

**PATENTED MEDICINE PRICES REVIEW BOARD**  
**IN THE MATTER OF the *Patent Act* R.S.C. 1985, c.P-4,**  
**as amended**  
**AND IN THE MATTER OF Alexion Pharmaceuticals Inc.**  
**(the “Respondent”) and the medicine “Soliris”**

**AFFIDAVIT OF ERIC LUN**

I, Eric Lun, of New Westminster, British Columbia, SWEAR THAT:

1. I am the Executive Director of the Drug Intelligence and Optimization Branch, Medical Beneficiary and Pharmaceutical Services Division of the Ministry of Health of British Columbia (“the Ministry of Health”). As such, I have personal knowledge of the facts and matters hereinafter deposed to in this Affidavit, except where stated to be based on information and belief, and where so stated I verily believe the same to be true.
2. I am making this Affidavit on behalf of the Ministry of Health, but I am advised by my counter-parts in Ontario, Manitoba, and Newfoundland and Labrador (“the Represented Jurisdictions”) that they support the position set out in this Affidavit.
3. The reason that the Ministry of Health and the Represented Jurisdictions seek to participate in this matter is to provide the Board with information about public funding of medicines in general and eculizumab (Soliris) in particular, and to request that the Board order that the Respondent reduce the price of Soliris to match the lowest price for Soliris among all comparator countries, both prospectively and retroactively.
4. The Ministry of Health operates the PharmaCare Program, which provides financial assistance to eligible British Columbia residents for the purchase of certain eligible prescription drugs and designated medical supplies.

5. The Ministry of Health also provides financial assistance on an exceptional basis for the purchase of the drug product Soliris to certain individuals in British Columbia who have been diagnosed with Paroxysmal Nocturnal Hemoglobinuria ("PNH").
6. I am advised by my counter-parts in the Represented Jurisdictions that the provincial governments of those jurisdictions also provide financial assistance for the purchase of Soliris, either through their public drug plans or through other public funding mechanisms.
7. At the Canadian list price of \$6,742.50 per 300 mg vial and using recommended doses, the annual cost of Soliris for treatment of PNH is approximately \$540,000 in the first year of treatment and \$526,000 in subsequent years per patient. At list price, the cost of Soliris for treatment of Atypical Hemolytic Uremic Syndrome ("aHUS") is more than \$700,000 per year per patient, based on recommended doses. As these medications may be used on a long-term basis (or potentially for the rest of a patient's life), the cumulative drug costs at list prices for 5, 10 or 20 years of therapy for a single PNH patient may be more than \$2.5 million, \$5 million, or \$10 million, respectively.
8. The cost of Soliris is significantly higher than most other drugs funded by provincial governments for other diseases. This results in an opportunity cost, such that the funding of one patient on Soliris will result in fewer dollars for numerous patients with other diseases. By way of illustration, in British Columbia, the average annual PharmaCare drug ingredient expenditure per beneficiary is approximately \$950 (based on PharmaCare data in FY 12/13 during which 722 other unique drugs were covered; <http://www.health.gov.bc.ca/pharmacare/pdf/PCareTrends2012-13.pdf>). On an opportunity cost basis, for example, this means that the expenditure used to fund Soliris for a single PNH patient could have been used to provide drug coverage for more than 550 other PharmaCare beneficiaries, on average.
9. Even when compared to other high cost drugs funded by provincial governments for other diseases, the cost of Soliris is significantly more expensive. To illustrate this, I provide the following examples of certain other drugs considered high cost and

funded by the Ministry of Health (the stated drugs costs are based upon list cost and do not include other mark ups):

