CADTH

CADTH DRUG REIMBURSEMENT REVIEW

Pharmacoeconomic Report

ECULIZUMAB (SOLIRIS)

Alexion Pharma Canada Corporation

Indication: Adult patients with generalized Myasthenia Gravis

Service Line: CADTH Common Drug Review
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CADTH

About CADTH: CADTH is an independent, not-for-profit organization responsible for providing Canada's health care decision-makers with objective evidence to help make informed decisions about the optimal use of drugs, medical devices, diagnostics, and procedures in our health care system.

Funding: CADTH receives funding from Canada's federal, provincial, and territorial governments, with the exception of Quebec.

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Abbreviations

AChR	acetylcholine receptor
AE	adverse event
BIA	budget impact analysis
BMI	body-mass index
EQ-5D	Euro-Quality of Life 5-Dimensions questionnaire
gMG	generalized myasthenia gravis
ICER	incremental cost-effectiveness ratio
ICU	intensive care unit
IST	immunosuppressive therapy
IVIG	intravenous immunoglobulin
MDC	Muscular Dystrophy Canada
MG	myasthenia gravis
MG-ADL	Myasthenia Gravis Activities of Daily Living
MuSK	muscle-specific kinase
PLEX	plasma exchange
QALY	quality-adjusted life-year
SOC	standard of care
WTP	willingness-to-pay

Executive Summary

The executive summary is comprised of two tables (Table 1 and Table 2) and a conclusion.

Table 1: Submitted for Review

Item	Description
Drug product	Eculizumab (Soliris), 30 mL parenteral solution (10 mg/mL), intravenous injection
Submitted price	Eculizumab, 300 mg single-use vial for IV injection: $6,742.00
Indication	Adult patients with generalized myasthenia gravis (gMG). Eculizumab was studied in clinical trials in patients who were anti-acetylcholine receptor (AChR) antibody positive and refractory, defined as failure of treatment with two or more immunosuppressive therapies (ISTs), either in combination or as monotherapy, or failed at least one IST and required chronic plasmapheresis, plasma exchange (PLEX) or intravenous immunoglobulin (IVIG) to control symptoms. Patients continued to receive standard therapy throughout the pivotal clinical trial.
Health Canada approval status	NOC
Health Canada review pathway	Priority review
NOC date	August 20, 2018
Reimbursement request	As per indication
Sponsor	Alexion Pharmaceuticals
Submission history	Previously reviewed: Yes Paroxysmal nocturnal hemoglobinuria Indication: Treatment of patients with paroxysmal nocturnal hemoglobinuria to reduce hemolysis Recommendation date: February 18, 2010 Recommendation: Do not list [reimburse] at the submitted price Atypical hemolytic uremic syndrome Indication: Treatment of patients with atypical hemolytic uremic syndrome to reduce complement-mediated thrombotic microangiopathy Recommendation date: July 18, 2013 Recommendation: Do not list Neuromyelitis optica spectrum disorder Indication: Treatment of patients with neuromyelitis optica spectrum disorder who are aquaporin-4-antibody–positive. Recommendation date: Review currently ongoing at CADTH

AChR = acetylcholine receptor; IST = immunosuppressant therapy; IV = intravenous; IVIG = intravenous immunoglobulin; MG = myasthenia gravis; NOC = Notice of Compliance; PLEX = plasma exchange.

Table 2: Summary of Economic Evaluation

Component	Description
Type of economic evaluation	Cost-utility analysis Markov model
Target population	Adult patients with generalized myasthenia gravis who are AChR-antibody–positive with refractory MG, defined as having failed treatment with at least two immunosuppressive therapies (ISTs), either in combination or as monotherapy, or having failed at least one IST and requiring chronic plasmapheresis or plasma exchange (PLEX) or intravenous immunoglobulin (IVIG) to control symptoms.
Treatment	Eculizumab in addition to standard of care (which included pyridostigmine, azathioprine, mycophenolate mofetil, cyclosporine, tacrolimus, methotrexate, cyclophosphamide, dexamethasone, prednisone)
Comparator	Standard of care
Perspective	Canadian publicly funded health care payer
Outcomes	Quality-adjusted life-years (QALYs), life-years
Time horizon	Lifetime (52.5 years)
Key data source	REGAIN trial
Submitted results for base case	Incremental cost-effectiveness ratio (ICER) = $1,329,219 per QALY
Key limitations	• Rituximab was not included as a comparator, despite clinical expert opinion suggesting use of rituximab for the indicated population in practice. A meta-analysis of open-label trials and retrospective studies suggests approximately 50% of the indicated population would respond to rituximab therapy. • The sponsor's model did not reflect clinical expert understanding of MG. The sponsor assumed a treatment-dependent decline in MG-ADL score over time on SOC; applied a mortality rate in myasthenic crisis higher than would be expected in Canadian clinical practice; assigned a disutility weight for myasthenic crisis that would result in a health state valuation worse than death; and limited treatment-related adverse events to the first six months of therapy. • The model did not reflect the anticipated use of eculizumab. Clinical experts suggested that the MG-ADL threshold chosen to define treatment response was more restrictive than would be used in clinical practice. Additionally, the sponsor assumed ongoing use of eculizumab, while clinical experts suggested that eculizumab treatment would likely be used intermittently or for a shorter term for many patients. • The indicated population was not fully represented by the population studied in the REGAIN trial, and it is thus unknown whether the efficacy and safety of eculizumab is similar in patients who were excluded. • Not all relevant costs, such as outpatient administration and meningococcal vaccinations, were captured in the sponsor's base case. • Few parameters were varied probabilistically in the model and, of those that were, most were varied arbitrarily, assuming a range of 20% around the mean rather than informed by the source of information.
CADTH reanalysis results	• CADTH revised the sponsor's economic analysis by removing the MG-ADL score decline; reducing the mortality rate associated with myasthenic crisis; adjusting routine follow-up costs; adding administration and vaccination costs; and adding probabilistic variation to certain model parameters. In the reanalysis, the ICER was $1,505,712 per QALY compared to SOC alone. A price reduction of 91% would be required to achieve an ICER below $50,000 per QALY gained. • Many structural assumptions could not be examined within the sponsor's model, limiting CADTH's ability to examine the impact of those assumptions and to generate precise estimates.

AChR = acetylcholine receptor; ICER = incremental cost-effectiveness ratio; IST = immunosuppressant therapy; IVIG = intravenous immunoglobulin; MG = myasthenia gravis; MG-ADL = Myasthenia Gravis Activities of Daily Living; PLEX = plasma exchange; QALY= quality-adjusted life-year; SOC = standard of care.

Conclusions

CADTH made the following changes to the sponsor's economic model to account for identified limitations: removed the assumption of Myasthenia Gravis Activities of Daily Living (MG-ADL) score deterioration over time on standard of care (SOC); reduced the mortality rate from myasthenic crisis; reduced the frequency of routine clinician visits; assumed all vaccination and administration costs would be covered by the public payer; and assigned correct probabilistic distributions to the model inputs. CADTH's reanalyses resulted in the same findings as the sponsor: adding eculizumab to SOC compared to SOC alone is not cost-effective at conventionally accepted incremental cost-effectiveness ratio (ICER) thresholds. Based on CADTH reanalysis, eculizumab plus SOC compared to SOC alone is associated with an ICER of $1,505,712 per quality-adjusted life-year (QALY) gained and has a 0% probability of being cost-effective for patients with refractory AChR-antibody–positive generalized myasthenia gravis (gMG) at a willingness-to-pay (WTP) threshold of $50,000 per QALY. A price reduction of 91% would be required to achieve an ICER below a WTP threshold $50,000 per QALY.

The submitted price of eculizumab is the key driver of the cost-effectiveness estimates. Important limitations remain that CADTH was unable to address, including assumptions made about the natural history of gMG and the anticipated use of eculizumab. Together, these introduce structural and parameter uncertainties that affect the overall precision of the cost-effectiveness estimates. The majority of incremental QALYs (> 90%) occurred beyond the observation period of the clinical trial and its extension study; as extrapolations were made based on several assumptions with high levels of uncertainty, the magnitude of this QALY gain is also uncertain. These limitations affected CADTH's ability to conduct a precise health economic analysis. Despite the limitations noted above, it is very unlikely that eculizumab would be considered cost-effective without considerable price reduction.

Stakeholder Input Relevant to the Economic Review

This section is a summary of the feedback received from the patient groups that participated in the CADTH review process (specifically, information that pertains to the economic submission).

Input was received from Muscular Dystrophy Canada (MDC). MDC conducted interviews of 120 patients with gMG and 70 caregivers. Of the patients interviewed, 75% reported debilitating chronic progression, including choking, slurred speech, impaired swallowing, breathing issues, and disabling fatigue. Patients with debilitating chronic progression reported that they had at least five hospital admissions within the previous five years, with an average of two weeks' admission for swallowing issues, while 35% of patients reported at least one admission to the intensive care unit (ICU) for respiratory failure. Forty-five percent of patients reported requiring in-home support for all activities of daily living, with a high impact on financial well-being, with 75% of respondents indicating they had to leave employment. Fifteen percent reported no longer being able to care for their children, resulting in their partner or parents having to leave employment.

