



## CDEC RECORD OF ADVICE

### **ECULIZUMAB (Soliris — Alexion Pharmaceuticals Inc.) New Indication: Atypical Hemolytic Uremic Syndrome**

This document summarizes the Canadian Drug Expert Committee (CDEC) response to the CADTH Common Drug Review (CDR)—participating drug plans' request for advice regarding the eculizumab (Soliris) [CDEC Final Recommendation](#) (July 18, 2013) and should be read in conjunction with the [CDEC Final Recommendation](#) document. Note that CDEC's deliberations at the May 2015 CDEC meeting did not result in a revision to the original recommendation dated July 18, 2013.

#### **Background:**

Eculizumab has a Health Canada indication for the treatment of patients with atypical hemolytic uremic syndrome (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, who weigh more than 40 kg and have aHUS. In children younger than 13 years and/or who weigh 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 who weigh 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 for the treatment of aHUS was reviewed by CDEC in 2013 and received a "do not list" recommendation for the following reason: Two small, uncontrolled prospective studies had significant important limitations, including a lack of clear diagnostic criteria for aHUS, the absence of a comparator group to examine outcome differences, short duration of follow-up, and lack of clinically important outcome data for patients with aHUS. Therefore, the clinical benefit of eculizumab could not be adequately established.

#### **Request for Advice:**

Since the [CDEC Final Recommendation](#) for eculizumab was issued in July 2013, the public drug plans that participate in the CDR process have noted the following:

- A randomized controlled trial (RCT) could be very challenging to conduct, due to the rarity of aHUS.
- Clinicians and patients have communicated to some drug plans that plasma exchange/plasma infusion (PE/PI) provides modest symptomatic relief, but has limited long-term efficacy.
- Additional studies involving eculizumab have been published that contain data that were not available at the time of the 2013 CDR review of eculizumab.
- International jurisdictions, including the Australian Pharmaceutical Benefits Advisory Committee (PBAC) and the United Kingdom's National Institute for Health and Care Excellence (NICE), have recommended the use of eculizumab in the treatment of aHUS.

Taking into account the above-noted considerations, the CDR-participating drug plans have proposed that patients with aHUS who meet all three of the following diagnostic criteria be eligible for reimbursement of eculizumab treatment:

1. Confirmed diagnosis of aHUS at initial presentation, defined by presence of TMA:
  - a) ADAMTS-13 activity  $\geq 10\%$  on blood samples taken prior to PE/PI; and
  - b) STEC-test negative
2. Evidence of ongoing active TMA, defined by laboratory test abnormalities despite plasmapheresis (minimum of 4 plasma exchanges required over 4 successive days). Patients must demonstrate:
  - a) Unexplained (not a secondary TMA) thrombocytopenia (platelet count  $<150 \times 10^9/L$ ); AND hemolysis as indicated by the documentation of two of the following: schistocytes on the blood film; low or absent haptoglobin; or lactate dehydrogenase (LDH) above normal, OR
  - b) Tissue biopsy confirming TMA in patients who don't have evidence of platelet consumption and hemolysis
3. Evidence of at least one of the following documented clinical features of active organ damage or impairment:
  - a) Kidney impairment as demonstrated by one of the following: a decline in estimated glomerular filtration rate (eGFR) of  $>20\%$  in a patient with pre-existing renal impairment; and/or serum creatinine (SCr)  $>$  upper limit of normal (ULN) for age or GFR  $< 60$  and renal function deteriorating despite prior PE/PI in patients who have no history of pre-existing renal impairment (i.e., who have no baseline eGFR measurement); or SCr  $>$  the age-appropriate ULN in pediatric patients (subject to advice from a pediatric nephrologist), OR
  - b) Onset of neurological impairment related to TMA.

The CDR-participating drug plans submitted a request for advice to CDEC on the following:

1. In light of the current situation where no RCT data are available to compare the relative efficacy of eculizumab versus PE/PI in the treatment of aHUS, and acknowledging the limited long term benefits of PE/PI in the treatment of aHUS, can CDEC review the current proposed funding criteria and comment on whether they endorse the niche population of patients for which funding is being recommended, which is based on the currently available published evidence and clinical expert opinion?
2. Can CDEC provide any specific comments on the proposed initiation funding criteria, identify any concerns they have with the criteria for diagnosis and initiation (i.e., the defined group of patients who would be eligible for funding), and provide suggestions on further refinement of the proposed group of eligible patients who are most likely to derive benefit from eculizumab?

