CADTH

CADTH COMMON DRUG REVIEW

CADTH Canadian Drug Expert Committee Recommendation

(Final)

ECULIZUMAB (SOLIRIS — ALEXION PHARMA CANADA CORP.)

Indication: The treatment of neuromyelitis optica spectrum disorder (NMOSD).

RECOMMENDATION
The CADTH Canadian Drug Expert Committee recommends that eculizumab be reimbursed for the treatment of NMOSD in adult patients who are anti-aquaporin-4 antibody positive only if the following conditions are met.

Conditions for Reimbursement
Initiation criteria
1. The patient must have had at least two relapses of NMOSD in the previous 12 months or three relapses in the previous 24 months with at least one relapse in the last 12 months prior to initiation of treatment
   1.1. despite an adequate trial of other accessible preventive treatments for NMOSD, or
   1.2. the patient cannot tolerate other preventive treatments for NMOSD.
2. Patients must have an Expanded Disability Status Scale (EDSS) score of seven points or less.
3. Eculizumab should not be initiated during a NMOSD relapse episode.
4. The maximum duration of initial authorization is 12 months.

Renewal criteria
EDSS scores should be measured and provided by the physician every six months after the initial authorization to determine continuation of reimbursement of eculizumab.

Discontinuation criteria
Reimbursement of eculizumab treatment should be discontinued if the patient's EDSS score is eight points or greater.

Prescribing conditions
The prescribing of eculizumab for the treatment of NMOSD should be restricted to a neurologist with expertise in treating NMOSD.

Pricing conditions
A reduction in price.

Service Line: CADTH Drug Reimbursement Recommendation
Version: Final
Publication Date: August 24, 2020
Report Length: 9 Pages

CADTH

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

ECULIZUMAB (SOLIRIS — ALEXION PHARMA CANADA CORP.)

Indication: The treatment of neuromyelitis optica spectrum disorder (NMOSD)

Recommendation

The CADTH Canadian Drug Expert Committee (CDEC) recommends that eculizumab be reimbursed for the treatment of NMOSD in adult patients who are anti-aquaporin-4 (AQP4) antibody positive only if the following conditions are met.

Conditions for Reimbursement

Initiation criteria

1. The patient must have had at least two relapses of NMOSD in the previous 12 months or three relapses in the previous 24 months with at least one relapse in the last 12 months that occurred before the initiation of treatment
   1.1. despite an adequate trial of other accessible preventive treatments for NMOSD
   1.2. the patient cannot tolerate other preventive treatments for NMOSD.
2. Patients must have an Expanded Disability Status Scale (EDSS) score of seven points or less.
3. Eculizumab should not be initiated during a NMOSD relapse episode.
4. The maximum duration of initial authorization is 12 months.

Renewal criteria

The physician should measure and provide EDSS scores every six months after the initial authorization to determine if the continuation of eculizumab reimbursement should occur.

Discontinuation criteria

Reimbursement of eculizumab treatment should be discontinued if the patient's EDSS score is eight points or greater.

Prescribing conditions

The prescribing of eculizumab for the treatment of NMOSD should be restricted to a neurologist with expertise in treating NMOSD.

Pricing conditions

A reduction in price.

Reasons for the Recommendation

1. One double-blind, randomized controlled trial (RCT) (PREVENT; N = 143) demonstrated that eculizumab, compared with placebo, resulted in a statistically significant reduction in the risk of adjudicated on-trial relapse in a carefully selected population of patients with NMOSD who were anti-AQP4 antibody positive (hazard ratio of 0.058; 95% CI, 0.017 to 0.197; P < 0.0001). The magnitude of the treatment effect with eculizumab in reducing the risk of relapse appears to be clinically meaningful based on input from clinicians with expertise in the management of NMOSD.
2. The inclusion criteria for PREVENT required patients to have an EDSS score less than seven points and to have had at least two relapses of NMOSD in the last 12 months, or three relapses in the last 24 months with at least one relapse in the last 12 months before study enrolment. As well, greater than 90% of patients enrolled in PREVENT had received corticosteroids and other immunosuppressive therapies (ISTs) before randomization, and approximately 78% of patients treated with eculizumab were receiving background corticosteroids, azathioprine, mycophenolate, or other ISTs during the trial. Therefore, CDEC considered the evidence primarily supports using eculizumab after currently available therapies have not been effective in preventing relapses of NMOSD.
3. 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 $1,508,152 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 $701,168 per patient after the first year). A price reduction of 96% is required for eculizumab plus SoC to achieve an ICER below $50,000 per QALY gained.