Patients reported current use of corticosteroids, cyclosporine, and azathioprine, with 45% reported having tried medication that was not effective. Patients reported that these medications decreased the frequency of exacerbations but did not impact their ability to work or live independently. Adverse events (AEs) reported included nausea, fatigue, and diarrhea. Corticosteroid use led to concerns about hypertension and type 2 diabetes.

Patients identified three aspects of myasthenia gravis (MG) that they want better controlled: intensity of exacerbations, maintenance of their independence, and the frequency and severity of hospital admissions. There was consensus that new options were needed for those who had not experienced positive outcomes with their current treatments.

Several of these concerns were addressed in the sponsor's model:

- Treatment efficacy was incorporated using results from the pivotal trial, including change in the MG-ADL score, improvements in which were associated with increased quality of life and reduced frequency of exacerbations and myasthenic crises.
- Chronic progression of MG was modelled by assuming a worsening of 0.5 points in MG-ADL score when not using eculizumab.
- Disutility (health loss) was applied for patients with exacerbations or myasthenic crises.
- AEs associated with treatment were included, although they were not associated with quality-of-life effects.
- A societal perspective was explored in scenario analyses to assess the impact of indirect costs associated with MG.

In addition, CADTH addressed some of these concerns as follows:

- A scenario analysis was conducted, assuming exacerbations not associated with ICU stays led to a 14-day admission to hospital. Myasthenic crises and exacerbations requiring ICU stays were not assumed to change in this scenario.

- Patients described deteriorating health as a key concern. Clinical experts consulted by CADTH disagreed with the sponsor's assumption that the health of patients with gMG would decline on SOC and remain steady on eculizumab. CADTH found insufficient support in the literature to resolve this potential conflict in perspectives and built the base case without making an assumption about decline. Re-introducing this assumption of worsening health did not affect the overall finding of 0% cost-effectiveness at a WTP of $100,000 per QALY.

Economic Review

The current review is for eculizumab (Soliris) for the treatment of adult patients who are AChR-antibody–positive and have refractory gMG, defined as having failed treatment with at least two immunosuppressive therapies (ISTs), either in combination or as monotherapy, or having failed at least one IST and requiring chronic plasmapheresis or plasma exchange (PLEX) or intravenous immunoglobulin (IVIG) to control symptoms.

Economic Evaluation

Summary of Sponsor's Economic Evaluation

Overview

The sponsor submitted an economic analysis to examine the cost-effectiveness of eculizumab plus SOC compared to SOC alone in adults with treatment-refractory AChR-antibody–positive gMG. Refractory status was defined as having previously failed treatment with at least two ISTs, or having failed at least one IST and requiring chronic plasmapheresis/PLEX, or IVIG to control symptoms. SOC could include a mixture of ISTs, including azathioprine, mycophenolate mofetil, cyclosporine, tacrolimus, methotrexate, cyclophosphamide, dexamethasone, and prednisone, as well as the oral cholinesterase inhibitor pyridostigmine. The analysis performed was from the perspective of a Canadian public health care payer, over a lifetime time horizon (up to 52.5 years). A discount rate of 1.5% per year was applied to costs and QALYs.

The recommended dose of eculizumab is 900 mg weekly for the first four weeks, then 1,200 mg at week 5, and then 1,200 mg every two weeks thereafter. At the submitted price of $6,742 per 300 mg vial, the cost of therapy is $728,136 per patient in the first year, and $701,168 per patient per year thereafter. The weighted average cost of SOC within the model was $1,010 per patient per year.

Model Structure and Inputs

The sponsor's economic evaluation was structured as a Markov cohort model, consisting of an initial refractory gMG health state, health states defined by change in MG-ADL (see CADTH Clinical Report, Appendix 4 for details of the scale) score after six months of therapy, short-term exacerbation or myasthenic crisis states, and death. Patients entered the model in the refractory gMG state, with characteristics consistent with the population of the REGAIN pivotal trial at baseline, where the mean patient age was 47.2 years, mean MG-ADL total score was 10.2, mean body-mass index (BMI) was 30.9 kg/m^2, and 66% of patients were female.[1,2] After six months of therapy, consisting of either eculizumab plus SOC or SOC alone, patients' MG-ADL score could change according to a distribution consistent with those at the six-month assessment point of the REGAIN trial (Table 10).

Eculizumab treatment response was defined as an improvement (decrease) of three or more points on the MG-ADL. Patients who reached this response threshold within six months were considered responders and continued to receive eculizumab therapy. Patients whose response did not meet this threshold were considered nonresponders and were assumed to discontinue eculizumab therapy, receiving SOC thereafter. Patients could only experience AEs consistent with those reported in the REGAIN trial,[1] including headache, upper respiratory infection, nasopharyngitis, nausea, or diarrhea during the initial six-month treatment period.

After six months, patients could then experience clinical events, defined as exacerbations or myasthenic crises. The event rates were determined using a Poisson regression analysis to estimate the relationship between MG-ADL score and the rate of clinical events during the six months of follow-up in the REGAIN trial (Table 11). Based on events reported in the REGAIN trial, the model assumed 91.4% of events are exacerbations (defined in the REGAIN trial as either substantial symptomatic worsening to a two-point change in any single MG-ADL item, excluding ocular, or health in jeopardy if rescue medication was not given), while the remaining 8.6% of events were myasthenic crises (defined as weakness from MG severe enough to necessitate intubation or to delay extubation following surgery, and for whom respiratory failure was due to weakness of respiratory muscles).[1] Each myasthenic crisis was associated with a 12% risk of death, based on a 2020 multi-centre analysis of cases.[3] Apart from during myasthenic crises, patients were assumed to have the same mortality rate as their age- and gender-matched general population. Patients who had responded were also assumed to discontinue eculizumab therapy at a rate of 7.7% of the original total every six-month cycle, due to difficulties in adherence for long-term intravenous infusion therapy of biologics, based on a self-reported biologic treatment adherence study. Under this assumption, more than 50% of patients discontinued treatment by 3.5 years and 100% by 6.5 years.

Patients accrued costs and QALYs specific to their health state and costs related to treatment as they transitioned through the health states in the model. Utility values were derived using MG-ADL score as a predictor of the Euro-Quality of Life 5-Dimensions questionnaire (EQ-5D) utility score (US index), developed by conducting post hoc analyses on the REGAIN trial data. A mixed-effects model with a random intercept was used to estimate the impact of MG-ADL total score on change in EQ-5D scores over time (Table 12). Additional factors found to be predictive of the change in utility from baseline were BMI and baseline EQ-5D score, which were added to the mixed-effects model. Exacerbations and myasthenic crises were associated with disutilities in the model, derived from patient-level data in the REGAIN trial, where an exacerbation was associated with a weighted average disutility of –0.200 for 11.8 days, while a myasthenic crisis resulted in a disutility of –0.720 for 31.1 days.

Costs included drug-acquisition costs for eculizumab and SOC, where eculizumab cost $53,558 per 28-day cycle in the maintenance phase, while SOC cost an average of $77.49 per 28-day cycle. In the base case, the sponsor assumed that 50% of patients would receive eculizumab in outpatient centres and that this cost would be covered by the sponsor. No administration costs were thus included for these patients. The other 50% of patients receiving eculizumab were assumed to receive their treatment as home-based care, at an estimated cost of $165.81 per administration based on the average hourly wage of a registered nurse,[4] administration supplies, and driving time. Four percent of patients receiving eculizumab were assumed to require a meningococcal vaccination, based on the rate reported in the REGAIN trial; this cost was also assumed to be covered by the sponsor. All patients were assumed to visit a primary care physician (50%) or specialist (50%) once every 28 days.[5] The sponsor considered costs associated with treating AEs as well as the costs due to exacerbations and myasthenic crises, including hospital and ICU usage, as well as the possibility of PLEX or IVIG use and post-event rehabilitation or nursing care (Table 13).

Summary of Sponsor's Economic Evaluation Results

The sponsor submitted probabilistic analyses consisting of 5,000 iterations.

Base-Case Results

In the base case, the sponsor reported that eculizumab plus standard of care was associated with an additional cost of $1,211,288 and 0.90 additional QALYs when compared to SOC alone, leading to an ICER of $1,329,219 per QALY (Table 3). Eculizumab plus SOC was also associated with an additional 0.35 life-years when compared to SOC alone. Disaggregated cost results can be found in Appendix 3; the key cost drivers were the cost of eculizumab, which was partly offset by reduced costs of treating exacerbations and myasthenic crises for patients using eculizumab. At WTP thresholds of $50,000 and $100,000 per QALY, 0% of iterations would be considered cost-effective. Deterministic results were similar.