### Summary of CDEC Considerations:

CDEC considered the following in order to address the request for advice:

- Input from two patient groups
- The *CDEC Final Recommendation* for eculizumab (July 18, 2013)
- The CDEC brief for the 2013 CDR review of eculizumab
- Input on the proposed criteria, from Canadian clinicians with expertise in treating aHUS
- A comparison of the proposed criteria with recommendations from PBAC, NICE, and the Renal Association's aHUS Rare Disease Group
- Clinical studies obtained from an updated literature search and from the manufacturer.

### Patient Group Input

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

- Patient groups emphasized that there is an unmet medical need for aHUS patients, which could be met by providing access to eculizumab.
- Patient groups noted that both PBAC and NICE have recommended funding for eculizumab based on the same evidence available to CDEC.
- Patients with aHUS report high amounts of emotional, financial, and responsibility-related stress, leading to feelings of isolation, fear, hopelessness, anxiety, and depression.
- Patient groups noted that PT does not address the underlying cause of aHUS and can be associated with serious risks, in addition to increased fatigue, confused thinking, and nausea post-treatment. PT is available only in major hospitals; therefore, many patients must travel for treatment, which increases the 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 parents' absenteeism from work at 20% to 40%.
- 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 upward of seven hours.

### Summary of 2013 CDR Systematic Review

No RCTs were 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, multi-centre, single-arm, open-label trials conducted in adults and adolescents aged 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 primary end points were change in platelet counts (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.

In the two prospective trials (C08-002 and C08-003), all but one patient discontinued PT while on eculizumab treatment. In both studies, several patients who had required dialysis pre-eculizumab were able to discontinue dialysis during eculizumab treatment. The majority of patients in these studies were TMA event-free (80% to 88%) and a complete TMA response was reported for 65%

and 25% of patients in C08-002 and C08-003, respectively. TMA response was sustained for a mean of 120 days in study C08-002 and for a mean of 80 days in study C08-003. In addition, the following results were noted for biochemical markers (C08-002 and C08-003, respectively): 76% and 90% of patients experienced a normalization of platelet count and LDH level during the treatment period; 59% and 35% improved by at least one stage in chronic kidney disease; 65% and 15% had a decrease of  $\geq 25\%$  in SCr level; and 47% and 5% improved by  $\geq 15$  mL/minute/1.73 m<sup>2</sup> in eGFR.

Almost every patient in the prospective trials experienced at least one adverse event (97%). The most common adverse events were hypertension (47%), headache (41%), and anemia (35%) in study C08-002 and upper respiratory tract infection (40%) and hypertension (25%) in C08-003. 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 withdrew from study C08-002 due to an adverse event.

### **Summary of New Clinical Evidence**

An updated literature search identified longer-term data from the two prospective studies included in the original 2013 CDR systematic review (C08-002 and C08-003), one new prospective study (C10-003; N = 22), and one new retrospective case series (Baskin et al., 2014; N = 10).

- The two- and three-year analyses of patients in C08-002 and C08-003 demonstrated that longer-term eculizumab therapy maintained inhibition of complement activity, TMA, and improvements in hematologic parameters and renal function. Furthermore, eculizumab continued to prevent progression to end-stage renal disease in the majority of patients with aHUS.
- In study C10-003, 22 patients younger than 18 years with aHUS were treated with eculizumab and evaluated at 26 weeks and at one year. The proportion of patients who achieved a complete TMA response was 64% and 68% at 26 weeks and at one year, respectively. Platelet levels and eGFR increased significantly from baseline through the study period. Of the patients requiring dialysis at baseline, 82% were able to discontinue dialysis by week 26 and remained dialysis-free at one year. Quality of life was shown to be improved, with a statistically significant least squares mean change from baseline on the Pediatric Functional Assessment of Chronic Illness Therapy – Fatigue (Peds-FACIT-F) scale of 19.7 (range: 15.6 to 23.7).
- The case series (Baskin et al., 2014) evaluated 10 children with aHUS who were treated with eculizumab. It was reported that full recovery of hematologic parameters and renal function was obtained in all patients. The time from first eculizumab treatment to the recovery of hematologic parameters, hypertension, renal function, and proteinuria ranged from six to 15 days, five to 19 days, seven to 27 days, and 21 to 68 days, respectively.

