Common Drug Review
Request for Advice Report

August 2015

Drug	eculizumab (Soliris) 10 mg/mL injectable solution
Indication	Treatment of patients with atypical hemolytic uremic syndrome to reduce complement-mediated thrombotic microangiopathy
Manufacturer	Alexion Pharmaceuticals Inc.
Request for Advice Questions	1. In light of the current situation where no randomized controlled data are available to compare the relative efficacy of eculizumab versus PT/PE in the treatment of aHUS and acknowledging the limited long term benefits of PT/PE 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, and identify any concerns they have with the criteria for diagnosis and initiation criteria (i.e., the defined group of patients who would be eligible for funding) or have suggestions on further refinement of the proposed group of eligible patients who are most likely to derive benefit from eculizumab?

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The report contains an evidence-based clinical and/or pharmacoeconomic drug review, based on published and unpublished material, including manufacturer submissions; studies identified through independent, systematic literature searches; and patient-group submissions. In accordance with *CDR Update — Issue 87*, manufacturers may request that confidential information be redacted from the CDR Clinical and Pharmacoeconomic Review Reports.

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ABBREVIATIONS

aHUS	atypical hemolytic uremic syndrome
AE	adverse event
CDEC	Canadian Drug Expert Committee
CDR	CADTH Common Drug Review
CI	confidence interval
eGFR	estimated glomerular filtration rate
EQ-5D	EuroQol 5-Dimensions Questionnaire
HRQoL	health-related quality of life
LDH	lactate dehydrogenase
NICE	National Institute for Health and Care Excellence
PBAC	Pharmaceutical Benefits Advisory Committee
PT	plasma therapy
PI	plasma infusion
PE	plasma exchange
RCT	randomized controlled trial
RFA	Request for Advice
SAE	serious adverse event
SD	standard deviation
STEC	Shiga toxin–producing *Escherichia coli*
TEAE	treatment-emergent adverse event
TMA	thrombotic microangiopathy
ULN	upper limit of normal
WDAE	withdrawal due to adverse event

1. 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).[1] 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 younger than 13 years 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 5, 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.

In July 2013, the Canadian Drug Expert Committee (CDEC) recommended that eculizumab not be listed for aHUS due to uncertainty regarding the magnitude of the clinical benefit of eculizumab in aHUS patients. A summary of the 2013 CDEC recommendation is presented in Table 1, while the complete recommendation is presented in APPENDIX 1.

TABLE 1: 2013 CDEC RECOMMENDATION FOR ECULIZUMAB IN ATYPICAL HEMOLYTIC UREMIC SYNDROME

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

The CDEC recommendation was based on reviews by the CADTH Common Drug Review (CDR) of clinical evidence and pharmacoeconomic evidence, material submitted by the manufacturer, expert opinion, and patient input. The clinical evidence base considered by CDEC was contained within the CDR clinical review, which concluded the following:

- The evidence of benefits and harms of eculizumab relied on two single-arm, open-label prospective trials (studies C08-002 and C08-003) conducted in a total of six adolescents and 31 adult patients, and one retrospective chart review of 30 patients that included 15 children and four adolescents (Study C09-001r). In all studies, the majority of patients experienced improvements in hematological and renal outcomes while receiving eculizumab and discontinuing PT. However, given the uncontrolled nature of the included studies, it is difficult to determine the extent to which observed improvements are due to eculizumab. A controlled clinical trial against PT would assist in confirming the comparative benefit of eculizumab and potentially identify specific subpopulations of aHUS patients for whom eculizumab could provide the most benefit.

2. REQUEST FOR ADVICE

Although CDEC recommended in 2013 that eculizumab not be reimbursed for aHUS patients, the drug has been made available through exceptional access programs by some of the public drug plans that participate in the CDR process, based on the following considerations:

- First, the manufacturer has indicated that a randomized controlled trial (RCT) would be very challenging to conduct due to the rarity of the disease, and because there are ethical concerns with conducting high-quality trials in patients with such a life-threatening disease.
- Second, clinicians and patients have communicated to some drug plans that plasma infusion or plasma exchange (PI/PE) provides modest symptomatic relief, but has limited long-term efficacy.
- Third, since the finalization and posting of the CDEC recommendation in July 2013, additional studies involving eculizumab have been published, which contain data that were not considered by CDEC.
- Finally, some international jurisdictions (specifically, the Pharmaceutical Benefits Advisory Committee [PBAC] of Australia and the National Institute for Health and Care Excellence [NICE] in the UK) have endorsed funding of eculizumab for aHUS.