Table 3: Summary of the Sponsor's Economic Evaluation Results

Drug	Total Costs ($)	Incremental Costs ($)	Total QALYs	Incremental QALYs	ICER vs. SOC ($/QALY)
SOC alone	3,690,170	–	15.03	–	–
Eculizumab plus SOC	4,901,459	1,211,288	15.93	0.90	1,329,219

ICER = incremental cost-effectiveness ratio; SOC = standard of care; QALY = quality-adjusted life-year; vs. = versus.

Source: Sponsor's pharmacoeconomic submission, updated model.[6]

Sensitivity and Scenario Analysis Results

The sponsor conducted a variety of deterministic sensitivity analyses to test the influence that changes in individual model parameters had on the cost-effectiveness of eculizumab. Those with the greatest effect on the resulting ICERs included the relationship between MG-ADL score and health utility (i.e., the coefficient of MG-ADL, β3, see Table 12 for equation), altering the change in MG-ADL score by category at month 6 (e.g., patients in the category –5 to –6 change in MG-ADL total score are instead assumed to have –4 or –6 change in total score), altering the annual eculizumab discontinuation rate, assuming a different eculizumab dose intensity, or assuming different annual clinical event (exacerbation and crisis) rates.

A number of scenario analyses were also conducted, including varying the discount rate, considering a societal perspective, including disutility experienced by caregivers, adjusting the efficacy inputs to exclude patients requiring rescue therapy, exploring the impact of varying the rate at which MG-ADL score increases (worsens) over time for patients receiving SOC alone, including administration and vaccination costs, and reducing the time horizon. Some scenario analyses (deteriorating MG-ADL score for patients using SOC alone, eculizumab discontinuation rate) produced counterintuitive results.

CADTH Appraisal of the Sponsor's Economic Evaluation

CADTH identified several key limitations to the sponsor's analysis that have notable implications for the economic analysis.

- **Rituximab was not considered as a comparator:** Based on clinical experts consulted by CADTH, rituximab, while not indicated for gMG, is currently used as a treatment for patients who are refractory to other therapies. The sponsor did not include rituximab as a comparator and stated that rituximab, when used in addition to SOC, is less effective in treating AChR-antibody–positive gMG than when used to treat those with the muscle-specific kinase (MuSK) serotype.[6] While rituximab does appear to be more effective in patients with the MuSK serotype,[7] this does neither preclude it from also being effective in AChR-antibody–positive gMG, nor does it detract from the fact that rituximab is used

for such patients in clinical practice. A recent systematic review of nonrandomized studies reported that 68% of AChR-antibody–positive patients experienced significant clinical improvement, 36% experienced full remission, and a mean of 54% (range 27% to 64%) reached minimal manifestation status, defined in a 2016 international guideline as having "no symptoms or functional limitations of MG but … some weakness on examination of some muscles."[7] Clinical experts consulted by CADTH estimated a similar proportion of patient response to rituximab. No clinical studies or indirect comparisons were submitted or found comparing the efficacy of eculizumab to rituximab in patients with gMG, and, thus, the cost-effectiveness of eculizumab plus SOC compared to rituximab plus SOC is unknown. Eculizumab ($700,000 per patient per year) is more expensive than rituximab ($10,000 to $15,000 per patient per year, Appendix 1). The clinical experts further highlighted that rituximab is a common, efficacious off-label therapy for gMG, although access to and reimbursement of rituximab vary across Canada.

  - CADTH was unable to address this limitation as part of the reanalysis.

- **The sponsor's model lacks face validity:** Several key inputs regarding the natural history of refractory gMG in the model did not align with available clinical literature and feedback from clinical experts consulted by CADTH:

  - The sponsor assumed a deteriorating course for patients receiving SOC alone, with MG-ADL score increasing (worsening) by a score of 0.5 per year, while assuming that patients undergoing active treatment with eculizumab would not deteriorate. While the open-label extension study ECU-MG-302 does suggest that MG-ADL score remains stable over up to 2.5 years while patients are treated with eculizumab, no information was submitted supporting whether MG-ADL score would remain stable or deteriorate for patients who continue on SOC alone, or who discontinue eculizumab. This assumption directly impacts health utility and clinical event rate based on treatment group assignment, without comparative evidence to support the assumption. The clinical experts consulted by CADTH did not agree with the sponsor's assumption that MG-ADL score would worsen over time for patients treated with SOC in Canada, nor could long-term data be found to support the assumption.

    - In reanalyses, CADTH assumed that MG-ADL score would remain stable after the initial improvement at six months for both treatment groups. The model was not sufficiently flexible to allow for testing of alternative assumptions, such as MG-ADL scores worsening after exacerbations or crises, or higher risk of worsening at higher scores rather than by treatment group. The effect of a deteriorating course for patients using SOC alone was explored through scenario analysis.

  - The clinical experts consulted by CADTH suggested that the sponsor's mortality rate of 12% for patients experiencing a myasthenic crisis did not reflect clinical outcomes in Canadian practice and instead estimated a mortality rate of 5%. The population of 250 patients reported in the Neumann et al. (2020) retrospective study, the basis of the sponsor's estimate of 12%, were older than those in the REGAIN trial (mean age 67 versus 47 years, respectively) and more likely to be male (57% versus 34%). Furthermore, as reported by the study authors, the study is likely to include patients with more severe gMG, because participating centres were specialized referral ICUs.[1,3] In contrast, in a 2009 retrospective study, only 4.47% of the 2,014 patients experiencing a myasthenic crisis died.[8]

    - CADTH assumed a 5% probability of mortality in myasthenic crisis in its base case.

  - A disutility of –0.72 was assigned to patients in myasthenic crisis based on the EQ-5D score of a single patient measured the week before and after that patient had experienced a crisis during the REGAIN trial. This estimate fails to meet face validity, as it places a large proportion of patients experiencing a crisis in a state worse than death for a full month.

        - CADTH reviewers found that this assumption had a limited effect on overall cost-effectiveness and that no robust estimate was available in the literature. Accordingly, this value was left unadjusted for the CADTH base-case reanalysis. However, a scenario analysis was run using the disutility associated with mechanical ventilation in ICU (–0.39) as a proxy for myasthenic crisis.[9]
    - Limiting AEs to the first six months of the model does not meet face validity. Clinical experts consulted by CADTH did not agree with the sponsor's assumption that all treatment-related AEs would stop after the first six months. Additionally, cases of serious or fatal meningococcal infections have been reported in eculizumab-treated patients.[10] While the model included the option of meningococcal vaccination costs, no risk of meningococcal infection was incorporated.
        - The sponsor's model lacked sufficient flexibility to examine the impact of these assumptions on cost-effectiveness.
- **Model does not adequately reflect the anticipated use of eculizumab**: The sponsor assumed that patients who had not achieved an improvement of at least three points on the MG-ADL total score would discontinue eculizumab therapy after six months. However, while the clinical experts consulted by CADTH believed patients who show no improvement at six months are likely to be discontinued, they indicated that this definition of the response threshold differs from a definition of response that would likely be used in practice. They indicated that patients who had shown any improvement in MG-ADL score or other MG symptom measure would likely receive at least an additional three months of therapy to determine whether there was further improvement, whereas those who had worsened might be discontinued at an earlier assessment point. The clinical experts also stated that even patients who did not see an improvement in score but who had decreased their need for steroids by six months might continue on eculizumab. The model is insufficiently flexible to test these alternative response thresholds, nor could the time point of assessment for treatment discontinuation be altered. Additionally, the sponsor assumed that patients would receive eculizumab on a maintenance schedule until they discontinued because of the difficulty in adhering to the treatment regimen. A fixed number of patients (7.7% of those originally responding) were assumed to discontinue per six-month cycle, based on the inappropriate application of a proportion converted from an observational study that reported 48% of patients with rheumatoid arthritis on a biologic discontinued therapy over a median follow-up time of 4.1 years. Because the sponsor applied this assumption, all patients in the model had discontinued eculizumab by 6.5 years of therapy. The clinical experts consulted by CADTH suggested that clinicians would likely try to discontinue eculizumab after approximately two years, to see whether patients might fare well on SOC alone thereafter, rather than continuing until the patient could no longer adhere to therapy. While the available clinical literature does not support a specific timeline for re-evaluation and discontinuation, and treatment decisions in general require symptom evaluation and discussion between physician and patient, the sponsor's model lacked the flexibility to reflect modifications in potential treatment approaches. Additionally, the sponsor's assumption that patients would immediately revert to MG-ADL scores consistent with those of the SOC arm upon discontinuation of eculizumab was inconsistent with carry-over effects reported in a phase II crossover pilot study.[11]
    - CADTH was unable to address this limitation as part of the reanalysis.
- **Indicated population is not fully represented by population studied in REGAIN:** The REGAIN trial excluded patients who had had a thymectomy within 12 months before screening, who were in myasthenic crisis (Myasthenia Gravis Foundation of America class V), or who had used IVIG or PLEX within four weeks or rituximab within six months before randomization. The clinical experts consulted by CADTH did not believe such characteristics would preclude patients from receiving eculizumab in clinical practice. It is not known whether the clinical efficacy and safety of eculizumab are the same in these patients (excluded from the study) as in those studied. Additionally, the clinical experts consulted by CADTH indicated that rituximab is a

common therapy for refractory gMG. However, only 11% of patients in the REGAIN trial had tried rituximab before trial enrolment; the efficacy of eculizumab in patients who had failed to respond to rituximab is thus uncertain.

