CADTH

CADTH COMMON DRUG REVIEW

# CADTH Canadian Drug Expert Committee Recommendation

(Final)

**ECULIZUMAB (SOLIRIS — ALEXION PHARMA CANADA CORP.)**
Indication: Adult patients with refractory generalized myasthenia gravis.

**RECOMMENDATION**
The CADTH Canadian Drug Expert Committee recommends that eculizumab be reimbursed for the treatment of adults with refractory generalized myasthenia gravis (gMG) only if the following conditions are met.

### Conditions for Reimbursement

**Initiation Criteria**
1. The patient has refractory gMG defined as not achieving symptom control after:
   - 1.1. an adequate trial of two or more immunosuppressive therapies (ISTs), either in combination or as monotherapy in the previous 12 months, OR
   - 1.2. an adequate trial of at least one IST and chronic plasmapheresis or plasma exchange or intravenous immunoglobulin at least four times (every three months) in the previous 12 months.
2. The patient has all of the following:
   - 2.1. positive serologic test for anti-acetylcholine receptor antibodies
   - 2.2. a Myasthenia Gravis Activities of Daily Living (MG-ADL) score at baseline of six or higher
   - 2.3. Myasthenia Gravis Foundation of America class II to IV disease.
3. The patient does not have a thymoma or is within 12 months of thymectomy.
4. Eculizumab should not be initiated during a gMG exacerbation or crisis.
5. MG-ADL score and Quantitative Myasthenia Gravis (QMG) score must be measured and provided by the physician at baseline.
6. Maximum duration of initial authorization is six months.

**Renewal Criteria**
1. First six months renewal: reimbursement of treatment with eculizumab should continue if, after the initial six months of treatment, there is a documented improvement in the MG-ADL of three points or greater and in the QMG of five points or greater (without an increase in corticosteroid or IST dosage). Reassessment should occur every six months thereafter.
2. Subsequent six-month renewals: no worsening of MG-ADL and QMG scores.

**Discontinuation Criteria**
1. Reimbursement of treatment with eculizumab should be discontinued if any of the following occur:
   - 1.1. failure to achieve a reduction in MG-ADL score of three or more points and in QMG score of five or more points at six months, OR
   - 1.2. worsening of gMG symptoms as compared with baseline requiring intervention (i.e., hospitalization for MG-related reasons, including MG crisis; respiratory failure with or without oropharyngeal muscle weakness; increased need for intravenous immunoglobulin, plasma exchange, or other medications for gMG), OR
   - 1.3. a serious adverse event related to eculizumab or meningococcal infection.

**Prescribing Conditions**
1. Eculizumab should be prescribed by or in consultation with a neurologist with expertise in the diagnosis and management of gMG.
2. Eculizumab should not be used concomitantly with rituximab.

**Pricing Conditions**
A reduction in price.


Service Line: CADTH Drug Reimbursement Recommendation
Version: 1.0
Publication Date: October 2020
Report Length: 9 Pages

CADTH



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

CADTH

# ECULIZUMAB (SOLIRIS — ALEXION PHARMA CANADA CORP.)

Indication: Adult patients with refractory generalized myasthenia gravis.

## Recommendation

The CADTH Canadian Drug Expert Committee (CDEC) recommends that eculizumab be reimbursed for the treatment of adults with refractory generalized myasthenia gravis (gMG) only if the following conditions are met.

## Conditions for Reimbursement

**Initiation Criteria**

1. The patient has refractory gMG defined as not achieving symptom control after:
   - 1.1. an adequate trial of two or more immunosuppressive therapies (ISTs), either in combination or as monotherapy in the previous 12 months, OR
   - 1.2. an adequate trial of at least one IST and chronic plasmapheresis or plasma exchange (PLEX) or intravenous immunoglobulin (IVIg) at least four times (every three months) in the previous 12 months.
2. The patient has all of the following:
   - 2.1. positive serologic test for anti-acetylcholine receptor (AChR) antibodies
   - 2.2. a Myasthenia Gravis Activities of Daily Living (MG-ADL) score at baseline of six or higher
   - 2.3. Myasthenia Gravis Foundation of America (MGFA) class II to IV disease.
3. The patient does not have a thymoma or is within 12 months of thymectomy.
4. Eculizumab should not be initiated during a gMG exacerbation or crisis.
5. MG-ADL score and Quantitative Myasthenia Gravis (QMG) score must be measured and provided by the physician at baseline.
6. Maximum duration of initial authorization is six months.