Consequently, the plans that participate in the CDR process have submitted a "Request for Advice" (RFA) regarding criteria that could be used to provide access to a specific population of aHUS patients for eculizumab (Soliris) for the treatment of aHUS. Specifically, the 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 ≥ 10% on blood samples taken prior to PE/PI; and
   b) Shiga toxin–producing *Escherichia coli* (STEC) test negative.

2. **Evidence of ongoing active TMA, defined by laboratory test abnormalities despite plasmapheresis (minimum of four plasma exchanges required over four successive days). Patients must demonstrate:**
   a) Unexplained (not a secondary TMA) thrombocytopenia (platelet count < 150×10^9/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 RFA submitted by the participating plans requests advice on the following two questions:

1. In light of the current situation where no randomized controlled data are available to compare the relative efficacy of eculizumab versus PT/PE in the treatment of aHUS and acknowledging the limited long term benefits of PT/PE 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. [emphasis added]
2. **Can CDEC provide any specific comments on the proposed initiation funding criteria**, and identify any concerns they have with the criteria for diagnosis and initiation criteria (i.e., the defined group of patients who would be eligible for funding) **or have suggestions on further refinement of the proposed group of eligible patients** who are most likely to derive benefit from eculizumab. [emphasis added]

3. CADTH COMMON DRUG REVIEW APPROACH TO THE REQUEST FOR ADVICE

To address the questions of the RFA, CDR reviewers attempted to systematically identify relevant clinical evidence using several strategies and sources. First, CDR updated the literature search performed for the original CDR clinical review report to identify any new evidence related to eculizumab in aHUS. Second, CDR performed a new literature search for published and unpublished evidence related to eculizumab in aHUS without restrictions related to study date, study type, or language (see APPENDIX 2 for detailed methodology). The literature search was performed by an information specialist using a peer-reviewed search strategy. Third, information provided by the manufacturer of eculizumab in response to a request by CDR was included in the evidence retrieved by the CDR searches. All studies that were retrieved by CDR search or that were provided by the manufacturer were screened independently by two CDR reviewers. Studies were selected for inclusion in this report if they were carried out in patients with aHUS who met all of the proposed diagnostic criteria for reimbursement. The detailed selection criteria are presented in Table 2.

TABLE 2: INCLUSION CRITERIA FOR THE CURRENT CDR REVIEW

Patient Population	Children and adults patients who meet the following criteria: **1. Confirmed diagnosis of aHUS at initial presentation, defined by presence of TMA** a) ADAMTS-13 activity ≥ 5%[a] on blood samples taken prior to PE/PI,[b] and b) STEC-negative test. **2. Evidence of ongoing active TMA, defined by laboratory test abnormalities despite plasmapheresis (minimum of 4 PEs daily required over 4 successive days).[c] Patients must demonstrate:** a) Unexplained (not a secondary TMA) thrombocytopenia (platelet count < 150×10^9/L); AND hemolysis as indicated by the documentation of 2 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.

	3. Evidence of at least one of the following documented clinical features of active organ damage or impairment: • Kidney impairment as demonstrated by one of the following: • decline in estimated 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 • Onset of neurological impairment related to TMA.
Intervention	Eculizumab intravenous infusion at recommended doses
Comparators	PT (PE or PI), immunosuppressant, supportive care, or no comparison
Outcomes	**Key efficacy outcomes:** Mortality, PT-free status, dialysis-free status, presence of severe bleeding, and patient-related outcomes or HRQoL **Other efficacy outcomes:** TMA response, renal function, hematological parameters **Harms outcomes:** AEs, SAEs, WDAEs, infections, infusion reactions
Study Design	Published and unpublished trials, including observational or case series

ADAMTS-13 = a disintegrin and metalloproteinase with a thrombospondin type 1 motif, member 13; aHUS = atypical hemolytic uremic syndrome; AE = adverse event; CDR = CADTH Common Drug Review; eGFR = estimated glomerular filtration rate; HRQoL = health-related quality of life; LDH = lactate dehydrogenase; PE = plasma exchange; PI = plasma infusion; PT = plasma therapy; SAE = serious adverse event; SCr = serum creatinine; STEC = Shiga toxin–producing *Escherichia coli*; TMA = thrombotic microangiopathy; ULN = upper limit of normal; WDAE = withdrawal due to adverse event.

