not modelled. Effectiveness of ravulizumab plus usual care in the pharmacoeconomic model was based on observations from the CHAMPION trial, which excluded patients with MFGA class I and V as well as patients with MG-ADL total score ≤ 5. The cost-effectiveness of ravulizumab in these patients is unknown. Rituximab and chronic IVIG or plasma exchange were not included as comparators, which was deemed inappropriate based on clinical practice guidelines and clinical expert feedback obtained by CADTH for this review. The model structure, based on the MG-ADL score change categories, did not reflect the natural history of anti-AChR antibody-positive gMG and did not represent homogenous health states. This modelling approach prevented CADTH 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 patients' MG-ADL score by 0.5 points annually) for all patients receiving usual care, which was not supported by published literature or clinical expert feedback. This assumption directly impacted clinical event rates and biased the results in favour of ravulizumab. Eculizumab is indicated for gMG and was identified as a relevant comparator to ravulizumab by clinical experts consulted for this review. The CADTH Clinical Review concluded that evidence from a sponsor-submitted MAIC comparing ravulizumab with eculizumab is highly uncertain. As such, CADTH was unable to estimate the cost-effectiveness of ravulizumab vs. eculizumab.
CADTH reanalysis results	<ul style="list-style-type: none"> In the CADTH reanalysis, CADTH removed the assumption that all patients receiving usual care will deteriorate by assuming no annual increase in MG-ADL score. CADTH was not able to address several key limitations, including the full Health Canada indication not being modelled, exclusion of relevant comparators, structural limitations with the sponsor's model, and uncertainty in clinical efficacy between ravulizumab and eculizumab. In CADTH's base case, compared with usual care alone, ravulizumab plus usual care was associated with an ICER of \$3,715,084 per QALY gained (incremental QALYs: 0.69; incremental costs: \$2,588,863). A price reduction of at least 97% (from \$7,296.67 to \$218.90 per 300 mg vial) would be needed for ravulizumab to be cost-effective at a WTP threshold of \$50,000 per QALY gained compared with usual care alone.

AChR = acetylcholine receptor; gMG = generalized myasthenia gravis; ICER = incremental cost-effectiveness ratio; IST = immunosuppressive therapy; IVIG = IV immunoglobulin; LY = life-year; MAIC = matching-adjusted indirect comparison; MGFA = Myasthenia Gravis Foundation of America; MG-ADL = Myasthenia Gravis Activities of Daily Living; QALY = quality-adjusted life-year; vs. versus; WTP = willingness to pay.

Budget Impact

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

- The modelled population was based on CHAMPION trial inclusion criteria, which was narrower than the Health Canada indication.
- Relevant comparators, such as rituximab, IVIG, and plasma exchange were excluded.
- The treatment costs of ravulizumab and eculizumab were underestimated because usual care costs were excluded.
- The percentage of patients who would require treatment was underestimated because the sponsor noted that all refractory symptomatic patients would require treatment.
- The market share of eculizumab was overestimated compared with feedback received by CADTH clinical experts.

- The prevalence of MG and the proportion of patients with public drug coverage was uncertain.
- The rates of ravulizumab uptake are uncertain.
- The market share of ravulizumab was uncertain and may have been underestimated.

In CADTH reanalyses, the reimbursed population was aligned with the Health Canada indication, usual care costs were added to ravulizumab and eculizumab treatment costs, all patients with anti-AChR antibody gMG who were symptomatic were assumed to require treatment, and the market share of eculizumab was decreased. CADTH reanalyses suggest that the overall budget impact to the public drug plans of introducing ravulizumab for the treatment of symptomatic anti-AChR antibody-positive gMG is \$2,647,080,911 over 3 years (year 1: \$436,033,428; year 2: \$878,648,052; year 3: \$1,332,399,432).

The estimated budget impact is sensitive to assumptions regarding the eligible population. The budget impact decreased to \$342,002,854 over 3 years when the eligible population was restricted by MGFA class and MG-ADL. However, the budget impact excluded relevant comparators, especially for the population of patients who are refractory to other treatments, and is highly uncertain.

Request for Reconsideration

The sponsor filed a Request for Reconsideration for the draft recommendation for the treatment of adult patients with anti-AChR antibody-positive gMG. In their request, the sponsor requested that CDEC reconsider their review of ravulizumab based on the following:

- According to the sponsor, the study design of the CHAMPION trial allowed for robust comparison of ravulizumab with relevant standard-of-care treatments in gMG.
- According to the sponsor, there are significant unmet needs in patients with gMG who are symptomatic despite treatment due to the limitations of current standard of care. The sponsor noted that ravulizumab selectively targets the underlying disease pathogenesis and has a rapid onset of action, sustained clinical benefit, and well-tolerated safety profile that fulfills the current gaps in the management of patients with gMG.
- The sponsor proposed that the reimbursement criteria for ravulizumab align with the unmet needs of patients, the studied population most represented by the pivotal CHAMPION trial, and clinician feedback to ensure access for patients who have the greatest need for ravulizumab, specifically in patients with gMG who remain symptomatic (MG-ADL \geq 6 and MGFA class II to IV) despite 2 or more prior ISTs.
- According to the sponsor, the potential budget impact of ravulizumab is overstated by CADTH.

In the meeting to discuss the sponsor's request for reconsideration, CDEC considered the following information:

- feedback from the sponsor
- information from the initial submission related to the issues identified by the sponsor



- feedback from 2 clinical experts with expertise in the diagnosis and management of patients with gMG
- feedback from the public drug plans
- feedback from 1 clinical group: NMD4C Neuromuscular Clinician Group
- feedback from 2 patient groups: Muscular Dystrophy Canada and Canadian Organization for Rare Disorders

All stakeholder feedback received in response to the draft recommendation from the clinician groups and the public drug programs is available on the CADTH website.

CDEC Information

Members of the Committee

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

Initial meeting date: March 22, 2023

Regrets: 1 expert committee member did not attend.

Conflicts of interest: None

Reconsideration meeting date: July 26, 2023

Regrets: 2 expert committee members did not attend

Conflicts of interest: None



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