  - CADTH was unable to address this limitation as part of the reanalysis.

- **Inappropriate assumptions on administration, routine care, and meningococcal vaccination costs:** The sponsor assumed that half of patients would receive eculizumab at outpatient clinics, while the rest would receive it at home. In the submitted model, the sponsor assumed that all administration costs at outpatient clinics would be covered by the sponsor, as would all meningococcal vaccination costs. However, the sponsor did not provide supporting documentation indicating that these costs would be covered in their submission materials. Additionally, the clinical experts consulted by CADTH did not agree with the sponsor's assumption that patients would see a primary care or specialist every 28 days in clinical practice; instead, they suggested that patients receiving SOC for gMG would see their specialist twice per year, while patients receiving eculizumab would be monitored more frequently, with specialist visits approximately every two months.

  - As part of the base-case reanalysis, CADTH included all administration and vaccinations costs. All routine care visits were assumed to be to a specialist, with patients receiving SOC visiting twice per year, while those on eculizumab visited six times per year.

- **Probabilistic variation based on arbitrary values**: Relatively few parameters were varied probabilistically in the sponsor's model, and, of those that were, most were varied arbitrarily, assuming a standard error of 20% around the mean, rather than being informed by trial variation or confidence intervals from source data.

  - In reanalyses, CADTH implemented probabilistic distributions for patient starting age and BMI, using the patient characteristics reported in the REGAIN trial, as well as for the risk of AEs. CADTH was unable to vary other inputs to capture their real underlying distributions. As a result, the model does not reflect the true parameter uncertainty, which is of particular concern in decision-making for a relatively rare condition with limited natural history data; instead, the model was based on a single small trial and required many assumptions.

Additionally, the sponsor made the following key assumptions, which have been appraised by CADTH (Table 4).

Table 4: Key Assumptions of the Submitted Economic Evaluation (Not Noted as Limitations to the Submission)

Sponsor's Key Assumption	CADTH Comment
Most common AEs in REGAIN resulted in ambulatory care visits, with costs as reported by the Ontario Case Costing Initiative	Inappropriate: The AEs in the model were those most frequently reported in REGAIN, most of which were not serious (e.g., nonserious headaches, upper respiratory infections, nasopharyngitis, nausea, or diarrhea). The management of these events may not require hospital intervention. Most simply require pharmaceutical management (e.g., analgesic, antibiotics, antinauseants), for which costs are likely to be lower than the AE treatment costs assumed by the sponsor. However, as AEs occurred at similar frequencies between groups, this issue is unlikely to bias the model results.
50% of patients receive eculizumab in outpatient administration centres, while the remainder receive treatment as home visits	Uncertain: Clinical experts consulted by CADTH suggest that the proportion of patients receiving eculizumab through a home setting was too high. However, assuming that administration costs are included for all patients, this difference in cost has little impact on the ICER, as outpatient and home-based setting costs were similar in the model.

AE = adverse event; ICER = incremental cost-effectiveness ratio.

CADTH Reanalyses of the Economic Evaluation

Base-Case Results

CADTH undertook reanalyses to address limitations in the model, where possible, as outlined in Table 5.

Table 5: CADTH Revisions to the Submitted Economic Evaluation

Stepped Analysis	Sponsor's Value or Assumption	CADTH Value or Assumption
Corrections to sponsor's base case		
None		
Changes to derive the CADTH base case		
1. MG-ADL score over time	MG-ADL scores do not worsen over time for the duration of eculizumab treatment MG-ADL score in SOC group increases (i.e., worsens) by 0.5 per year	Neither group worsens in MG-ADL score over time
2. Mortality rate in myasthenic crisis	12%	5%
3. Clinician routine care visits	Clinicians: 50% GP, 50% specialist Visits per year: 13 (every 28 days)	Clinicians: 100% specialist Visits per year: 6 for patients on eculizumab + SOC, 2 for patients on SOC alone
4. Administration and vaccination costs	Sponsor covered administration costs for patients treated in outpatient centres Sponsor covered vaccination costs for meningococcal meningitis	All administration and vaccination costs covered by public payers
5. Variability in the patient population and rate of AEs	Patient starting age, BMI, and probability of experiencing AEs were not modelled with probabilistic variation	Patient starting age, BMI, and probability of experiencing AEs reflected the input distribution reported in REGAIN trial
CADTH base case		Reanalysis 1 through 5

AE = adverse event; BMI = body-mass index; GP = general practitioner; MG-ADL = Myasthenia Gravis Activities of Daily Living; SOC = standard of care.

The results of these stepwise analyses can be found in Table 6, resulting in the CADTH base case, in which eculizumab plus SOC was associated with 0.98 additional QALYs at an additional cost of $1,472,917, for an ICER of $1,505,712 per QALY when compared to SOC alone. The model was most sensitive to changes in the acquisition cost of eculizumab.

Like the sponsor's base case, 0% of iterations found that eculizumab plus SOC would be considered the most cost-effective strategy at a WTP threshold of either $50,000 or $100,000 per QALY.

Notably, most of the cost of eculizumab is known and occurs early in the model, while the majority (> 90%) of the clinical benefit (QALYs gained) is uncertain and occurs during the period extrapolated rather than the observation period. The observation period for the REGAIN trial and extension study was 2.5 years, and, thus, all clinical benefit accrued after this time point is extrapolated.

Table 6: Summary of the Stepped Analysis of the CADTH Reanalysis Results

Stepped Analysis	Drug	Total Costs ($)	Total QALYs	ICER ($/QALYs)
Sponsor's base case	SOC	3,690,170	15.03	–
	Eculizumab + SOC	4,901,459	15.93	1,329,219
CADTH reanalysis 1 (MG-ADL score stable over time)	SOC	700,283	20.31	–
	Eculizumab + SOC	2,158,575	21.30	1,469,474
CADTH reanalysis 2 (crisis mortality 5%)	SOC	3,804,883	15.16	–
	Eculizumab + SOC	5,007,189	16.04	1,362,803
CADTH reanalysis 3 (specialist visits)	SOC	3,653,768	14.97	–
	Eculizumab + SOC	4,876,149	15.87	1,362,834
CADTH reanalysis 4 (vaccines and administration costs)	SOC	3,665,156	14.98	–
	Eculizumab + SOC	4,885,416	15.88	1,359,849
CADTH reanalysis 5 (variation)	SOC	3,660,304	14.92	-
	Eculizumab + SOC	4,873,780	15.82	1,351,806
CADTH base case (1 through 5)	SOC	684,203	20.32	-
	Eculizumab + SOC	2,157,120	21.30	1,505,712

ICER = incremental cost-effectiveness ratio; MG-ADL = Myasthenia Gravis Activities of Daily Living; QALY = quality-adjusted life-year; SOC = standard of care.

Scenario Analysis Results

A number of scenario analyses were run to examine which assumptions had large impacts on model results:

- **Scenario analysis A:** The disutility in myasthenic crisis was assumed to be –0.39, consistent with mechanical ventilation in ICU (–0.39) as a proxy for myasthenic crisis,[9] replacing the sponsor's figure of –0.72.
- **Scenario analysis B:** MG-ADL score was assumed to worsen by 0.5 points per year on SOC, consistent with the sponsor's assumption, rather than remaining stable as in the CADTH base case.
- **Scenario analysis C:** A societal perspective was taken, in which costs associated with productivity loss and informal care were included, in addition to direct medical costs.
- **Scenario analysis D1 and D2:** The sponsor's eculizumab discontinuation rate of 7.7% per six-month cycle was halved and doubled, respectively.
- **Scenario analysis E:** Consistent with patient input which suggested exacerbations lead to two-week hospital stays, exacerbations not involving the ICU were assumed to have a 14-day impact on costs and disutility, rather than the sponsor's assumption of 31.1 days. Exacerbations involving ICU stays and myasthenic crises were not altered.
- **Scenario analysis F:** Consistent with the sponsor's base case, vaccination and administration costs for patients receiving treatment through outpatient clinics were excluded.

Results for these scenario analyses can be found in Table 16 (Appendix 4). The model was found to be sensitive to the rate at which patients who responded to eculizumab discontinued treatment (Scenarios D1 and D2).

CADTH conducted a series of price-reduction scenarios exploring the impact of lowering the cost of eculizumab on the sponsor's and CADTH's base-case results (Table 7). Using the

CADTH base case, to be considered cost-effective at WTP thresholds of $50,000 and $100,000 per QALY, the price of eculizumab would need to be reduced by 88% and 91%, respectively.