[a] Note: Although in the proposed criteria, the ADAMTS-13 cut-off for confirming the diagnosis of aHUS is ≥ 10% in Canada, because different laboratory technologies for testing ADAMTS-13 have been used, the cut-off for diagnosis of aHUS is ≥ 5% in the US, Europe, and other countries. Thus, ADAMTS-13 cut-off ≥ 5% has been chosen in the inclusion criteria in this review for identifying the evidence.

[b] If the sample for ADAMTS-13 was not collected prior to PE or PI, platelet counts > 30,000/mm^3 (30×10^9/L) and SCr > 150 µmol/L at TMA presentation will be accepted as predictive of ADAMTS-13 ≥ 10% in TMA patients. In this case, measurement of ADAMTS-13 can be taken 1 to 2 weeks following last PE. The ADAMTS-13 result must be provided within 30 days of commencement of eculizumab AND at least 1 week after last PE; subsequent doses of eculizumab cannot be administered to a patient unless the compliant result has been provided.

[c] Note: Pediatric patients (defined as age < 12 years) are not required to be treated with plasmapheresis in order to have funding consideration for eculizumab, but must have evidence of ongoing active TMA, as defined above. If a patient has a family history of TMA and is genetically positive for aHUS, the patient is not required to be treated with plasmapheresis in order to have funding consideration for eculizumab, as long as he or she has evidence of ongoing active TMA as defined above, along with renal or neurological involvement.

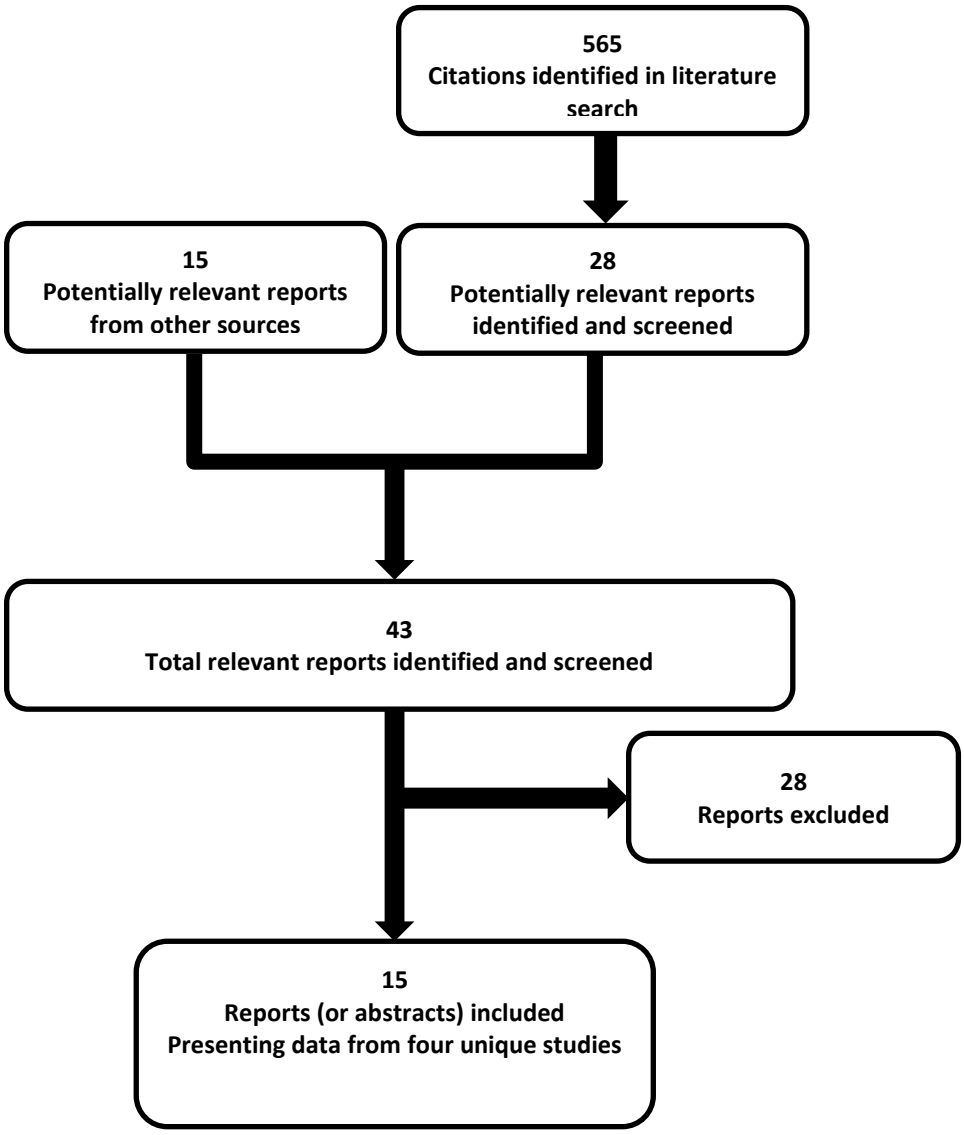
In addition to updating the clinical evidence base, a leading clinical expert in the field of aHUS treatment was consulted to provide an additional clinical context regarding the proposed reimbursement criteria for aHUS and the potential unmet need in the Canadian setting. Finally, several additional clinical experts were consulted to review this report and the proposed reimbursement criteria.