**Renewal Criteria**

1. First six months renewal: reimbursement of treatment with eculizumab should continue if, after the initial six months of treatment, there is a documented improvement in the MG-ADL of three points or greater and in the QMG of five points or greater (without an increase in corticosteroid or IST dosage). Reassessment should occur every six months thereafter.
2. Subsequent six-month renewals: no worsening of MG-ADL and QMG scores.

**Discontinuation Criteria**

1. Reimbursement of treatment with eculizumab should be discontinued if any of the following occur:
   - 1.1. failure to achieve a reduction in MG-ADL score of three or more points and in QMG score of five or more points at six months, OR
   - 1.2. worsening of gMG symptoms as compared with baseline requiring intervention (i.e., hospitalization for MG-related reasons, including MG crisis; respiratory failure with or without oropharyngeal muscle weakness; increased need for IVIg, PLEX, or other medications for gMG), OR
   - 1.3. a serious adverse event related to eculizumab or meningococcal infection.

**Prescribing Conditions**

1. Eculizumab should be prescribed by or in consultation with a neurologist with expertise in the diagnosis and management of gMG.
2. Eculizumab should not be used concomitantly with rituximab.

**Pricing Conditions**

1. A reduction in price.

## Reasons for the Recommendation

1. One double-blind, randomized controlled trial (RCT) (REGAIN; N = 125) found that eculizumab improves activities of daily living and reduces disease severity in patients with refractory gMG who are positive for AChR antibodies versus placebo after six months of treatment. Although the REGAIN trial did not find a statistically significant difference between groups in the worst-rank analysis of the primary outcome, change from baseline activities of daily living measured by the MG-ADL; sensitivity analyses indicated that eculizumab provides a benefit over placebo for improving patients' ability to engage in their daily activities. Key secondary analyses showed that a greater proportion of patients who received eculizumab (60%) achieved an improvement of at least three points in MG-ADL score compared to those allocated to placebo (40%; between-group difference of 20.0%; 95% confidence interval [CI], 2.8% to 37.2%; P = 0.0229). A similar result was observed for the physician-reported QMG disease severity score, measured as the change from baseline (least squares [LS] mean difference of –16.0; 95% CI, –28.48 to –3.43; P = 0.0129) and the proportion of patients who achieved an improvement of at least five points in the QMG (difference in proportions of 26.2%; 95% CI, 10.4% to 41.8%; P = 0.0018). CDEC considered these results to be clinically meaningful based on the reported minimally important clinical difference of two points on the MG-ADL and approximately three points on the QMG. However, the effects of eculizumab on health-related quality of life (QoL) and exacerbations of MG are uncertain because of limitations associated with the analysis of these outcomes in the REGAIN trial. The sustainability of the treatment effect appears to be maintained beyond six months as suggested by an open-label extension study; however, the longer-term data are limited by its open-label and non-comparative study design.
2. CADTH's reanalyses of the sponsor's pharmacoeconomic model suggested that the incremental cost-effectiveness ratio (ICER) for eculizumab plus standard of care (SOC) is $1,505,712 per quality-adjusted life-year (QALY) compared to SOC alone. Therefore, eculizumab is not considered to be a cost-effective treatment option at the submitted price ($6,742 per 300 mg single-use vial for IV injection; annual cost of $728,136 per patient after the first year). A price reduction of 91% is required for eculizumab plus SOC to achieve an ICER below $50,000 per QALY gained.