- (a) Infliximab (Remicade) costs up to \$25,000 per year per patient. Infliximab is used for the long-term symptomatic treatment of various rheumatic or gastrointestinal disorders.
  - (b) Sofosbuvir-ledipasvir (Harvoni) costs about \$70,000 per patient for a 12-week treatment course and is used as a potentially curative treatment for chronic hepatitis C infection.
  - (c) Ivacaftor (Kalydeco) costs about \$306,000 per year per patient and is used for the long-term symptomatic treatment of a rare form of cystic fibrosis, and like Soliris is funded on an exceptional case basis in BC.
  - (d) Imiglucerase (Cerezyme) costs about \$350,000 per year per patient and is used for the long-term symptomatic treatment of the rare Gaucher's disease, and like Soliris is funded on an exceptional case basis in BC.
10. The provincial governments in Canada are major payors for Soliris for the treatment of PNH, and therefore the provincial governments have a critically vested interest in the price of this drug product.
  11. The Common Drug Review (CDR) reviews drugs for potential reimbursement by participating jurisdictions. In 2010, the CDR's advisory committee, the Canadian Expert Drug Advisory Committee ("CEDAC"), recommended that Soliris not be listed at the submitted price for treatment of PNH, stating that, "Eculizumab would not be considered cost-effective without a substantial reduction in the submitted price." Attached to this my Affidavit and marked as Exhibit A is a copy of the CEDAC's Recommendation on Soliris for PNH.
  12. In agreeing to consider funding Soliris through government funding, the provinces and territories completed national negotiations for a confidential price for the product for its use in PNH. To secure confidential lower prices, participating jurisdictions each complete their own confidential product listing agreements with the

manufacturer and therefore cannot disclose the terms or conditions of such agreements. However, the list price of Soliris is referenced in the negotiations in order to determine overall value. Therefore, an excessive list price results in provincial governments being inherently disadvantaged in the listing negotiations and in the subsequent ongoing funding of Soliris purchases.

13. Because public government payors in Canada have negotiated a price lower than the list price for PNH, it might be argued that the effective price paid in Canada by government payors is "non-excessive" relative to international comparator prices. However, it should be noted that given the excessive pricing for Soliris, governments in other countries, including drug plans in the United Kingdom, Ireland and New Zealand, have also resorted to negotiations with the Respondent. The Respondent would be the best source to confirm other comparator countries with whom it has negotiated lower non-transparent prices. The following media articles (links below) provide some indication of the countries where such negotiations have been completed.

<http://www.pharmaphorum.com/articles/soliris-the-worlds-most-expensive-drug-will-nice-judge-it-affordable>, <http://www.irishtimes.com/news/health/how-can-the-hse-put-a-price-on-your-life-1.2053192>, <http://tvnz.co.nz/national-news/pharmac-willing-negotiate-life-saving-treatment-5324999>

14. The public list price is also an important reference point for other public drug coverage policies. In addition to the drug ingredient cost, provincial governments also pay mark-ups or other professional fees to pharmacies as part of their remuneration to supply drugs to patients. Currently mark-up fees payable by provincial governments are calculated as a percentage of the drug ingredient costs based upon the public list price. The fees are typically in the 6-10% range, but may be as high as 30% (Yukon). In the case of Soliris, a mark-up fee of 8% would add more than \$42,000 annually to the overall cost of the drug for each PNH patient funded. To assist in managing the potential amount of the mark-up, jurisdictions may use various strategies to avoid or minimize paying the mark-up on Soliris, such as through capitation policies.

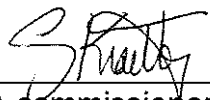
15. In 2013, the CDR's advisory committee, now known as the Canadian Drug Expert Committee ("CDEC"), recommended that Soliris not be listed for treatment of aHUS. In making those recommendations, the Committee stated that the "two uncontrolled prospective studies had several important limitations. Therefore the clinical benefit of eculizumab could not be adequately established." Attached to this my Affidavit and marked as Exhibit B is a copy of the CDEC's Recommendation on Soliris for aHUS. The public drug plans are currently seeking advice from CDEC regarding the use of Soliris in aHUS. Attached to this my Affidavit and marked as Exhibit C is a copy of the Canadian Agency for Drugs and Technology in Health Common Drug Review Submission Status document confirming the request for advice.
16. Because of the 2013 CDEC "do not list" recommendation for aHUS, the provinces and territories have not negotiated for a confidential lower price for use of Soliris in aHUS. As such, if a province or territory chooses to cover a patient for an indication other than PNH on an exceptional basis, that jurisdiction will be required to pay the full list price of the product (unless some other agreement has been made between that jurisdiction and the manufacturer).
17. Although provincial governments pay for a significant proportion of Soliris treatments, there are other payors as well – hospitals (which may provide funding independently of public drug plans), drug benefit insurers and private payors. These payors are not able to benefit from any negotiated agreements that the provincial governments may have with the Respondent. These other payors would need to pay the full list price of the product unless there was an agreement in place between the payor and the Respondent. For example, I am aware of a Vancouver hospital in BC that pays the full list price of the product plus 5% mark-up for a patient; this was a funding decision made independently from the Ministry of Health.
18. The Ministry of Health and the Represented Jurisdictions respectfully request that in making its decision, the Board consider the significant challenges that provincial governments face as a result of the pricing of Soliris.