### **Recommendations and Criteria From Other Agencies**

PBAC and NICE have recommended funding for eculizumab for aHUS patients. The PBAC criteria closely resemble those proposed by the CDR-participating plans; however, a notable difference is that the PBAC criteria do not require patients to have been previously treated with plasmapheresis. By contrast, the criteria proposed by the CDR-participating drug plans specify that patients are required to have had a minimum of four plasma exchanges over four successive days. NICE guidance does not specify criteria for diagnosis or initiation, but recommends the following:

- Coordination of eculizumab use through an expert centre

- Monitoring systems to record the number of people with a diagnosis of aHUS and the number who have eculizumab, and the dose and duration of treatment
- A national protocol for starting and stopping eculizumab for clinical reasons
- A research program with robust methods to evaluate when stopping treatment or dose adjustment might occur.

### ***Input from Canadian Clinicians With Expertise in Treating aHUS***

Three clinical experts were consulted by CDR during the review, two of whom participated in CDEC's deliberations and provided clinical advice and clarifications to questions posed by the Committee. All three experts endorsed the intent of the criteria that have been proposed by the CDR-participating drug plans as a means of providing access to eculizumab for those aHUS patients most likely to benefit from treatment. In addition to the proposed criteria, the clinical experts suggested additional requirements to rule out alternative diagnoses and to allow coverage for a subpopulation of renal transplant patients with aHUS (described below). These criteria should allow for aHUS patients with the greatest unmet medical need to be treated with eculizumab, which is aligned with the hope articulated by the representative patient groups.

### **Response to the Request for Advice:**

#### **1. Question from the Drug Plans:**

In light of the current situation where no RCT data are available to compare the relative efficacy of eculizumab versus PE/PI in the treatment of aHUS, and acknowledging the limited long term benefits of PE/PI in the treatment of aHUS, can CDEC review the current proposed funding criteria and comment on whether they endorse the niche population of patients for which funding is being recommended, which is based on the currently available published evidence and clinical expert opinion?

#### **CDEC Response:**

CDEC considers the quality of the clinical data in support of treating aHUS with eculizumab to be poor; however, the Committee acknowledges it is unlikely that high-quality data will become available in the near future. Based on a detailed review of the available clinical data, patient group input, and input from clinical experts, the Committee concludes that there is potential benefit of treatment with eculizumab for individuals with aHUS as defined by the criteria proposed by the CDR-participating drug plans. However, CDEC noted that there remains considerable uncertainty regarding the long-term clinical benefit of eculizumab and that this treatment is associated with a very high cost per patient.

#### **2. Question from the Drug Plans:**

Can CDEC provide any specific comments on the proposed initiation funding criteria, identify any concerns they have with the criteria for diagnosis and initiation (i.e., the defined group of patients who would be eligible for funding), and provide suggestions on further refinement of the proposed group of eligible patients who are most likely to derive benefit from eculizumab?

#### **CDEC Response:**

CDEC's response to each of the individual proposed criteria is provided below. Of note, the proposed criteria would include 1 and 2 and either 3 or 4.

### Proposed criterion 1:

*Confirmed diagnosis of aHUS at initial presentation, defined by presence of TMA:*

- a) *ADAMTS-13 activity  $\geq$  10% on blood samples taken prior to PE/PI; and*
- b) *STEC-test negative*

CDEC response:

The Committee discussed the need to obtain the ADAMTS-13 sample prior to the initiation of PE/PI. It was noted that drug plans could consider alternative language for this criterion, to provide options in situations where the ADAMTS-13 sample has not been collected. With regard to the requirement for a Shiga toxin–producing *Escherichia coli* (STEC) test, it was noted that this is reasonable for children with suspected aHUS, but may not be required for adults in the absence of a history of diarrhea within the preceding weeks.