## Implementation Considerations

- Determining whether a patient has had an adequate trial of ISTs, PLEX, and/or IVIg will require that the treating physician provide information regarding the therapies administered, their doses, and their durations of use. It is acknowledged that an adequate trial may include patients who have been initiated on the aforementioned therapies, but subsequently discontinued treatment due to intolerable side effects and/or a lack of efficacy.

## Discussion Points

- Refractory gMG is a rare and chronic condition with significant impacts on patient functioning. CDEC heard from patient and clinical expert input that patients with refractory gMG have few treatment options after SOC medications and that the use of chronic IVIg and PLEX are not effectively meeting treatment goals. CDEC concluded that the available evidence — which is limited to the refractory gMG patient population — supported the use of eculizumab in this population of patients.
- The REGAIN trial excluded patients who had a history of thymoma and who had had a thymectomy within 12 months prior to trial screening. These patients are not excluded from the Health Canada indication for eculizumab. CDEC heard input from clinical experts that these factors would not prevent them from prescribing eculizumab in clinical practice; however, the efficacy and harms of eculizumab in such patients are unknown.
- CDEC noted that patients in REGAIN had received corticosteroids (> 93%), azathioprine (approximately 75%), and mycophenolate (> 43%) as the primary ISTs tried before trial enrolment, which is consistent with clinical practice in Canada for the treatment of gMG.
- CDEC heard clinician input that rituximab is used, when accessible, in patients with refractory gMG who have failed on two or more ISTs. Patients were excluded from REGAIN if they had received rituximab within three months before screening and were not permitted to receive rituximab during the study. Only 11% of participants in REGAIN had previously received rituximab; therefore, the benefits, risks, and cost-effectiveness of eculizumab after a trial of rituximab in patients with refractory gMG is uncertain.
- CDEC heard clinician input that eculizumab would be used most often for patients who had tried a trial of PLEX or IVIg. The REGAIN trial did include this patient population. Subgroup analyses in this specific patient population were not available.

- The six-month duration of the initial authorization of reimbursement and the six-month assessments for renewal are based on the REGAIN trial, which utilized a six-month (26 week) period of time to assess benefit. Assessment at six months was confirmed as clinically appropriate by the clinical experts consulted.
- CDEC heard clinical expert input that if a patient has had stable gMG after two years of continuous treatment with eculizumab, prescribers should consider discontinuing treatment with eculizumab.
- Within the relatively small RCT (REGAIN) population, there were no serious indications of harm beyond those already identified in the product monograph for eculizumab. However, eculizumab has been associated with significant but rare harms in other populations, such as anemia, high blood pressure, and infections, particularly meningococcal infections. The product monograph for eculizumab recommends all patients be vaccinated with meningococcal vaccines prior to, or at the time of, initiating eculizumab.

## Background

Eculizumab is a monoclonal antibody that binds with high affinity to the complement protein C5, inhibiting its cleavage into C5a and C5b. It prevents the generation of complement complexes and ameliorates the destruction of the post-synaptic structure in patients with gMG. Eculizumab has a Health Canada indication for adults with gMG who are anti-AChR antibody positive and refractory (which is defined as failure of treatment with two or more ISTs, either in combination or as monotherapy) or who have failed at least one IST and require chronic plasmapheresis, PLEX, or IVIg to control symptoms.

Patients continued to receive standard therapy throughout the REGAIN trial.

Eculizumab is available as 30 mL parenteral solution (10 mg/mL) for slow IV injection (at a concentration of 5 mg/mL). The Health Canada–approved dosage is 900 mg weekly for the first four weeks followed by 1,200 mg for the fifth dose one week later, then 1,200 mg every two weeks thereafter.

## Submission History

Eculizumab has been previously reviewed by CADTH for:

- paroxysmal nocturnal hemoglobinuria, for which it received a recommendation of “do not list at the submitted price” (February 19, 2010)
- atypical hemolytic uremic syndrome, for which it received a recommendation of “do not list” (July 18, 2013)
- neuromyelitis optica spectrum disorder, for which it received a recommendation of “reimburse with criteria and conditions” (August 19, 2020).