19. The Ministry of Health and the Represented Jurisdictions respectfully request that the Board:

(a) order the Respondent to reduce the price of Soliris to match the lowest price for Soliris among all comparator countries effective within 30 days of the date of the Board's Order, and

(b) order that the Respondent offset the cumulative revenues it has received during the period of January 1, 2012 to the effective date of the Board's Order noted in (a) by making a payment to Her Majesty in Right of Canada, within 30 days of the Board's order, in an amount that is equal to the excess revenues the Board estimates that the Respondent has generated from the sale of Soliris at an excessive price, using the lowest price for Soliris among all comparator countries as the reference for the appropriate price for the product.

20. I swear this affidavit in support of the request of the Ministry of Health and the Represented Jurisdictions for the remedy set out above.

SWORN BEFORE ME )  
at Victoria, British Columbia )  
on April 1, 2015. )  
 )  
A commissioner for taking )  
affidavits for British Columbia )

  
\_\_\_\_\_  
Eric Lun

**SHARNA KRAITBERG**  
Barrister and Solicitor

This is Exhibit A  
referred to in the Affidavit  
of ERIC LUN  
sworn before me this 1<sup>st</sup> day  
of April 2015  
[Signature]  
A Commissioner for taking Affidavits  
within British Columbia



# COMMON DRUG REVIEW

## 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  $\geq 100,000$  cells/mm<sup>3</sup>. 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, ■■■ patients were exposed to eculizumab, but not all had ■■■. 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.

CADTH is not legally responsible for any damages arising from the use or misuse of any information contained in or implied by the contents of this document.

The statements, conclusions, and views expressed herein do not necessarily represent the view of Health Canada or any provincial, territorial, or federal government or the manufacturer.

This is Exhibit B  
referred to in the Affidavit  
of ERIC LON  
sworn before me this 1<sup>ST</sup> day  
of April, 2015  
Shelley  
A Commissioner for Taking Affidavits  
within British Columbia



Canadian Agency for  
Drugs and Technologies  
in Health

# COMMON DRUG REVIEW

## CDEC FINAL RECOMMENDATION

### ECULIZUMAB

(Soliris — Alexion Pharmaceuticals Inc.)

New Indication: Atypical Hemolytic Uremic Syndrome

#### Recommendation:

The Canadian Drug Expert Committee (CDEC) recommends that eculizumab not be listed.

#### Reasons for the Recommendation:

Two uncontrolled prospective studies had several important limitations, including a lack of clear diagnostic criteria for atypical hemolytic uremic syndrome (aHUS), the absence of a comparator group to examine outcome differences, short duration of follow-up, and lack of data regarding clinically important outcomes for patients with aHUS. Therefore, the clinical benefit of eculizumab could not be adequately established.

#### Background:

Eculizumab has a Health Canada indication for the treatment of patients with aHUS to reduce complement-mediated thrombotic microangiopathy (TMA). Eculizumab has been issued a marketing authorization without conditions for adults and adolescents aged 13 to 17 years, weighing more than 40 kg who have aHUS. In children less than 13 years of age and/or weighing less than 40 kg, eculizumab has been issued a marketing authorization with conditions (i.e., Notice of Compliance with Conditions), pending the results of studies to verify its clinical benefit.

