CEDAC FINAL RECOMMENDATION

ECULIZUMAB
(Soliris – Alexion Pharmaceuticals, Inc.)
Indication: Paroxysmal Nocturnal Hemoglobinuria

Recommendation:
The Canadian Expert Drug Advisory Committee (CEDAC) recommends that eculizumab not be listed at the submitted price.

Reason for the Recommendation:
In the one double-blind randomized controlled trial included in the CDR systematic review, a clinically and statistically significant reduction in hemolysis was observed for eculizumab compared with placebo. The cost of eculizumab is exceptionally high at over $500,000 per year. Eculizumab would not be considered cost-effective without a substantial reduction in the submitted price. The CDR estimated an incremental cost per quality-adjusted life-year of $2.4 million for eculizumab plus supportive care compared with supportive care alone based on 26 week trial data where quality of life benefits for a lifetime condition may not have been fully captured.

Of Note:
Using conventional criteria, eculizumab has not been shown to be cost-effective, though cost-effectiveness is only one factor that is used by drug plans in making funding decisions. It has been argued that the costs of drugs to treat rare diseases are often high because of the relatively small number of patients for whom the drug is indicated.

Background:
Eculizumab has a Health Canada indication for the treatment of patients with paroxysmal nocturnal hemoglobinuria (PNH) to reduce hemolysis. It is a monoclonal antibody that binds to complement protein C5, thereby inhibiting terminal complement-mediated intravascular hemolysis.

The Health Canada recommended dose of eculizumab is 600 mg given intravenously (IV) once weekly for four weeks, then 900 mg IV at week five, followed by 900 mg IV every 14 days as a maintenance dose. It is supplied as a 300 mg single-use vial containing 10 mg/mL of preservative-free eculizumab solution for intravenous infusion.

Patients with PNH have a genetic mutation that results in the lack of expression of glycosylphosphatidylinositol (GPI) anchor proteins on blood cells. This leads to the clonal expansion of abnormal blood cells that are susceptible to terminal complement-mediated destruction, leading to intravascular hemolysis. These blood cells, or clones, are categorized as normal (type I), partially GPI-deficient (type II), and completely GPI-deficient (type III). PNH is a non-malignant condition and may result in shortened survival and significant morbidity, including thrombosis, cytopenias, end-organ damage, reduced quality of life, and fatigue. Therapeutic management primarily consists of supportive care, which includes blood transfusions and medications, such as anticoagulants, corticosteroids, and immunosuppressants. Bone marrow transplantation may also be considered a treatment option for some patients. Eculizumab therapy would be continued long term.

Summary of CEDAC Considerations:
The Committee considered the following information prepared by the Common Drug Review (CDR): a systematic review of randomized controlled trials (RCTs) and open-label, non-randomized studies of eculizumab that included 10 or more patients as well as an assessment of manufacturer-provided pharmacoeconomic information. A priority review of this submission was requested by the manufacturer and granted by CDR.

Clinical Trials
The CDR systematic review included one manufacturer-sponsored, double-blind RCT, and three open-label non-randomized manufacturer-sponsored trials of eculizumab. The Committee's discussion focused on the results from the RCT.

The double-blind RCT, TRIUMPH (N = 87), evaluated the efficacy of eculizumab compared with placebo given for 26 weeks to patients with PNH. Eculizumab was administered IV with an induction dose of 600 mg every seven days for four weeks, then a 900 mg dose seven days later on week five, followed by 900 mg every 14 days thereafter.

TRIUMPH included patients who had required four or more transfusions in the 12 months prior to study enrolment, and a minimum platelet count of ≥ 100,000 cells/mm^3. Patients were stratified by the number of transfusions required at baseline. Patients were required to be vaccinated with *Neisseria meningitidis* vaccine at least 14 days before initiating eculizumab. Stable doses of concomitant medications were allowed (anticoagulants, systemic corticosteroids, androgen steroids, immunosuppressants, erythropoietin, and iron and folate supplements). Because changes in medications were not permitted, the impact of eculizumab on supportive therapy is unknown. Study withdrawals were low, with 98% (85 of 87) of patients completing the study.