## Summary of Evidence Considered by CDEC

CDEC considered the following information prepared by CADTH: a systematic review of one RCT of eculizumab, a review of supportive studies (a long-term extension study and a phase II study), and a critique of the sponsor’s pharmacoeconomic evaluation. CDEC also considered input from a panel of clinical experts with experience in treating patients with gMG, and patient group–submitted information about outcomes and issues important to patients.

### Summary of Patient Input

The Muscular Dystrophy Canada group provided input for this submission, for which it obtained perspectives via a survey of 120 patients with gMG and 70 caregivers of those with gMG. The following is a summary of key input from the perspective of the patient group(s):

- Patients describe how debilitating MG is — it is characterized by weakness and fatigue of muscles, including choking, slurred speech, impaired swallowing, and even breathing difficulties — and how it affects their daily lives, with more than 75% reporting debilitating chronic progression and 35% mentioning admission to the intensive care unit on at least one occasion.

- Almost half of the patients report trying several medications due to periods of ineffectiveness, noting that while their current medications can decrease exacerbations, they often have no impact on the intensity of the exacerbations, on their QoL, or on their ability to work. Also, they cite concerns about side effects (like nausea, fatigue, and diarrhea) from their current treatments, and worry about comorbidities and long-term effects when using corticosteroids.
- Patients and caregivers agreed that better treatment options are needed, especially those that could improve QoL, increase their independence in daily activities, decrease both the frequency and intensity of exacerbations, and offer fewer and shorter hospital admissions.

## Clinical Trials

The systematic review included one double-blind, placebo-controlled, 26-week RCT (the REGAIN study), which was conducted from 2014 to 2016 in 76 sites across 17 countries in North America (including three sites in Canada), Latin America, Europe, and Asia.

The trial randomized a total of 125 patients to receive eculizumab (N = 62) or placebo (N = 63). Patients randomized to eculizumab received the dosing regimen described in the product monograph. Randomization was 1:1 and was stratified by MGFA classification. Patients were enrolled if they were diagnosed with refractory gMG and were seropositive to AChR antibodies, had an MG-ADL score at baseline of six or greater, and MGFA class II to IV disease. “Refractory” was defined as patients who had received two or more ISTs, or at least one IST with IVIg or PLEX at least four times per year, for 12 months without symptom control. The study excluded patients with a history of thymoma or thymic neoplasms, thymectomy within 12 months before screening, use of IVIg or PLEX within four weeks before randomization, or use of rituximab within six months before screening. Although 57 and 61 patients completed the study in the intervention and placebo groups, respectively, all randomized patients were analyzed in the intention-to-treat and safety analyses.

The key limitation of the REGAIN study was that it failed to demonstrate a statistically significant difference between treatment groups in the primary end point (change from baseline to week 26 in MG-ADL total score) based on the worst-rank analysis of covariance (ANCOVA) approach. Sensitivity analyses based on the change from baseline in MG-ADL score and repeated measures methods demonstrated a statistically significant difference in favour of eculizumab for this outcome. Therefore, the primary outcome analysis was sensitive to the method of analysis and how administration of rescue therapy or study discontinuation were handled. And, as mentioned, the generalizability of the results of REGAIN are reduced because the trial excluded patients with a history or thymoma, those receiving thymectomy within 12 months of trial screening, and those receiving rituximab within three months of screening.

One open-label extension study (ECU-MG-302) was reviewed to evaluate the longer-term safety and efficacy of eculizumab. The study enrolled 117 patients who were eligible from the REGAIN study to continue receiving eculizumab or switch from placebo to eculizumab. A total of 87 patients (74.4%) completed the study, with 30 discontinuing the study drug, mostly due to “withdrawal by patient” and adverse events, while more than half of the patients had dropped out from the study by week 130.