Discussion Points

- Patient group input to CADTH identified an unmet need in the treatment of NMOSD that, CDEC concluded, could potentially be met by eculizumab.
- Although the results of the adjudicated primary outcome were robust for the determination of relapse by the treating physician and for post-hoc analyses treating discontinuations as failures in the eculizumab arm, the magnitude of the treatment effect was lower with the alternative analysis approaches. Therefore, the treatment effect of eculizumab may be smaller than that observed with the adjudicated on-trial relapse assessment in PREVENT.
- The effect of eculizumab on disability, as measured by change in EDSS score, is uncertain as the P value did not meet conventional levels of statistical significance (P = 0.0597). Likewise, the effects of eculizumab on health-related quality of life and symptom measures are also uncertain because these tests were conducted in violation of the pre-specified statistical testing hierarchy.
- The PREVENT study did not apply defined study treatment discontinuation criteria. CDEC heard from clinical experts that preventive treatment for relapse is of limited clinical benefit when patients are severely disabled, corresponding to an EDSS score of eight or more points.
- Patients were excluded if they had used rituximab three months before screening and were not permitted to use rituximab during the study. CDEC heard clinician input that rituximab is potentially used as a first-line therapy for the prevention of relapses in NMOSD. Therefore, the generalizability of results of PREVENT among patients with a recent history of use of rituximab is uncertain.
- Patients had a mean annualized relapse rate (ARR) of 1.99 (standard deviation 0.94) in the 24 months before screening for the study, with optic neuritis in 56%, transverse myelitis in 81%, brainstem symptoms in 23%, and cerebral symptoms in 10%.
- The trial was also limited by unexplained differential dropout (16.7% with eculizumab versus 6.4% with placebo) and by many major protocol violations (approximately 40% of patients per treatment group). Although the effect of the protocol violations on the estimate of study outcomes is difficult to ascertain, the large number suggests the potential for some concerns with overall study quality.
- A longer-term extension study was limited by its open-label and observational design but suggested continuing benefit regarding fewer relapses over several years with eculizumab treatment.
- Within this relatively small RCT, 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 has a Health Canada indication for the treatment of NMOSD in adult patients who are anti-AQP4 antibody positive. Eculizumab is not intended for acute treatment of an NMOSD relapse. Eculizumab is a monoclonal antibody. It is available as a 30 mL parenteral solution (10 mg/mL) for IV injection and the Health Canada–approved dose is 900 mg weekly for the first 4 weeks, followed by 1,200 mg for the fifth dose 1 week later, then 1,200 mg every two weeks thereafter.

Submission History

Eculizumab was previously reviewed for the treatment of atypical hemolytic uremic syndrome and paroxysmal nocturnal hemoglobinuria and both received a recommendation of do not list (July 18, 2013 and February 18, 2010, respectively).

Summary of Evidence Considered by CDEC

CDEC considered the following information prepared by CADTH: a systematic review that included a single RCT (and the extension study) of eculizumab and a critique of the sponsor's pharmacoeconomic evaluation. The committee also considered input from clinical experts with experience in treating patients with NMOSD, and patient group–submitted information about outcomes and issues important to patients.

Summary of Patient Input

One patient group, The Multiple Sclerosis Society, provided input for this submission. Patient perspectives were obtained from an online survey conducted in early 2020 that received 11 responses from patients and caregivers. The following is a summary of key input from the perspective of the patient group:

- Patients with NMOSD and those affected by it described the significant impact of living with NMOSD and the debilitating nature of the damage caused by attacks. The impact on their vision and mobility can lead to disability and effect all areas of a person's life including employment, family income, increased need for assistance or caregiving, loss of independence, isolation, cognitive decline, and increased mobility challenges.
- In the absence of an approved treatment for NMOSD, many patients report using off-label drugs such as azathioprine and rituximab.
- Patients reported that they have tried other treatments including naturopathic treatments, natural supplements, acupuncture, cupping, and chiropractic adjustments because they felt they were out of options.
- In their hopes for new therapies patients put a high priority on the reduction or avoidance of diseases attacks and the consequent accrued disability from the attacks.