The three non-randomized studies were all open-label prospective, manufacturer-sponsored trials:

- The SHEPHERD study (N = 97) was a multinational before and after long-term safety study evaluating eculizumab over 52 weeks. SHEPHERD included a broader population of patients with PNH compared with TRIUMPH, including patients with minimal transfusion requirements and those with thrombocytopenia.
- Study C02-001 (N = 11) examined the tolerability, efficacy, pharmacokinetics, and pharmacodynamics of eculizumab. Patients who completed the initial 12-week treatment were eligible for subsequent extension phases up to 104 weeks.

- Study C07-001 (N = 29) is an unpublished study evaluating eculizumab over 12 weeks in Japanese patients with PNH. The inclusion criteria were similar to those of the SHEPHERD trial.

Open-label extension phases of these studies were also reviewed, including Study E05-001 (N = 195, up to 104 weeks), which evaluated the long-term harms of eculizumab in patients with PNH who participated in TRIUMPH, SHEPHERD, and Study C02-001.

The proportion of type III red blood cell clones in patients at baseline was generally greater than 30% in all four studies. The median proportion in TRIUMPH was 28.9% and 32.9% in eculizumab and placebo groups respectively. In the non-randomized studies, the median proportion ranged from 33.5% to 39.2%.

Outcomes

The two primary outcomes of the TRIUMPH study were the stabilization of hemoglobin levels (defined as a hemoglobin value maintained above the level at which transfusion was required) and the number of packed red blood cell units transfused during the 26-week study period. The primary end point of the SHEPHERD study and Study C07-001 was hemolysis as measured by lactate dehydrogenase (LDH). The primary outcome of Study C02-001 was not specified.

Other key outcomes were defined a priori in the CDR systematic review protocol. Of these, the Committee discussed the following: thrombotic events; transfusion avoidance; the proportion of PNH type III red blood cell clones; quality of life, including changes in fatigue levels; serious adverse events; and adverse events.

Quality of life was assessed using the Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-Fatigue) scale and the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ-C30) as general composite measures.

TRIUMPH was not designed to detect an effect of eculizumab on survival or on the incidence of thrombotic events, which is the strongest risk factor for death in patients with PNH.

Results

Efficacy or Effectiveness

- In the TRIUMPH study, eculizumab resulted in a statistically significant reduction in hemolysis as measured by LDH when compared with placebo. A statistically significant increase in the proportion of patients achieving transfusion avoidance was also observed, favouring eculizumab.
- In the TRIUMPH study, hemoglobin stabilization was achieved in 49% of patients treated with eculizumab and in none of the placebo patients ($P < 0.001$), indicating that these patients did not require any transfusions during the 26-week study. A statistically significant reduction in the number of packed red blood cell units transfused was also achieved in the eculizumab group compared with the placebo group.
- Eculizumab-treated patients showed statistically significant improvements in quality of life compared with placebo-treated patients, using the FACIT-Fatigue scale and the majority of the EORTC subscales.
- In the TRIUMPH study, there were no thrombotic events in the eculizumab group, and one in the placebo group despite anticoagulation. Analysis of combined extension study data

from the TRIUMPH, SHEPHERD, and C02-001 studies were suggestive of a significant reduction in thrombotic event rates; however, limitations associated with retrospective data collection and non-randomized studies limit the scientific validity of these data.
- Data on hemoglobin stabilization, transfusion requirements, hemolysis, and quality of life from the three non-randomized studies were supportive of findings from the TRIUMPH study.

Harms (Safety and Tolerability)
- No deaths occurred in the TRIUMPH study, and serious adverse events, adverse events, and withdrawals due to adverse events were similar between eculizumab and placebo. The most common serious adverse events across all studies included breakthrough exacerbations of PNH, hemolysis, anemia, and infections. The most common adverse events reported in all the studies were headache and nasopharyngitis.
- There is a theoretical possibility of a rebound effect upon discontinuation of eculizumab. This is currently being monitored and no cases have been identified to date, although in [redacted] patients in whom eculizumab infusion was [redacted], [redacted], severe [redacted] was reported.
- A smaller proportion of eculizumab patients compared with placebo patients had a serious infection in the TRIUMPH trial (2.3% versus 9.1% respectively). Similarly the proportion of patients reporting serious infections was low in the non-randomized studies, ranging from 3% to 9% across studies. Data on infections may be confounded by concomitant use of corticosteroids and immunosuppressant agents, especially in the uncontrolled trials.
- No cases of meningococcal infection were reported in the included studies but, to date, [redacted] cases of meningococcal infection have been reported in patients receiving eculizumab (three in clinical trials and [redacted] from post-marketing surveillance). Vaccination was confirmed in two of the three cases reported in clinical trials. One infection was due to [redacted], for which no vaccine exists.