4. FINDINGS

4.1 Quantity of Evidence Available

The literature search yielded 565 citations. Upon screening titles and abstracts, 28 potentially relevant articles or abstracts were retrieved for further review. In addition, 15 potential relevant reference articles or abstracts were provided by the manufacturer or the drug plan RFA submission. Therefore, a total of 43 reports or abstracts were screened. Among these, 15 reports or abstracts, based on four unique clinical studies, met the inclusion criteria for the review. Twenty-eight reports or abstracts[2-29] were excluded due to irrelevant populations or outcomes, or duplicate data, or because they were individual case reports. A detailed flow diagram for inclusion and exclusion is presented in **Figure 1**.

Figure 1: Flow Diagram for Inclusion and Exclusion of Studies



Among the four clinical studies that included patients who meet all of the proposed reimbursement criteria, two studies represented new clinical studies that were not included in the previous CDR review for aHUS. The 15 reports and abstracts identified by CDR included clinical data for the two new studies, as well as newly published data for the two studies that were included in the previous CDR report. Specifically, Study C10-003 was described by three conference abstracts[30-32] and was conducted in pediatric patients (age < 18 years). The second new study[33] was a case series report, in which data were retrieved from the medical records of children who had received PE as treatment for aHUS. The other two studies (studies C08-002 and C08-003), presented in two full-text articles[34,35] and nine conferences abstracts,[17,36-43] were conducted in adolescent and adult patients with aHUS. The findings at week 26 were included in the previous CDR report. The key features of the four included studies are summarized in Table 3.

TABLE 3: KEY CHARACTERISTICS OF INCLUDED STUDIES

Study	Design/ Country	Population	Sample Size	Data Presented in the Previous CDR Review	New Evidence for this Review
Study C08-002[34]	Prospective, single-arm study; Europe, US, and Canada	Adult	17	Results through week 26	Results for year 1 to 3
Study C08-003[35]	Prospective, single-arm study; Europe, US, and Canada	Adult and adolescent	23	Results through week 26	Results for year 1 to 3
Study C10-003[30-32]	Prospective, single-arm study; Europe, US, and Canada	Pediatrics	22	No	Yes
Case series reported by Baskin et al.[33]	Case series report; Turkey	Pediatrics	10	No	Yes

CDR = CADTH Common Drug Review.

4.2 Study Characteristics

The definitions of the primary and secondary outcomes in the three included studies[30,34,35] are presented in Table 4. No clear outcome definition was identified for the case series report.[33]

TABLE 4: OUTCOME DEFINITIONS FOR STUDIES C08-002, C08-003, AND C10-003

Outcomes	Definition
Primary outcomes	
Platelet count increase[35]	Platelet count increase: change in platelet count from baseline to week 26 and the proportion of patients with platelet count normalization (≥ 150 × 10^9/L; proportion of patients with platelet count normalization sustained for at least 2 consecutive measurements for ≥ 4 weeks was an additional analysis).
TMA event-free status[35]	TMA event-free status: absence of all of the following for ≥ 12 consecutive weeks: (1) a decrease in platelet count of > 25%, (2) PE/PI, and (3) new dialysis.
Hematologic normalization[35]	Hematologic normalization: platelet count normalization (≥ 150 × 10^9/L) and LDH ≤ ULN sustained for at least 2 consecutive measurements, which span a period of ≥ 4 weeks.
Secondary outcomes	
TMA outcomes	TMA event-free status (in Study C08-002 only); TMA intervention rate: the number of PE/PIs and new dialysis (interventions per patient per day); rate during the pre-eculizumab period compared with the rate during the eculizumab treatment period. Complete TMA response: hematologic normalization plus improvement in renal function (25% reduction from baseline in SCr in 2 consecutive measurements for ≥ 4 weeks).
Hematologic outcomes	Change in hemoglobin ≥ 20 g/L from baseline; LDH ≤ ULN.
Renal function parameters	eGFR increase ≥ 15 mL/min/1.73 m^2. SCr decrease ≥ 25%. Improvement in proteinuria by ≥ 1 grade. CKD improvement of ≥ 1 stage.
Change in HRQoL	Change in EQ-5D using TTO value set for US population. Attainment of MID in US TTO value (0.06).
Additional	Proteinuria: change in grade according to dipstick measurement (negative, trace 1+, 2+, 3+, and 4+); urine protein-to-creatinine ratio; change in urine protein-to-creatinine ratio from baseline.