Following an induction phase of 900 mg weekly for four weeks and 1,200 mg at week five, the recommended maintenance dosage is 1,200 mg every two weeks. Children weighing less than 40 kg are dosed according to weight. A supplemental eculizumab dose is administered when plasma therapy (PT) is required. Eculizumab is available as a 10 mg/mL solution for intravenous injection.

#### Submission History:

Eculizumab was previously reviewed by the Canadian Expert Drug Advisory Committee (CEDAC) for paroxysmal nocturnal hemoglobinuria to reduce hemolysis; it received a recommendation that it “not be listed at the submitted price” (see Notice of CEDAC Final Recommendation, February 19, 2010).

## Common Drug Review

CDEC Meeting — June 19, 2013

Notice of CDEC Final Recommendation — July 18, 2013

© 2013 CADTH

Page 1 of 6

### **Summary of CDEC Considerations:**

CDEC considered the following information prepared by the Common Drug Review (CDR): a systematic review of eculizumab trials, a critique of the manufacturer's pharmacoeconomic evaluation, and patient group-submitted information about outcomes and issues important to patients.

### **Patient Input Information**

The following is a summary of information provided by one patient group that responded to the CDR call for patient input:

- Patients with aHUS report high amounts of emotional, financial, and responsibility-related stress leading to feelings of isolation, fear, hopelessness, anxiety, and depression.
- PT causes increased fatigue, confused thinking, and nausea post-treatment, and patients experience high total protein levels, increased blood pressure, and headaches. PT is only available in major hospitals; therefore, many patients must travel for treatment, which increases time and financial burdens on families. Parents of patients undergoing PT estimated that their children miss 30% to 40% of their school year, with the parent having 20% to 40% absenteeism from work.
- Patients indicated that treatment with eculizumab would not require the use of a central line and would allow them to avoid attending weekly or biweekly plasma infusions, which can last upwards of seven hours.

### **Clinical Trials**

There were no randomized controlled trials (RCTs) identified in the CDR systematic review; therefore, the review included three uncontrolled, manufacturer-sponsored studies conducted in patients with a diagnosis of aHUS, with or without identified gene mutations. Studies C08-002 (N = 17) and C08-003 (N = 20) were phase 2, prospective, multicentre, single-arm, open-label trials conducted in adults and adolescents ages 12 to 17 years. The study medication was administered for 26 weeks. Study C09-001 was a retrospective chart review of 30 patients that included children (0 to 11 years), adolescents (12 to 17 years), and adults. In study C08-002, patients were included if they were intolerant to PT or were resistant to PT, despite four or more treatments in the week before the start of study treatment. In study C08-003, patients were included if they were PT sensitive and had stable platelet counts during PT treatment. In study C09-001, both PT-resistant and PT-sensitive patients were considered for inclusion.

The trials included North American and European patients. The prospective trials were mainly conducted in adults (median 28 years) with more than 60% of patients being women; whereas, 50% of the patients in the retrospective chart review were children younger than 12 years, with an equal proportion of males and females. In studies C08-002 and C09-001, 40% of patients were experiencing their first attack of aHUS; whereas, in study C08-003, 25% of patients were experiencing a first attack. In studies C08-002 and C08-003, 35% and 10% of patients had received dialysis within the two months before eculizumab treatment respectively. In study C09-001, 37% of patients had at least gone through one dialysis session. Approximately 40% of patients had received a kidney transplant across all trials.



### Outcomes

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

- Mortality — a safety endpoint in the included studies.
- PT-free status — the number of PT sessions before and during eculizumab therapy.
- Dialysis-free status — the number of dialysis events before and during eculizumab therapy.
- Health-related quality of life (HRQoL) — measured with the European Quality of Life Scale (EuroQoL-5D time trade off index and the visual analogue scale [VAS]).
- TMA event-free status — absence of the following three events: decrease in platelet count of > 25% from baseline; PT while patient is receiving study drug; and new dialysis.
- Complete TMA response — defined as hematologic normalization and 25% reduction from baseline in serum creatinine.
- Hematologic normalization — normalization of both platelet count and lactate dehydrogenase.
- Chronic kidney disease (CKD) stage — improvement by at least one CKD stage.
- Serious adverse events, adverse events, and withdrawals due to adverse events.