Clinical Trials

The systematic review included one multicenter, double-blind, RCT in patients 18 years of age and older with a diagnosis of neuromyelitis optica or NMOSD. Patients in PREVENT (N = 143) were randomized 2:1 to receive eculizumab (900 mg weekly for the first four doses starting on day 1, followed by 1,200 mg every two weeks starting at week four) or placebo.

Key limitations of PREVENT were the disproportionately higher percentage of patients who discontinued treatment prematurely in the eculizumab group (16.7%) compared with the placebo group (6.4%), a large number of major protocol violations (39% in the eculizumab group, 43% in the placebo group), the likely underestimation of the ARR in both treatment groups related to censoring of patients after the primary outcome event (relapses after the first relapse), limited efficacy assessments based on clinically relevant subgroups, and inability to interpret findings related to functional status and health-related quality of life because the hierarchical statistical analysis failed at a higher order comparison.

No active comparator trials were identified for inclusion in the review.

Outcomes

Outcomes were defined a priori in CADTH's systematic review protocol. Of these, CDEC discussed the following: time-to-first adjudicated on-trial relapse, adjudicated on-trial ARR, EDSS, EQ-5D-3L, and SF-36, modified Rankin score (mRS), and Hauser Ambulation Index (HAI) score. Productivity (e.g., the ability to attend school, work) was an outcome identified in the review protocol as important to patients but was not assessed in PREVENT.

The primary efficacy outcome in PREVENT was time-to-first adjudicated on-trial relapse. On-trial relapse was defined as a new onset of neurologic symptoms or worsening of existing neurologic symptoms with an objective change (clinical sign) on the neurologic examination that persists for more than 24 hours. The signs and symptoms had to be attributed to NMOSD. The relapse had to be preceded by at least 30 days of clinical stability. Adjudicated on-trial relapse rate was computed for each group of patients based on the total number of relapses divided by the person-time in years. Adjudication of on-trial relapses was based on consensus of an independent relapse adjudication committee consisting of two neurologists and one neuro-ophthalmologist. The adjudication

committee was blinded to treatment group and reviewed all cases of attending physician-determined relapses and possible relapses (cases of interest) retrospectively using the same criteria as the attending physician.

Symptoms and disability were measured with EDSS, mRS, and HAI. The EDSS assesses disability through the eight Kurtzke functional systems (pyramidal, cerebellar, brainstem, sensory, bowel and bladder, visual, cerebral, other) and ambulation. The EDSS is an ordinal clinical rating scale that ranges from 0 (normal neurologic examination) to 10 (death) in half-point increments. Validity of the EDSS has been established and it is used as gold standard for evaluating new scales. No minimal important difference (MID) specific for NMOSD was found. Indirect estimates can be obtained from patients with multiple sclerosis where one study found that a change of 1.5 points as a single score was considered enough deterioration from the patient perspective. The mRS is a generic, clinician-reported scale for measuring the degree of disability or dependence in the daily activities of people who have suffered from a neurological disability. The scale ranges from 0 (no disability) to 6 (death). A MID was not identified in the literature for patients with NMOSD. The HAI evaluates gait and is used to assess the time and effort used by the patient to walk eight metres (26 feet). The scale ranges from 0 to 9, with 0 being the best score (asymptomatic; fully ambulatory with no assistance) and 9 being the worst (restricted to wheelchair; unable to transfer self independently). No MID studies were found for patients with NMOSD.

HRQoL was assessed using the EuroQol 5-Dimensions 5-Levels (EQ-5D-3L) questionnaire and the Short Form (36) Health Survey (SF-36). No studies assessing the validity or reliability of the scales were found in the literature for patients with NMOSD; although both have been validated in patients with multiple sclerosis. A MID was not identified in the literature for patients with NMOSD.