Table 7: CADTH Price-Reduction Analyses

	ICERs for Eculizumab + SOC vs. SOC Alone	
Price Reduction	**Sponsor Base Case ($/QALY)**	**CADTH Reanalysis ($/QALY)**
No price reduction	1,329,219	1,505,712
10%	1,177,789	1,356,468
20%	1,001,473	1,189,747
30%	825,077	1,029,509
40%	650,158	867,386
50%	472,141	703,489
60%	296,443	542,280
70%	123,132	378,393
80%	**Dominant**	215,764
90%	Dominant	**54,251**

ICER = incremental cost-effectiveness ratio; QALY = quality-adjusted life-year; SOC = standard of care; vs. = versus.

Issue for Consideration

- **Rural and remote access**: Access to eculizumab may require travelling to see specialists or receive infusions and may be difficult to access over a long term for patients in rural or remote settings. This is likely an equity issue and may be mitigated if home-based administration is available. This issue would similarly impact access to rituximab.

Overall Conclusions

CADTH's conclusions are aligned with the sponsor's, in that eculizumab plus SOC compared with SOC alone is not a cost-effective treatment for patients with treatment-refractory AChR-antibody–positive gMG. To address the identified limitations, CADTH removed the assumption of MG-ADL score deteriorating over time when the patient is on SOC; reduced the mortality rate from myasthenic crisis; reduced the frequency of routine clinician visits; included all vaccination and administration costs; and added probabilistic variation for patient characteristics and the probability of experiencing AEs. CADTH reanalysis of the sponsor's economic model suggests that eculizumab plus SOC compared to SOC alone is associated with an ICER of $1,505,712 per QALY gained, and has a 0% probability of being cost-effective for patients with refractory AChR-antibody–positive gMG at a WTP thresholds of $50,000 per QALY. A price reduction of 88% or 91% would be required to achieve an ICER below a WTP threshold of $100,000 or $50,000 per QALY, respectively.

The submitted price of eculizumab is the most influential driver in the cost-effectiveness model. While the cost of eculizumab is known and occurs early in the model, most (> 90%) of the clinical benefit (QALYs gained) was estimated through extrapolation beyond the observed time period of the REGAIN trial. The quality-adjusted survival extrapolations were made based on several assumptions, with high levels of untestable uncertainty, meaning that the cost-effectiveness of eculizumab is highly uncertain.

Important limitations remain that CADTH was unable to address, including assumptions about the natural history of gMG and the anticipated use of eculizumab. Additionally, the cost-effectiveness of eculizumab compared with rituximab is unknown. These limitations affected CADTH's ability to conduct a precise health economic analysis. Despite the limitations within the analysis, there was nevertheless a 0% probability that eculizumab would be considered cost-effective in the indicated population, even within the sponsor's originally submitted estimates.

Appendix 1: Cost-Comparison Table

The comparators presented in the following table have been deemed to be appropriate based on feedback from clinical expert(s). Comparators may be recommended (appropriate) practice or actual practice. Existing Product Listing Agreements are not reflected in the table and, as a result, the table may not represent the actual costs to public drug plans.

Table 8: CADTH Cost-Comparison Table of Medications Used for Myasthenia Gravis

Treatment	Strength	Form	Price	Recommended Dosage[a]	Daily Cost ($)	Annual Cost ($)
Eculizumab (Soliris)	300 mg/30 mL	Vial for intravenous infusion	6,742.0000[b]	900 mg weekly for 4 weeks, then 1,200 mg in at week 5, then 1,200 mg every 2 weeks thereafter[b]	**Year 1** 1,994.89 **Year 2** 1,921.01	**Year 1** 728,136 **Year 2** 701,168
Other biologics						
Rituximab (Rituxan)	100 mg/10 mL 500 mg/50 mL	Vial for intravenous infusion	482.3844[c] 2,411.5400[c]	375 mg/m^2 weekly for four doses[d] **Alternative dosage:** 1 g, followed by 1 g two weeks later, and then every 6 months	N/A	Cost/course: 13,505 Alternative dosage in year 1: 14,469
Rituximab (Truxima)	100 mg/10 mL 500 mg/50 mL		337.6135 1,688.0780		N/A	Cost/course: 9,453 Alternative dosage in year 1: 10,128
Glucocorticoids						
Prednisone (generics, Winpred)	1 mg 5 mg 50 mg	Tablet	0.1066 0.0220 0.1735	10 to 20 mg/day, increase by 5 mg/day per week until stable remission (target 1 mg/kg/day) **Alternative dosage** Begin with 60 to 80 mg/day taper after improvement	Initial dose: 0.04 to 0.09, increasing up to 0.31 until remission reached **Alternative dosage** 0.22 to 0.31, decreasing thereafter	Up to 111.51
Immunosuppressive agents						
Azathioprine	50 mg	Tablet	0.2405	Initiate at 2 to 3 mg/kg/day, taper to minimum effective dose, as low as 50 mg/day	0.24 to 1.20	88 to 438

Treatment	Strength	Form	Price	Recommended Dosage[a]	Daily Cost ($)	Annual Cost ($)
Cyclophosphamide (Procytox, generics)	25 mg 50 mg	Tablet	0.3520 0.4740	Initial dosage 2 mg/kg/day		
	200 mg 500 mg 1,000 mg 2,000 mg	IV vial for injection	70.0300[e] 84.5500[e] 52.0600[e] 91.0500[e]	500 mg/m^2 every 4 weeks until stabilization	1.85	679
Cyclosporin A (Neoral, generic)	10 mg 25 mg 50 mg 100 mg	Capsules	0.6520 0.9952 1.9400 3.8815	Target dosage: 5 to 6 mg/kg/day in 2 divided doses, adjust for serum trough level of 75 to 150 ng/mL	15.53 to 19.41	5,667 to 7,083
Methotrexate (generic, Metoject SC)	2.5 mg 10 mg	Tablets	0.6325 2.7000[f]	7.5 to 25 mg/week, orally or SC	1.90 to 6.32	99 to 329
	7.5 mg/0.15 mL 10 mg/0.2 mL 12.5 mg/0.25 mL 15 mg/0.3 mL 17.5 mg/0.35 mL 20 mg/0.4 mL 22.5 mg/0.45 mL 25 mg/0.5 mL	Pre-filled syringe for SC use	28.0800[f] 29.6400 31.2000 32.7600 32.0000 35.0000 35.0000 39.0000		28.08 to 39.00	1,460 to 2,028
Mycophenolate mofetil (Cellcept, generics)	250 mg 500 mg	Capsule Tablet	0.3712 0.7423	1,000 mg twice daily	2.97	1,084
Mycophenolate sodium (Myfortic, generics)	180 mg 360 mg	Enteric tablet	1.4983 2.9965	720 mg twice daily[g]	11.99	4,375
Tacrolimus (generics)	0.5 mg 1 mg 5 mg	Capsule	1.4775 1.8900 9.4650	3 to 5 mg per day[i]	5.67 to 9.46	2,070 to 3,455
Cholinesterase inhibitors						
Pyridostigmine (Mestinon)	60 mg 180 mg	Tablets SR tablets	0.5189 1.1573	Individualized based on response: 1 to 3 180 mg SR tabs once or twice daily usually sufficient to control symptoms[h]	1.16 to 6.94	422 to 2,535

Treatment	Strength	Form	Price	Recommended Dosage[a]	Daily Cost ($)	Annual Cost ($)
Blood products						
Intravenous immunoglobulin						$7,383 per exacerbation[j]
Plasma exchange						$1,575 per exacerbation[j]

IV = intravenous; N/A = not applicable; SC = subcutaneous; SR = slow release.

Note: All prices are from the Ontario Drug Benefit Formulary (accessed May 2020), unless otherwise indicated, and do not include dispensing fees.[12] Patients are assumed to weigh 80 kg, consistent with the median weight at baseline reported in the REGAIN trial.[2]

[a] Dosage is from the *International Consensus Guidance for Management of Myasthenia Gravis, Full Statement*, unless otherwise indicated.[13]

[b] Sponsor's submitted and marketed price, and product monograph–recommended dosage.[10]

[c] Ontario Drug Benefit Formulary Exceptional Access Program (accessed May 2020).[14]

[d] Assumes a standard body surface area (1.7 m^2) for adults and includes wastage of excess medication.