Cost and Cost-Effectiveness

The annual cost of eculizumab is $539,360 in the first year and $525,876 in subsequent years, based on recommended doses.

CDR provided information on potential cost offsets and benefits in quality of life for eculizumab. Quality of life was felt to be an important consideration given the fatigue associated with PNH, the time required to obtain blood transfusions, and the risks of transfusion-related complications. Quality of life information (EORTC scores) from the TRIUMPH trial was used to estimate utility scores for eculizumab plus supportive care and for supportive care alone, based on an algorithm validated in patients with esophageal cancer. Costs were based on the cost of eculizumab (at 26 weeks to reflect the TRIUMPH trial period) and it was assumed that no treatment was associated with zero costs. Potential cost offsets, such as thrombotic events avoided, tended to be small in comparison with the cost of eculizumab. CDR estimated that the incremental cost per quality-adjusted life-year of eculizumab plus supportive care was $2.4 million compared with supportive care alone, based on short-term trial data (26 weeks) where quality of life benefits for a lifetime condition may not have been fully captured. Consideration of longer-term benefits would reduce the incremental cost per quality-adjusted life-year, but not to an amount below $500,000.

Other Discussion Points:

- The incidence and prevalence of PNH were discussed, as well as the range of these estimates and the proportion of patients with symptomatic and asymptomatic PNH.
- The variability in definitions of rare disease was discussed by the Committee.
- The likelihood of patients discontinuing anticoagulation therapy while receiving eculizumab was discussed. The product monograph notes that the effect of withdrawing anticoagulation therapy during treatment with eculizumab has not been established, therefore, treatment with eculizumab should not change anticoagulant management.
- TRIUMPH was not designed to detect an effect of eculizumab on survival or on the incidence of thrombotic events, which is an important prognostic factor for survival in PNH.
- It was noted that the mechanism of action of eculizumab is to inhibit the complement cascade, which places patients at an increased risk of infection, particularly by *Neisseria* organisms including *N. meningitides*, and likely other encapsulated organisms.
- The importance of type III clones was discussed by the Committee. High proportions of type III clones, when considered along with other clinical factors, are associated with an increased likelihood of hemolysis and thrombotic events.
- The Committee discussed whether or not a subgroup of patients could be identified that would be expected to experience greater benefit from eculizumab, but could not identify such a subpopulation in the included studies.
- Differences between treatment groups with respect to baseline characteristics, such as disease duration, platelet count, and secondary causes were discussed. The Committee considered that the hemolysis effect size was large enough to overcome these potential biases and noted the difficulty in balancing baseline characteristics in trials with small sample sizes and in a heterogeneous condition such as PNH.
- The role of bone marrow transplantation, which is potentially curative in treating certain subtypes of PNH, was discussed. Bone marrow transplantation is usually only reserved for severely ill PNH patients.
- In the six-month reporting period of a recent Periodic Safety Update Report, [redacted] patients were exposed to eculizumab, but not all had [redacted]. Eculizumab is currently being evaluated for other indications.

CEDAC Members Participating:

Dr. Robert Peterson (Chair), Dr. Anne Holbrook (Vice-Chair), Dr. Michael Allan, Dr. Ken Bassett, Dr. Bruce Carleton, Dr. Doug Coyle, Mr. John Deven, Dr. Alan Forster, Dr. Laurie Mallery, Mr. Brad Neubauer, Dr. Lindsay Nicolle, Dr. Yvonne Shevchuk, and Dr. Kelly Zarnke.

Regrets:

None

Conflicts of Interest:

CEDAC members reported no conflicts of interest related to this submission.

About this Document:
CEDAC provides formulary listing recommendations to publicly funded drug plans. Both a technical recommendation and plain language version of the recommendation are posted on the CADTH website when available.

CDR clinical and pharmacoeconomic reviews are based on published and unpublished information available up to the time that CEDAC made its recommendation.

The manufacturer has reviewed this document and has requested the removal of confidential information in conformity with the CDR Confidentiality Guidelines.

The Final CEDAC Recommendation neither takes the place of a medical professional providing care to a particular patient nor is it intended to replace professional advice.

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