A phase II, randomized, double-blind, placebo-controlled, crossover, pilot study including 14 patients with the same inclusion criteria as the REGAIN trial was also reviewed. The study aimed to evaluate the safety of eculizumab and the feasibility of the REGAIN study. The efficacy analysis of the pilot study was limited by the insufficient length of the washout period (five weeks). A carryover effect of the previous treatment was observed in both arms, as neither returned to their baseline QMG score after five weeks. Given the presence of carryover effects, efficacy results related to period 2 or combined period 1 and 2 are difficult to interpret. The dosage regimen specified in the pilot study differs from the current dosage regimen specified in the product monograph for eculizumab. This difference in dosage limits the ability to generalize findings of the pilot study to the clinical population that would be treated with the drug. No concrete conclusions could be drawn from the results of this study.

## Outcomes

Outcomes were defined a priori in CADTH’s systematic review protocol. Of these, CDEC discussed the following:

- activities of daily living (measured with MG-ADL score)
- hospital admission (including intensive care unit admission due to MG exacerbation or crisis)
- disease severity (measured with QMG and Myasthenia Gravis Composite scores)

- dose reduction and number of existing medications
- need for rescue therapy
- health-related QoL (measured using the Myasthenia Gravis Quality of Life 15-item scale, the Quality of Life in Neurological Disorders-Fatigue scale, and EuroQoL 5-Dimensions scale)
- harms outcomes.

## Efficacy

The REGAIN study showed no statistically significant difference in its primary outcome, the change from baseline to week 26 in MG-ADL score between eculizumab and placebo (LS mean worst-rank treatment difference = −11.7; 95% CI, −24.3 to 0.96; P = 0.0698). When measuring the proportion of patients reaching an improvement of a three-point reduction in MG-ADL score (where experts consider a two-point reduction from baseline a meaningful clinical difference), 59.7% of patients in the eculizumab group versus 39.7% in the placebo group improved by at least three points, a difference of 20.0% (95% CI, 2.8 to 37.2; P = 0.0229). The differences from baseline in the actual scores of the MG-ADL reached statistical significance in the ANCOVA sensitivity analysis, with a difference in LS mean of −1.4 (95% CI, 2.77 to −0.07; P = 0.039).

For disease severity, the QMG worst-rank score was improved in the eculizumab group versus in the placebo group (LS mean rank-based treatment difference = −16.0; 95% CI −28.48 to −3.43; P = 0.0129). The proportion of patients with at least a five-point reduction in QMG score was 45.2% of patients in the eculizumab group versus 19.0% of patients in the placebo group, a difference in proportions of 26.2% (95% CI, 10.4 to 41.8; P = 0.0018).

MG exacerbations were reported by six patients (10%) in the eculizumab group and 15 patients (24%) in the placebo group. Six patients (10%) in the eculizumab group and 12 (19%) in the placebo group required rescue therapy. Also, fewer patients in the eculizumab group (9 [14.5%]) required hospitalizations as compared to those in the placebo group (18 [28.6%]). These data, however, were not compared statistically.

Although QoL measures (e.g., Myasthenia Gravis Quality of Life 15-item scale total score) showed greater improvements in the eculizumab group than in the placebo group, the results were not interpretable based on a higher-order comparison for the Myasthenia Gravis Composite score not being statistically significant per the pre-specified hierarchical analysis plan.

Throughout three years of follow-up, the open-label long-term extension study showed continued improvements with eculizumab from those observed in the REGAIN study in activities of daily living, muscle strength, functional ability, and QoL.

## Harms (Safety)

Adverse events occurred similarly in patients in the eculizumab group (85.5%) and placebo group (88.9%) in REGAIN. Serious adverse events were more frequently reported in patients treated with placebo (28.5%) than those treated with eculizumab (14.5%). [redacted] Notably, three patients died during the long-term study, one due to pulmonary embolism, another due to liver cirrhosis, and the third due to a lymphohistiocytosis associated with cytomegalovirus, though none of the deaths were reported as related to eculizumab or MG.