[e] DeltaPA database wholesale prices (accessed May 2020).[15]

[f] Saskatchewan Drug Plan Formulary (accessed May 2020).[16]

[g] Myfortic product monograph, dosage indicated for the prophylaxis of organ rejection in patients receiving allogeneic renal transplants, confirmed with clinical experts as also used for gMG.[17]

[h] Mestinon SR product monograph, dosage indicated for the symptomatic treatment of MG.[18]

[i] Dose reported for patients with therapy-refractory MG in *Clinical features, pathogenesis, and treatment of myasthenia gravis: a supplement to the Guidelines of the German Neurological Society*.[19]

[j] Source: Furlan et al. (2016).[20] Costs inflated from 2014 to 2020 Canadian dollars.[21]

Appendix 2: Submission Quality

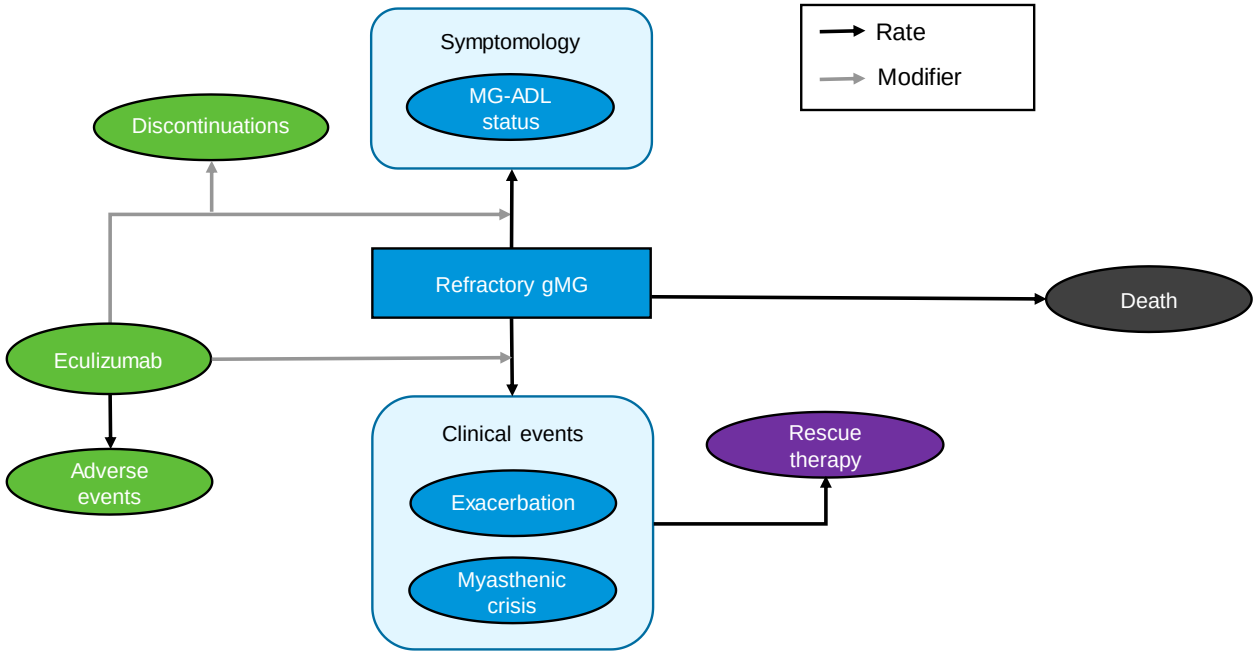
Table 9: Submission Quality

Description	Yes	No	Comments
Population is relevant, with no critical intervention missing, and no relevant outcome missing	☐	☒	Rituximab should have been considered, either as a comparator or as a medication that should be tried before eculizumab.
Model has been adequately programmed and has sufficient face validity	☐	☒	The model did not reflect current clinical understanding of gMG.
Model structure is adequate for decision problem	☐	☒	The model does not allow for eculizumab to be prescribed intermittently, as required, or for set periods of time.
Data incorporation into the model has been done adequately (e.g., parameters for probabilistic analysis)	☐	☒	Many of the model parameters did not vary probabilistically. Of those that did, many were arbitrarily assigned a range of 20% to account for parameter uncertainty. This limitation is largely a reflection of a lack of evidence.
Parameter and structural uncertainty were adequately assessed; analyses were adequate to inform the decision problem	☐	☒	CADTH was unable to test several key model assumptions.
The submission was well organized and complete; the information was easy to locate (clear and transparent reporting; technical documentation available in enough details)	☒	☐	Adequate: Fewer hard-coded inputs in the model would have increased the model's flexibility for evaluating relevant disease and treatment processes.

gMG = generalized myasthenia gravis.

Appendix 3: Additional Information on the Submitted Economic Evaluation

Figure 1: Model Structure



Source: Sponsor's pharmacoeconomic submission, Figure 3.[6]

Response to treatment, as defined by proportion of patients in each category of change in MG-ADL total score at six months, along with the mean change in score of each category, is outlined in Table 10.

Table 10: Proportion of Patients in Each MG-ADL Score Change Category at Month 6

MG-ADL Total Score Change Category	Proportion of Patients in Each Category		Mean Change in MG-ADL Score Within Each Category	
	Eculizumab + SOC	SOC	Eculizumab + SOC	SOC
< 3	40%	56%	0.36	–0.03
≥ 3	60%	44%	–3.00	–3.00
≥ 4	55%	40%	–4.00	–4.00
≥ 5	45%	29%	–5.00	–5.00
≥ 6	39%	21%	–6.00	–6.00
≥ 7	34%	13%	–7.00	–7.00
≥ 8	21%	6%	–10.31	–8.00

MG-ADL = Myasthenia Gravis Activities of Daily Living; SOC = standard of care.

Source: Sponsor's pharmacoeconomic submission, Table 3, all patients including those who required rescue therapy.[6]

Patients in the model had a differing annual rate of clinical events based on their MG-ADL total score, described in Table 11.

Table 11: Estimated Annual Event Rate by MG-ADL Total Score

MG-ADL Total Score	Annual Event Rate
0 to 4	0.136
4 to 7	0.293
7 to 10	0.565
10 to 13	1.088
13 to 16	2.098
16 to 19	4.045
19 to 22	7.799
22 +	13.477

MG-ADL = Myasthenia Gravis Activities of Daily Living.

Source: Sponsor's pharmacoeconomic submission, Table 5.[6]

Change in utility values from baseline were derived from a mixed-effects model using a US index to derive the equation described in Table 12, where change in utility depended on the patient's baseline EQ-5D score, MG-ADL score, and BMI.

Table 12: Utility Equation and Parameter Estimates

Utility Change Equation	
$Utility\ Change = \beta_0 + \beta_1 * EQ - 5D_{\ baseline} + \beta_2 * BMI_{baseline} + \ \beta_3 * MG - ADL_{baseline}$	
Parameter	**Value**
Baseline EQ-5D	0.6822
Intercept [β0]	0.6966
Coefficient of baseline EQ-5D [β1]	–0.6156
Coefficient of BMI [β2]	–0.0026
Coefficient of MG-ADL score [β3]	–0.0192

Exacerbations and myasthenic crises were associated with initial acute care costs and might also be associated with post-acute care costs, as described in Table 13. Hospital stay, with and without ICU, were based on length of stays from Neumann et al.[3] with cost per diem derived from the Ontario Case Costing Initiative and inflated to 2019 costs.[22] The cost of IVIG and PLEX therapy were derived from Neumann et al. and a cost-minimization analysis.[20] The cost of post-event nursing care was estimated using the daily rate for long-term care from the Ontario Long Term Care Association, with a length of stay of 19.1 days estimated by subtracting the median time spent on ventilatory support (12 days) from the median length of hospital stay (31.1 days).

Table 13: Resource Use During Clinical Events (Exacerbations and Crises)

Type of Care	% of Patients	Cost per Event
Exacerbation		
Acute care		
Outpatient care	80	712
Hospital stay, no ICU, 31.1 days	18	52,238
Hospital stay, with ICU, 21.7 days in ICU, 9.4 regular ward	2	102,415
IVIG or PLEX	100	8,362
Total acute costs		**20,383**
Post-acute care		
Outpatient care	100	712
PLEX	90	6,835
IVIG	10	9,057
Short-term nursing care	18	3,002
Total post-acute costs		**8,303**
Myasthenic crisis		
Acute care		
Hospital stay, no ICU, 31.1 days	30	52,238
Hospital stay, with ICU, 21.7 days in ICU, 9.4 regular ward	70	102,415
IVIG or PLEX	100	8,362
Total acute costs		95,724
Post-acute care		
Outpatient care	100	712
PLEX	50	6,835
IVIG	50	9,057
Long-term nursing care	46	3,002
Total post-acute costs		**10,039**

ICU = intensive care unit; IVIG = intravenous immunoglobulin; PE = PLEX = plasma exchange; SOC = standard of care.

Source: Adapted from the sponsor's pharmacoeconomic submission, Tables 12 and 13.[6] SOC costs assume Ontario Drug Benefit Formulary list prices.