Efficacy

In PREVENT, treatment with eculizumab showed a statistically significant reduction in the risk of an adjudicated on-trial relapse compared to placebo (HR = 0.058; 95% CI, 0.017 to 0.197; P < 0.0001), representing 94.2% risk reduction (95% CI, 80.3 to 98.3%), in favour of eculizumab. The magnitude of the treatment effect with eculizumab was attenuated when the impact of a higher proportion of patients prematurely withdrawing from the study in the eculizumab group (16.7%) compared with the placebo group (6.4%) was accounted for (post-hoc sensitivity analysis: HR = 0.297; 95% CI, 0.154 to 0.572; P = 0.0001), or when the assessment of relapse was performed by the treating physician instead of being centrally adjudicated (HR = 0.180; 95% CI, 0.095 to 0.343; P < 0.0001).

Similarly, the adjusted adjudicated on-trial ARR ratio showed statistically and clinically significant results (ARR = 0.045; 95% CI, 0.013 to 0.151; P < 0.0001), representing a 95.5% reduction in ARR (95% CI, 84.9% to 98.7%). Exploratory analysis suggested that treatment with eculizumab was associated with less severe relapses than treatment with placebo.

Subgroup analyses were generally considered descriptive; the analyses were limited by small sample sizes and limitations in defining the subgroups which prevented drawing statistical inferences.

The change from baseline in EDSS was –0.18 (SD = 0.814) for the eculizumab arm and 0.12 (SD = 0.945) for the placebo arm, P = 0.0597. Because the difference between treatment groups on the EDSS was not statistically significant, statistical inferences could not be made on the subsequent outcomes tested in the hierarchical analysis procedure, change from baseline in mRS score, change from baseline in HAI score, and change from baseline in the EQ-5D-3L questionnaire. Likewise, outcomes tested outside of the hierarchical testing procedure (such as SF-36) were considered descriptive because of the risk of inflated type I error.

The ongoing, open-label, long-term extension study suggested that the reduced risk of relapses of NMOSD was maintained over a longer period of time. However, the results of this study are not confirmatory of long-term benefit with eculizumab because of the design (open label, no comparator, before and after observational), and risk for selection bias due to the inclusion of a relatively small number of patients from PREVENT up until the cut-off date of the interim analysis.

Harms (Safety)

Adverse events occurred similarly in patients in the eculizumab group (91.7%) and placebo group (95.7%) in PREVENT. Serious adverse events were more frequently reported in patients treated with placebo (55.3%) than in the eculizumab group (31.3%); however, the difference in events was largely eliminated when worsening of NMOSD was excluded.

Notable harms identified in the protocol for this review included the following: serious infusion reactions, serious infections (e.g., meningococcal and respiratory), hemolysis/low hemoglobin. Infusion reactions occurred in 6.3% of patients in the eculizumab

arm and 4.3% of patients in the placebo arm. No cases of meningococcal infections were reported in PREVENT. Respiratory-related serious infections occurred similarly between treatment arms. In PREVENT, one patient in the eculizumab arm died during the trial. The death of this patient was attributed to infectious pleural effusion and was considered by the investigator to be "probably related to the study drug."

Overall, PREVENT did not find any new safety concerns beyond those identified in trials for other indications for eculizumab, and from those described in the product monograph for eculizumab. However, it should be noted that the sample size in PREVENT was relatively small with only 96 patients in the eculizumab group. The occurrence and frequency of adverse events in the longer-term extension study were similar to those in the main PREVENT study. However, the absence of a comparator group in the extension study makes it difficult to interpret the findings.

The comparative safety of eculizumab to other treatments for NMOSD could not be assessed based on the use of a placebo comparator in PREVENT and the absence of relevant indirect treatment comparisons.

Cost and Cost-Effectiveness

At the sponsor's submitted price of $6,742 per 300 mg vial, the annual cost of eculizumab was $728,136 in the first year and $701,168 thereafter, based on the recommended dosage for NMOSD.