The primary end points were platelet count change (C08-002) and the proportion of patients who achieved TMA event-free status (C08-003). If statistically significant, then a second primary end point, the proportion of patients who achieved hematologic normalization, was evaluated.

### Results

#### Efficacy

- There were no deaths in study C08-002 or C08-003 and two patients died in C09-001.
- All but one patient discontinued PT while on eculizumab treatment in the prospective trials (C08-002 and C08-003). In study C09-001, 30% of patients continued to receive PT while on eculizumab.
- In study C08-002, patients who had required dialysis pre-eculizumab (35%) were able to discontinue dialysis during eculizumab treatment, and one patient who was dialysis-free before eculizumab treatment required dialysis while on the study drug. In study C08-003, two patients who had received dialysis before eculizumab therapy were unable to discontinue dialysis during treatment with eculizumab. There were no new dialysis cases in study C08-003. In study C09-001, patients who had received dialysis were able to discontinue dialysis while on eculizumab treatment. There were two new dialysis patients during the treatment period of study C09-001.
- Patients' HRQoL was improved in both prospective trials; improvements were greatest in PT-resistant/intolerant patients (study C08-002). Some PT-sensitive patients (study C08-003) experienced deterioration in the HRQoL score while on eculizumab treatment.
- In studies C08-002, C08-003, and C09-001, 88%, 80%, and 57% of patients (respectively) were TMA event-free.
- In studies C08-002 and C08-003, 65% and 25% of patients (respectively) experienced a complete TMA response. TMA response was sustained for a mean of 120 days (standard deviation [SD] 49) in study C08-002 and for a mean of 80 days (SD 40) in study C08-003.
- In studies C08-002 and C08-003, 76% and 90% of patients (respectively) experienced a normalization of platelet count and lactate dehydrogenase level during the treatment period.
- In studies C08-002, C08-003, and C09-001, 59%, 35%, and 40% of patients (respectively) improved by at least one stage in CKD; 65%, 15% and 40% of patients (respectively) had a

---

## Common Drug Review

decrease of  $\geq 25\%$  in serum creatinine level; and 47%, 5% and 37% of patients (respectively) improved by  $\geq 15$  mL/minute/1.73 m<sup>2</sup> in estimated glomerular filtration rate (eGFR).

### **Harms (Safety and Tolerability)**

- Almost every patient in the prospective trials experienced at least one adverse event (97%); whereas, in the retrospective chart review, 73% of patients reported having at least one adverse event.
- The most common adverse events were hypertension (47%), headache (41%), and anemia (35%) in study C08-002; upper respiratory tract infection (40%) and hypertension (25%) in C08-003; and pyrexia (30%) and cough (23%) in C09-001. In all three trials, patients experienced diarrhea (27% to 35%) and vomiting (15% to 29%).
- Fifteen patients (88%) and five patients (25%) reported at least one serious adverse event in studies C08-002 and C08-003 respectively.
- In studies C08-002 and C08-003, there were 38 episodes of infection. Five infections were considered serious, for which patients required hospitalization.
- A total of 35% of patients experienced at least one hypertension-related event including six serious adverse events.
- One patient experienced gastrointestinal bleeding that was deemed to be possibly related to eculizumab treatment (study C08-003).
- One patient withdrew from study C08-002 due to an adverse event.

### **Cost and Cost-Effectiveness**

The manufacturer submitted an economic analysis comparing eculizumab plus non-biologic supportive care (excluding plasma exchange) with non-biologic supportive care (including plasma exchange) over a one-year time horizon, where supportive care included dialysis and supportive care treatment for end-stage renal disease, hospitalization, and physician consults. Due to a dearth of information available for the management of patients with aHUS, the manufacturer consulted five Canadian experts with an interest in aHUS to identify all relevant health care resources for the management of patients with aHUS, and the expected frequency of use. The manufacturer reported the annual cost per patient of treatment with eculizumab plus non-biologic supportive care (excluding plasma exchange) to be \$746,899 in the first year, compared with a cost of \$210,056 for treatment with plasma exchange plus non-biologic supportive care.