Detailed Results of the Sponsor's Base Case

Table 14: Sponsor's Base-Case Results, Disaggregated Costs, and QALYs

Category	Eculizumab + SOC ($)	SOC ($)	Incremental ($)
Costs by category			
Eculizumab drug-acquisition cost	1,577,106	0	1,577,106
Eculizumab infusion	4,965	0	4,965
Meningococcal vaccination	0	0	0
SOC drug-acquisition cost	39,711	39,205	506
Routine care	29,330[a]	28,957	373
Clinical event management	3,250,172	3,621,816	–371,643
AE management	174	192	–18
TOTAL	**4,901,459**	**3,690,170**	**1,211,288**
QALYs by health state			
Score change < 3	5.54	7.69	–2.15
Score change 3 to 4	0.77	0.61	0.16
Score change 4 to 5	1.60	1.74	–0.14
Score change 5 to 6	0.99	1.31	–0.32
Score change 6 to 7	0.86	1.36	–0.50
Score change 7 to 8	2.31	1.23	1.08
Score change ≥ 8	3.87	1.09	2.78
TOTAL	**15.93**	**15.03**	**0.90**
Life-years			
Life-years per patient	27.74	27.39	0.35

AE = adverse event; QALY = quality-adjusted life-year; SOC = standard of care.

[a] Corrected from sponsor's submission, which erroneously reported $0 for eculizumab routine care costs. Totals were unaffected.

Source: Sponsor's pharmacoeconomic submission, Table 20.[6]

Appendix 4: Additional Details on the CADTH Reanalyses and Sensitivity Analyses of the Economic Evaluation

Table 15: Disaggregated Summary of CADTH's Economic Evaluation Results

Category	Eculizumab + SOC ($)	SOC ($)	Incremental ($)
Costs by category			
Eculizumab drug-acquisition cost	1,579,338	0	1,579,338
Eculizumab infusion	11,205	0	11,205
Meningococcal vaccination	13	0	13
SOC drug-acquisition cost	40,934	40,518	415
Routine care	14,485	4,779	9,706
Clinical event management	510,972	638,713	–127,741
AE management	174	193	–19
TOTAL	**2,157,120**	**684,203**	**1,472,917**
QALYs by health state			
Score change < 3	7.65	10.61	–2.96
Score change 3 to 4	1.04	0.83	0.22
Score change 4 to 5	2.15	2.34	–0.19
Score change 5 to 6	1.32	1.75	–0.42
Score change 6 to 7	1.13	1.79	–0.66
Score change 7 to 8	3.01	1.61	1.41
Score change ≥ 8	5.00	1.41	3.59
TOTAL	**21.30**	**20.32**	**0.98**
Life-years			
Life-years per patient	28.48	28.19	0.29

AE = adverse event; QALY = quality-adjusted life-year; SOC = standard of care.

Scenario Analyses

A number of scenario analyses were run around the CADTH base case.

Table 16: Summary of the Scenario Analyses of the CADTH Base-Case Results

Stepped Analysis	Drug	Total Costs ($)	Total QALYs	ICER ($/QALYs)
CADTH base case	SOC	684,203	20.32	–
	Eculizumab + SOC	2,157,120	21.30	1,505,712
CADTH scenario A (Disutility for myasthenic crisis –0.39)	SOC	686,281	20.35	–
	Eculizumab + SOC	2,158,257	21.83	1,513,491
CADTH scenario B (SOC MG-ADL score worsens 0.5 annually)	SOC	3,770,270	15.17	–
	Eculizumab + SOC	4,989,064	16.05	1,383,609
CADTH scenario C (societal perspective)	SOC	839,739	20.34	–
	Eculizumab + SOC	2,276,041	21.32	1,464,613
CADTH scenario D1 (eculizumab discontinuation rate halved to 3.85% per cycle)	SOC	682,183	20.37	–
	Eculizumab + SOC	3,381,111	21.36	2,734,420
CADTH scenario D2 (eculizumab discontinuation rate doubled to 15.4% per cycle)	SOC	680,237	20.34	–
	Eculizumab + SOC	1,510,246	21.32	852,226
	Eculizumab + SOC	1,767,922	6.91	5,938,268
CADTH scenario E (exacerbations have 14-day costs and disutility)	SOC	596,484	20.26	–
	Eculizumab + SOC	2,086,632	21.24	1,511,567
CADTH scenario F (vaccinations and outpatient administration costs excluded)	SOC	680,847	20.36	–
	Eculizumab + SOC	2,147,476	21.34	1,500,341

ICER = incremental cost-effectiveness ratio; MG-ADL = Myasthenia Gravis Activities of Daily Living scale; QALY = quality-adjusted life-year; SOC = standard of care.

Appendix 5: Submitted Budget Impact Analysis and CADTH Appraisal

Key Take-Aways of the Budget Impact Analysis

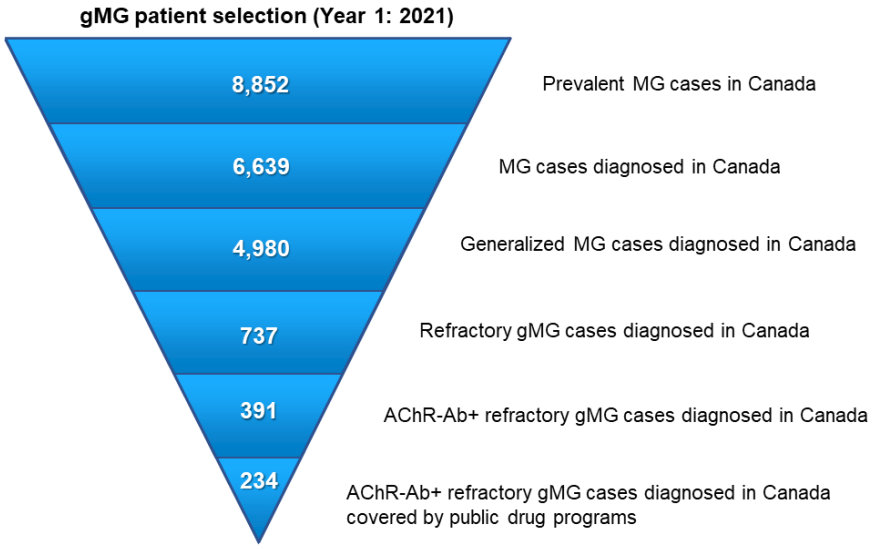
- CADTH identified the following key limitations with the sponsor's analysis:
  - The proportion of patients with gMG diagnosed correctly was underestimated, with no consideration of differing diagnosis rates between ocular MG and gMG.
  - The proportion of patients with public drug coverage was underestimated.
  - Contrary to common practice at CADTH, costs for patients were halved in year 1 of the budget impact analysis because the sponsor assumed treatment would begin halfway through the year.
- CADTH reanalyses corrected the following: the proportion of patients with gMG diagnosed, the proportion of patients with public drug coverage, and the inaccurate representation of treatment course in year 1.
- Based on CADTH reanalyses, the budget impact is expected to be $52,224,226 in year 1, $86,818,772 in year 2, and $110,357,145 in year 3, with a three-year budget impact of $249,400,143.

gMG = generalized myasthenia gravis; MG = myasthenia gravis.

Summary of Sponsor's Budget Impact Analysis

The submitted budget impact analysis6 (BIA) assessed the introduction of eculizumab for the treatment of adult patients with AChR-antibody–positive refractory gMG as compared to SOC alone (i.e., eculizumab + SOC versus SOC alone). By definition, patients with refractory gMG continue to experience disease progression despite having tried conventional therapies; SOC here refers to those therapies they would have likely already been receiving and includes oral cholinesterase inhibitors and ISTs. This population-based BIA was conducted over a three-year time horizon (January 2021 to December 2023), with 2020 as a baseline year 0. The costs considered in the analysis included drug-acquisition costs, dispensing fees, and markup, but did not include the costs of blood products (IVIG, PLEX), as the BIA explicitly considered drug formulary costs only. Drug administration costs were considered in scenario analysis. The sponsor's analysis assumed that patients would, on average, begin treatment halfway through year 1; thus, for every patient, all costs were approximately halved in the first year. An overview of the sponsor's estimate of the eligible population size can be found in Figure 2, with key inputs to the BIA described in Table 17.

Figure 2: Sponsor's Estimate of the Eligible Population Size



AChR-Ab+ = acetylcholine receptor–antibody–positive; gMG = generalized myasthenia gravis.

Source: Sponsor's pharmacoeconomic submission.[6]

Table 17: Summary of Key Model Parameters

Parameter	Sponsor's Estimate
Target population	
Prevalent cases MG in Canada (per million), n	230
% MG diagnosed	75
% gMG in MG	75
% refractory gMG in gMG	14.8[23]
% AChR-antibody–positive refractory gMG within refractory gMG	53[23]
% patients who would seek coverage by public drug program	60
Estimated number of patients treated with eculizumab by program	48/79/105
Market uptake (3 years)[a]	
Eculizumab + SOC, %	25/45/60
SOC only, %	75/55/40
Cost of treatment (per patient)	
Eculizumab (without dispensing fees and markup), $	
In first year of treatment	728,136
Half year[b]	377,552
In subsequent years	701,168

AChR = acetylcholine receptors; gMG = generalized myasthenia gravis; MG = myasthenia gravis; SOC = standard of care.