The sponsor submitted a cost-utility analysis comparing eculizumab plus SoC (a stable dose of ISTs and/or other concomitant medications such as corticosteroids, azathioprine, mycophenolate mofetil, methotrexate, tacrolimus, cyclosporine, or cyclophosphamide either in combination or monotherapy) with SoC alone for the treatment of adult patients with NMOSD who are anti-AQP4 antibody positive. The analysis was conducted from the perspective of the Canadian publicly funded health care system over a lifetime time horizon (defined as 65 years). A Markov model state transition model captured long-term costs and effects of a relapsing disease course that may result in long-term disability. The model included four unique health states (i.e., relapse-free, relapse, long-term disability [defined as being unable to walk without assistance and/or being functionally blind in at least one eye], and death). Patients with NMOSD and no presence of long-term disability entered the model in the relapse-free health state and could remain relapse-free or transition to either a relapse health state or death. Up to 10 relapses were permitted in the model and, with every subsequent relapse, patients were assumed to be at an increased risk of experiencing long-term disability or dying; thereby, entering the long-term disability or death health state respectively. If a patient entered long-term disability, they remained there until death and no further relapse recurrence was tracked. The sponsor assumed patients would stop eculizumab upon experiencing their first relapse event, and that, for those who discontinued treatment due to relapse, they would be managed with SoC. Comparative efficacy was estimated from time-to-relapse data for eculizumab and SoC as reported in the PREVENT trial, based on the eculizumab and placebo arms, respectively. Health state utility values associated with the relapse-free and relapse health states were derived using a mixed-effect regression model based on the EQ-5D-3L data collected in PREVENT and its extension study. In the sponsor's base case, the ICER for eculizumab was $1,382,186 per QALY gained compared to SoC alone.

CADTH identified several key limitations with the submitted analysis:

- The generalizability and validity of the comparative clinical efficacy is uncertain. The PREVENT trial recruited a highly active disease population more likely to experience a relapse. The relapse definition used in the model was based on adjudication by an independent committee, which likely does not reflect how the drug will be administered in Canadian practice settings.
- Long-term survival and quality of life was based on extrapolation. The exponential distribution used to model time-to-first relapse and time to subsequent relapses lacked face validity. Extrapolated outcomes could not be validated due to the lack of comparative clinical data and the majority (99%) of the incremental benefit occurred in the extrapolated period.
- Treatment discontinued after the first relapse, which did not reflect clinical management of eculizumab expected in practice according to the clinical experts consulted.
- The long-term disability health state combined patients with either a one or both disabilities (i.e., vision and/or mobility); thereby implicitly assuming no differences in costs and quality of life between these groups. No further relapse was modelled thereafter, which is not reflective of the natural history of the condition.
- Health state utility values may underestimate the impact of relapse on patients' health-related quality of life.

- All relevant costs were not captured under the public health care payer perspective and the model assumptions of drug administration may not reflect how eculizumab would be administered in the Canadian setting.

CADTH attempted to address the identified limitations by: switching the relapse definition to "all on-trial relapse;" selecting the gamma distribution to extrapolate time-to-first relapse; allowing patients to remain on treatment with eculizumab over their lifetime; incorporating both vaccination and drug administration costs; and, assuming eculizumab would only be administered in outpatient clinics. In the CADTH base case, the ICER for eculizumab plus SoC was $1,508,152 per QALY compared to SoC alone ($15,569,618 incremental costs and 10.32 incremental QALYs). A price reduction on eculizumab of 96% would be required to achieve an ICER below a willingness-to-pay threshold of $50,000 per QALY.

The results of CADTH's reanalysis are highly dependent on the treatment effects of eculizumab plus SoC compared to SoC alone; in which several limitations associated with the PREVENT trial could not be assessed in reanalyses. Results warrant careful interpretation since 99% of the incremental benefit for eculizumab plus SoC were accrued in time points beyond which clinical data were available. The cost-effectiveness of eculizumab compared to rituximab, mitoxantrone, or IV immunoglobulin G is unknown.

CDEC Members

Dr. James Silvius (Chair), Dr. Ahmed Bayoumi, 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.

July 15, 2020 Meeting

Regrets

One CDEC member did not attend

Conflicts of Interest

None