Based on the opinion of clinical experts, CDEC suggests that an additional criterion be added, which would permit the identification of patients without aHUS and who are unlikely to respond to PE/PI or eculizumab. The specific suggestions for alternative diagnoses included disseminated intravascular coagulation, disseminated malignancy, malignant hypertension, antiphospholipid antibody syndrome, lupus, scleroderma, and HIV. CDEC suggests the following revision:

Diagnosis of aHUS at initial presentation, defined by presence of TMA:

- a) *ADAMTS-13 activity  $\geq$  10% on blood samples taken prior to PE/PI; and*
- b) *STEC-test negative in all children, or adults with a history of diarrhea in the preceding two weeks; and*
- c) *Absence of alternative diagnosis that is unlikely to respond to PE/PI or eculizumab (such as disseminated intravascular coagulation, disseminated malignancy, malignant hypertension, antiphospholipid antibody syndrome, lupus, scleroderma, or HIV).*

### Proposed criterion 2:

*Evidence of ongoing active TMA, defined by laboratory test abnormalities despite plasmapheresis (minimum of 4 plasma exchanges required over 4 successive days). Patients must demonstrate:*

- a) *Unexplained (not a secondary TMA) thrombocytopenia (platelet count  $<150 \times 10^9/L$ ); AND hemolysis as indicated by the documentation of two of the following: schistocytes on the blood film; low or absent haptoglobin; or LDH above normal. OR*
- b) *Tissue biopsy confirming TMA in patients who don't have evidence of platelet consumption and hemolysis*

CDEC response:

The Committee has no suggested revisions for the criterion noted above. A clinical expert suggested that the need for plasmapheresis is a reasonable criterion for newly diagnosed patients; however, it would not necessarily be appropriate for individuals with a firmly established diagnosis of aHUS.

### Proposed criterion 3:

*Evidence of at least one of the following documented clinical features of active organ damage or impairment:*

- a) *Kidney impairment as demonstrated by one of the following: a decline in eGFR of > 20% in a patient with pre-existing renal impairment; and/or SCr > ULN for age or GFR < 60 and renal function deteriorating despite prior PE/PI in patients who have no history of pre-existing renal impairment (i.e., who have no baseline eGFR measurement); or SCr > the age-appropriate ULN in pediatric patients (subject to advice from a pediatric nephrologist), OR*
- b) *Onset of neurological impairment related to TMA*

### CDEC response:

Based on the opinion of clinical experts, CDEC suggests that this criterion could be expanded to include evidence of other TMA-related manifestations, such as cardiac ischemia, bowel ischemia, pancreatitis, and retinal vein occlusion.

### Additional criterion 4

Based on the opinion of clinical experts and a comparison with treatment guidelines from the United Kingdom, CDEC suggests that the CDR-participating drug plans consider the inclusion of the following new criterion:

- Transplant patients with a documented history of TMA with ADAMTS 13 > 10% would be eligible for eculizumab if they:
  - Develop TMA immediately following a kidney transplant; OR
  - Previously lost a transplanted kidney due to the development of TMA; OR
  - Have proven aHUS and require a kidney transplant.

### Additional condition

CDEC also suggests that the CDR-participating drug plans consider the inclusion of the following condition for listing eculizumab: *The diagnosis and treatment should be limited to expert centres or specialties*. CDEC acknowledges that the availability of clinical experts may vary across the country; however, given the rarity of the condition and the cost associated with eculizumab treatment, CDEC considers this condition to be reasonable.

## Conclusion

CDEC concluded that individuals living with aHUS have an unmet medical need. Following consideration of the clinical data, input from patient groups, Canadian clinical expert opinion, and reviews from international health technology assessment agencies, CDEC acknowledged that patients with aHUS may potentially benefit from eculizumab treatment. This *CDEC Record of Advice* is intended to help the CDR-participating drug plans refine the proposed criteria to better identify those individuals who are likely to derive the greatest benefit from treatment, should the drug plans decide to reimburse eculizumab.

Given the quality of the available clinical evidence, CDEC elected not to revise the eculizumab (Soliris) [CDEC Final Recommendation](#) (July 18, 2013). Although some longer-term efficacy data have become available since the original CDEC review of eculizumab for aHUS, there remains considerable uncertainty regarding the long-term clinical benefit. In addition, eculizumab is associated with a very high cost per patient, and jurisdictions will need to consider the opportunity costs of decision-making and drug plan and health care system sustainability when making listing decisions for this treatment.

**May 20-21, 2015 Meeting**

**CDEC Members:**

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**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.

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