[a] The BIA assumes that the reference scenario is SOC only. With the reimbursement of eculizumab, eculizumab is predicted to take the resulting market share from SOC.

[b] From submission: "The average patient would start treatment halfway through the year, resulting in a reduced number of maintenance administrations (11 instead of 24) in the first year."[6]

Source: Sponsor's pharmacoeconomic submission.[6]

Summary of Sponsor's Budget Impact Analysis Results

The sponsor's base case found that the incremental expenditures associated with the reimbursement of eculizumab in adult patients with gMG are expected to be $20,178,974 in year 1, $45,184,801 in year 2, and $65,178,630 in year 3. The total three-year budget impact for reimbursing eculizumab was estimated to be $130,542,404.6

CADTH Appraisal of the Sponsor's Budget Impact Analysis

CADTH identified several key limitations of the sponsor's analysis that have notable implications for the results of the BIA.

- **Diagnosis of gMG:** The sponsor's BIA model considered the proportion of cases of gMG that are diagnosed correctly to be 75%, regardless of the subtype. Clinical experts consulted by CADTH suggested that the majority of gMG cases (i.e., those diagnosed in neurology clinics) are correctly identified, whereas cases presenting at ocular clinics have a higher rate of false-negative findings. The sponsor's BIA model does not reflect these distinct diagnostic processes and does not allow for different rates of true-positive diagnoses in the two MG subtypes.
    - Clinical experts consulted by CADTH suggested that the proportion of gMG cases that go undiagnosed is closer to 2%. Therefore, the CADTH base case assumed that 98% of the prevalent cases of gMG in Canada would be correctly diagnosed and identified.
- **Underestimation of the proportion of patients with public coverage for the drug:** The sponsor assumed that 60% of patients would be eligible for public coverage for eculizumab.
    - Based on input from the clinical experts, CADTH's base case considered a higher proportion of patients in the base case (66%) receiving coverage through public sources. The values 50% and 100% were also explored in sensitivity analyses.
- **Inaccurate representation of treatment course in year 1:** The sponsor assumed that patients on eculizumab would start their treatment, on average, halfway through the year and would therefore require 11 maintenance doses in the first year after induction, instead of the full 24 maintenance doses required in years 2 and 3. This assumption was not considered appropriate.
    - As part of the BIA base case, CADTH assumed that patients in year 1 would incur the full costs associated with 24 maintenance doses of eculizumab.
- **Lifelong prescription of eculizumab:** The clinical experts consulted by CADTH believed that, after two years of treatment with eculizumab, many gMG patients would likely discontinue the use of eculizumab and switch to treatment with SOC.
    - CADTH explored this through scenario analysis, with gMG patients discontinuing eculizumab after two years of treatment. The BIA model lacked sufficient flexibility to consider a proportion of patients returning to eculizumab; accordingly, this scenario analysis likely underestimates the true budgetary impact.
- **Rituximab omitted as a comparator:** Clinical experts suggested that, if rituximab were available, a large proportion of gMG patients could be successfully treated with that drug. A recent systematic review reported that a mean of 54% of AChR-antibody–positive patients experienced minimal manifestation status following treatment with rituximab, defined as having no symptoms or functional limitations of MG.[7] Thus, 46% of patients in this review were not successfully treated with rituximab and could be candidates for other therapies.
    - CADTH explored a scenario analysis in which 46% of the total eligible patient population with refractory AChR-antibody–positive gMG received eculizumab,

following an unsuccessful trial of rituximab. This analysis considered two timing conditions: one in which patients started eculizumab at the beginning of year 1 and one in which they started eculizumab six months later, after the cessation of rituximab.

CADTH Reanalyses of the Budget Impact Analysis

Based on the limitations identified, CADTH's base-case analysis included corrected values for the proportion of MG diagnosed, and the proportion seeking public drug coverage (Table 18).

Table 18: CADTH Revisions to the Submitted Budget Impact Analysis

Stepped Analysis	Sponsor's Value or Assumption	CADTH Value or Assumption
Changes to derive the CADTH base case		
1. Corrected proportion of MG cases diagnosed	75%	98%
2. Corrected proportion of patients seeking public drug coverage	60%	66%
3. Corrected duration of treatment in year 1	Patients in year 1 would start treatment halfway through the year and incur half of the costs	Patients in year 1 would incur the full costs of treatment
CADTH base case	–	Reanalyses 1 to 3

MG = myasthenia gravis.

The results of the CADTH stepwise reanalyses are presented in summary format in Table 19, and a more detailed breakdown is presented in Table 20. Based on the CADTH base case, the expected budget impact for adult patients with refractory gMG is expected to be $52,224,226 in year 1, $86,818,772 in year 2, and $110,357,145 in year 3, with a three-year budget impact of $249,200,143.

Scenario analyses were conducted using the CADTH base case, with the scenarios that only considered patients refractory to rituximab having the largest impact on results. If eculizumab was assumed to be started immediately in year 1, the total BIA was $115,564,638 over three years, but if it was assumed to be started only after six months of rituximab, the three-year BIA was $104,831,965. When applying an 88% price reduction (price where the ICER of eculizumab plus SOC was approximately $100,000 per QALY), the overall three-year budget impact was reduced to $29,973,028. With a 91% price reduction (price where ICER is approximately $50,000 per QALY) the three-year budget impact was further lowered to $22,492,558.

Table 19: Summary of the CADTH Reanalyses of the Budget Impact Assessment

Stepped Analysis	Three-Year Total
Submitted base case	$130,542,404
CADTH reanalysis 1: Corrected proportion of MG cases diagnosed	$169,733,115
CADTH reanalysis 2: Corrected proportion of patients seeking public drug coverage	$184,954,168
CADTH reanalysis 3: Corrected duration of treatment in year 1	$249,400,143
CADTH base case	**$249,400,143**

Table 20: Detailed Breakdown of the CADTH Reanalyses of the Budget Impact Analysis

Stepped Analysis	Scenario	Year 1	Year 2	Year 3	Three-Year Total
Submitted base case	Reference	$321,770	$325,196	$330,255	$977,221
	New drug	$20,500,744	$45,509,996	$65,508,885	$131,519,625
	Budget impact	***$20,178,974***	***$45,184,801***	***$65,178,630***	***$130,542,404***
CADTH base case	Reference	$463,182	$470,122	$475,182	$1,408,485
	New drug	$52,687,408	$87,288,894	$110,832,326	$250,808,628
	Budget impact	***$52,224,226***	***$86,818,772***	***$110,357,145***	***$249,400,143***
CADTH scenario analysis 1: 50% of patients treated and covered under public drug programs	Reference	$349,124	$352,506	$357,699	$1,059,329
	New drug	$40,274,516	$65,271,758	$85,227,064	$190,773,337
	Budget impact	***$39,925,391***	***$64,919,252***	***$84,869,365***	***$189,714,009***
CADTH scenario analysis 2: 100% of patients treated and covered under public drug programs	Reference	$698,816	$705,610	$715,786	$2,120,213
	New drug	$79,858,181	$129,802,773	$168,175,461	$377,836,416
	Budget impact	***$79,159,365***	***$129,097,163***	***$167,459,675***	***$375,716,203***
CADTH scenario analysis 3: Patients discontinue treatment with eculizumab after 2 years	Reference	$463,182	$470,122	$475,182	$1,408,485
	New drug	$52,687,408	$85,069,404	$62,764,598	$200,521,410
	Budget impact	***$52,224,226***	***$84,599,282***	***$62,289,417***	***$199,112,925***
CADTH scenario analysis 4a: Patients must be refractory to rituximab to be eligible for eculizumab	Reference	$213,459	$215,150	$218,518	$647,127
	New drug	$24,723,698	$38,717,060	$52,771,007	$116,211,765
	Budget impact	***$24,510,239***	***$38,501,910***	***$52,552,489***	***$115,564,638***
CADTH scenario analysis 4b: Patients must be refractory to rituximab to be eligible for eculizumab; eculizumab treatment starts after 6 months of rituximab treatment	Reference	$213,459	$215,150	$218,518	$647,127
	New drug	$13,991,025	$38,717,060	$52,771,007	$105,479,092
	Budget impact	***$13,777,566***	***$38,501,910***	***$52,552,489***	***$104,831,965***
CADTH scenario analysis 5a: 88% price reduction (ICER approximately $100,000/QALY)	Reference	$463,182	$470,122	$475,182	$1,408,485
	New drug	$6,739,196	$10,904,155	$13,738,162	$31,381,513
	Budget impact	***$6,276,014***	***$10,434,033***	***$13,262,981***	***$29,973,028***
CADTH scenario analysis 5b: 91% price reduction (ICER approximately $50,000/QALY)	Reference	$463,182	$470,122	$475,182	$1,408,485
	New drug	$5,172,780	$8,300,130	$10,428,134	$23,901,044
	Budget impact	***$4,709,598***	***$7,830,008***	***$9,952,952***	***$22,492,558***

ICER = incremental cost-effectiveness ratio; QALY = quality-adjusted life-year.

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