The most common adverse events in the REGAIN study were headache and upper respiratory tract infection (10 [16%] for both events in the eculizumab group and 12 [19%] in the placebo group). No deaths or cases of meningococcal infection occurred during the study. No difference in the number of serious infections were noted.

## Cost and Cost-Effectiveness

At the sponsor's submitted price of $6,742 per 300 mg vial, the annual cost of eculizumab is $728,136 per patient in the first year, and $701,168 per year thereafter.

The sponsor submitted a cost-utility analysis comparing eculizumab plus SOC (consisting of monotherapy or combinations of azathioprine, mycophenolate mofetil, cyclosporine, tacrolimus, methotrexate, cyclophosphamide, dexamethasone, prednisone, or pyridostigmine) with SOC alone in adults with treatment-refractory AChR-positive gMG. The analysis was conducted from the

perspective of a Canadian publicly funded health care payer over a lifetime time horizon (52.5 years). The sponsor's economic evaluation was structured as a Markov cohort model, consisting of an initial refractory gMG score; health states defined by change in MG-ADL score after six months of therapy; short-term exacerbation or myasthenic crisis states; and death. Patients could experience adverse events during the initial six months of treatment. Those who did not respond to eculizumab (defined as an improvement in MG-ADL score of at least three points) discontinued eculizumab therapy and continued with SOC alone. Patients also discontinued eculizumab at a rate of 7.7% of the original total per six-month cycle thereafter. Exacerbations and myasthenic crises were associated with hospital resource use and health-state disutilities. Myasthenic crisis were associated with a 12% risk of death. Apart from during myasthenic crises, patients otherwise had the same mortality as the age- and gender-matched general population. In the sponsor's base case, the ICER associated with eculizumab plus SOC was $1,329,219 per QALY gained compared to SOC alone.

CADTH identified several key limitations with the submitted analysis:

- Rituximab was not included as a comparator. A panel of clinical experts consulted by CADTH for this review indicated that rituximab is used in clinical 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 experts' understanding of gMG. The sponsor assumed a decline in MG-ADL score over time for patients receiving 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 shorter term for many patients.
- The indicated population was not fully represented by the population studied in the REGAIN trial. Patients were excluded from REGAIN if they had had a thymectomy within 12 months prior to screening, were in myasthenic crisis, or had received IVIg or PLEX within four weeks or rituximab within six months before randomization. However, clinical experts believed that these patients would likely still receive eculizumab in clinical practice. The effect that this exclusion may have on incremental effectiveness is unknown.
- Not all relevant costs, such as outpatient administration and meningococcal vaccinations, were captured in the sponsor's base-case analysis.
- 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 revised the sponsor's analysis by removing the MG-ADL score decline for SOC; reducing mortality associated with myasthenic crisis; adjusting routine follow-up costs; adding administration and vaccination costs; and adding probabilistic variation to certain model parameters. CADTH estimated the ICER to be $1,505,712 per QALY compared to SOC alone. Use of eculizumab had a 0% probability of cost-effectiveness at thresholds of $50,000 and $100,000 per QALY gained. A price reduction of 91% would be required to achieve an ICER below $50,000 per QALY gained.

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 about the natural history of gMG and the anticipated use of eculizumab; these introduce structural and parameter uncertainties that impact 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.

## CDEC Members

Dr. James Silvius (Chair), Dr. Ahmed Bayoumi, Ms. Sally Bean, Dr. Bruce Carleton, Dr. Alun Edwards, Mr. Bob Gagne, Dr. Ran Goldman, Dr. Allan Grill, Mr. Allen Lefebvre, Ms. Heather Neville, Dr. Rakesh Patel, Dr. Danyaal Raza, Dr. Emily Reynen, Dr. Yvonne Shevchuk, and Dr. Adil Virani.

## August 19, 2020 Meeting

## Regrets

One CDEC member did not attend.

## Conflicts of Interest

None