A number of limitations were noted with the economic submission:

- Quality of life information was collected in the eculizumab clinical trial, which could have been used to present a more informative cost-utility analysis to examine the relative cost-effectiveness of eculizumab in patients with aHUS.
- The difficulty in diagnosing aHUS in patients may substantially inflate the total cost of treatment (budget impact) for public plans due to the extremely high price of eculizumab.
- The eculizumab product monograph indicates that treatment should not be stopped once initiated. Thus, the cost of eculizumab treatment would be incurred for the remainder of the patient's life, the length of which is unknown as there is no reliable data indicating the life expectancy of a patient with aHUS, before or after treatment with eculizumab.

- The estimates of cost and duration of plasma exchange, which drive non-biologic supportive care, are highly uncertain; this then has an impact on the determination of the assessment of incremental cost for eculizumab.
- No information was presented to assess the efficacy of the PT.
- Eculizumab may be used in combination with plasma exchange, which was not accounted for in the manufacturer's economic submission. The CDR re-analysis showed that concomitant treatment would greatly increase the incremental cost of treatment of eculizumab up to \$940,084 per patient per year.

The annual drug cost per patient for eculizumab treatment ranges from \$121,356 to \$728,136, depending on the weight of the patient. The annual incremental cost of eculizumab treatment may lie between \$500,000 and \$600,000 per patient compared with non-biologic supportive care plus plasma exchange; however due to the paucity of data, there is considerable uncertainty with this estimate.

### Other Discussion Points:

CDEC noted the following:

- Eculizumab was evaluated in a broad selection of patients with aHUS, including both PT-resistant and PT-sensitive patients, patients with first and subsequent episodes of aHUS, those with and without genetic mutations, patients with or without kidney transplants, and patients with and without a history of dialysis. Despite subgroup analyses conducted for the prospective trials, the small number of patients included prevented the identification of subpopulations that are most likely to benefit from eculizumab therapy.
- Given that the studies included in the CDR review were uncontrolled and of short duration, the impact of eculizumab on the development of renal complications and mortality is unclear.
- Baseline EQ-5D scores were higher than might be expected for a severe disease, including 11 patients who reported a score of 0.94, which could make assessing improvements difficult due to a ceiling effect.
- The included studies mainly enrolled adults and a few adolescents; therefore, a formal evaluation in pediatric patients would be beneficial.
- There are limited data for use of eculizumab in children (< 12 years) with aHUS.
- Limitations of currently available diagnostics have the potential to result in their use where there is suspicion but not confirmation of aHUS, with significant cost consequence.

### Research Gaps:

CDEC noted that there is insufficient evidence regarding the following:

- Efficacy and safety of eculizumab in children (< 12 years) with aHUS.
- Clinical benefit of eculizumab on overall survival for patients with aHUS.
- Clinical indicators of therapeutic failure for patients treated with eculizumab.
- Effect of eculizumab on hemoglobin levels in the absence of treatment with erythropoietin.
- Relative benefit of eculizumab in relation to PT.
- Subgroups likely to respond or need ongoing therapy.

**CDEC Members:**

Dr. Robert Peterson (Chair), Dr. Lindsay Nicolle (Vice-Chair), Dr. Ahmed Bayoumi, Dr. Bruce Carleton, Ms. Cate Dobhran, Mr. Frank Gavin, Dr. John Hawboldt, Dr. Peter Jamieson, Dr. Julia Lowe, Dr. Kerry Mansell, Dr. Irvin Mayers, Dr. Yvonne Shevchuk, Dr. James Silvius, and Dr. Adil Virani.

**June 19, 2013 Meeting****Regrets:**

None

**Conflicts of Interest:**

None

**About This Document:**

CDEC provides formulary listing recommendations or advice to CDR participating drug plans. CDR clinical and pharmacoeconomic reviews are based on published and unpublished information available up to the time that CDEC deliberated on a review and made a recommendation or issued a record of advice. Patient information submitted by Canadian patient groups is included in the CDR reviews and used in the CDEC deliberations.

The manufacturer has reviewed this document and has not requested the removal of confidential information in conformity with the *CDR Confidentiality Guidelines*.

The CDEC recommendation or record of advice neither takes the place of a medical professional providing care to a particular patient nor is it intended to replace professional advice.

CADTH is not legally responsible for any damages arising from the use or misuse of any information contained in or implied by the contents of this document.

The statements, conclusions, and views expressed herein do not necessarily represent the view of Health Canada or any provincial, territorial, or federal government or the manufacturer.

This is Exhibit C  
referred to in the Affidavit

of Eric Lun

sworn before me this 1<sup>st</sup> day

of April, 2015

[Signature]  
A Commissioner for Taking Affidavits  
within British Columbia

# CADTH

## Common Drug Review Submission Status

Product: Soliris  
 Generic Name: Ieculizumab  
 Manufacturer: Alexion Pharma Canada  
 Indication: Hemolytic Uremic Syndrome, Atypical  
 Submission Type: Request for Advice

Date Submission Received: 2015-Feb-09  
 Date NOC Issued: 2013-Mar-01  
 Original Targeted CDEC Meeting: 2015-May-20

Key Milestone <sup>1</sup>	Target Date	Actual CDR Date	Comments
CADTH request for advice approach determined	2015-Feb-24	2015-Feb-24	- 2015-Feb-09: Manufacturer informed of request for advice - Information or comments due 2015-Feb-24 - Manufacturer information/comments received: 2015-Feb-24 - Review has been initiated 2015-Feb-25
Draft CDR Request for Advice report sent to manufacturer	2015-Apr-13		
Comments from manufacturer on draft CDR Request for Advice report received by CADTH	2015-Apr-22		
Redaction response from manufacturer on draft CDR Request for Advice report received by CADTH	2015-Apr-29		
CDEC meeting	2015-May-20		
If the request for advice does not result in a new or revised CDEC recommendation: CDEC Record of Advice sent to drug plans and manufacturer			
CDEC Record of Advice report posted <sup>3</sup>			
CDR Request for Advice report posted <sup>3</sup>			
OR			
If the request for advice results in a new or revised CDEC recommendation: CDEC recommendation & redacted CDR Request for Advice report sent to drug plans and manufacturer			
Embargo period <sup>2</sup> and validation of redacted CDR Request for Advice report Manufacturer may make a request for reconsideration and drug plans may make a request for clarification of the recommendation			
CDEC Final Recommendation sent to drug plans and manufacturer (No request for clarification is made AND no request for reconsideration is made or request for reconsideration is resolved)			
CDEC Final Recommendation posted <sup>3</sup>			
Final CDR Request for Advice report posted <sup>3</sup>			
OR			
Clarification and final recommendation sent to drug plans and manufacturer (Clarification requested, no request for reconsideration made) <sup>4</sup>			
CDEC Final Recommendation posted <sup>3</sup>			
Final CDR Request for Advice report posted <sup>3</sup>			
OR			
Placed on CDEC agenda for reconsideration (At manufacturer's request) <sup>4</sup>			
CDEC Final Recommendation sent to drug plans and manufacturer			
CDEC Final Recommendation posted <sup>3</sup>			
Final CDR Request for Advice report posted <sup>3</sup>			

<sup>1</sup> Please refer to the *Procedure for the CADTH Common Drug Review* in the Common Drug Review section of [www.cadth.ca](http://www.cadth.ca) for complete details regarding the CDR request for advice process and targeted time frames for key milestones.

<sup>2</sup> The recommendation is held in confidence by all stakeholders and not acted upon until after CADTH has issued the notice of final recommendation. A manufacturer may request an extension of up to 20 extra business days solely for the purpose of preparing and filing a request for reconsideration (i.e., a total of 30 business days)

<sup>3</sup> The target date for posting a CDEC Record of Advice, the CDEC Final Recommendation and CDR Request for Advice report depends on several factors including the need for consultation with the manufacturer regarding redaction issues.

<sup>4</sup> The time frame required to address a request for clarification at the drug plans' request or request for reconsideration at the manufacturer's request depends on the amount of work required to address the request and the available dates for CDEC meetings.