CKD = chronic kidney disease; eGFR = estimated glomerular filtration rate; EQ-5D = EuroQol 5-Dimensions Questionnaire; HRQoL = health-related quality of life; LDH = lactate dehydrogenase; MID = minimally important difference; PE/PI = plasma exchange or plasma infusion; SCr = serum creatinine; TMA = thrombotic microangiopathy; TTO = time trade-off; ULN = upper limit of normal.
Note: Criteria were required to be sustained for ≥ 2 consecutive measurements, which span a period of ≥ 4 weeks.
Source: Licht et al.[35] Table 2, p. 5.

The demographic and baseline characteristics of the four included studies are presented in Table 5.

4.2.1 Pediatric patients (age < 18 years)

Two studies (Study C10-003[30-32] and Baskin[33]) were conducted in patients with aHUS who were younger than 18 years. The findings at 26 weeks for Study C10-003 were presented in two conference abstracts[30,31] and data for one year were presented in a conference abstract.[32] Study C10-003 was an open-label, single-arm, phase 2 trial of eculizumab in pediatric patients with aHUS. Inclusion criteria included platelet count less than the lower limit of normal at baseline, lactate dehydrogenase (LDH) more than 1.5 times the upper limit of normal (ULN) at the start of the current manifestation, and elevated SCr at screening. An identified complement abnormality was not required. Patients with STEC-HUS or severe ADAMTS-13 deficiency (< 5%) were excluded. The primary outcome was the proportion of patients who achieved complete TMA response. Dosing was based on weight cohorts, and the regimen was designed in collaboration with investigators and regulatory agencies to ensure that > 95% of patients had complete and sustained terminal complement inhibition (defined as > 80% inhibition in a hemolytic assay). Twenty-two patients (aged one month to 17 years) were enrolled and 19 completed

26 weeks of treatment. The median time from the current manifestation to enrolment was 0.20 months (range: 0.03 to 4.26). At the one-year update, the mean (standard deviation; SD) treatment duration was 12.5 (6.38) months, with a median (range) of 12.6 (0.0 to 24.5) months. In the retrospective study (Baskin et al.[33]), 10 patients (seven girls, three boys) were included. All were younger than 12 years old, except for one patient, who was 12.5 years old (range: 1.5 to 12.5). Time from aHUS onset to PE/PI was two to 10 days. Three of the 10 patients were aHUS relapse and seven patients were newly diagnosed as aHUS. The number of PIs ranged from six to 62. The number of PEs ranged from 10 to 49. A median number of two doses of eculizumab was required to achieve clinical and laboratory improvement (range: 1 to 5 doses).

4.2.2 Adolescent and adult patients

The findings from the two studies (C08-002[34] and C08-003[35]) that were previously included in the original CDR review were presented in two full-text publications[34,35] and nine conference abstracts.[17,36-43] In studies C08-002[34] and C08-003,[35] patients received eculizumab at the standard Health Canada–approved dose for patients ≥ 40 kg; 900 mg infused intravenously once a week for four weeks, after which the dose was increased to 1,200 mg at week 5 and every two weeks thereafter, for a total of 26 weeks. 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 prior. In Study C08-003, patients were included if they were PT sensitive and had stable platelet counts during PT treatment (≥ 1 PT session every two weeks, but no more than three PT sessions per week in the eight weeks prior).

TABLE 5: BASELINE DEMOGRAPHICS AND DISEASE CHARACTERISTICS FOR THE FOUR INCLUDED STUDIES

Parameter	C08-002[34] (N = 17)	C08-003[35] (N = 20)	C10-003[30-32] (N = 22)	Baskin et al.[33] (N = 10)[a]
Age, years, median (range)	28 (17 to 68)	28 (13 to 63)	6.5 (0.0 to 17.0)	4 (1.5 to 12.5)[b]
Aged ≥ 12 years, n (%)	17 (100)	20 (100)	4 (18.2)	1 (10)
Female, n (%)	12 (71)	12 (60)	10 (45)	7(70)
Presence of ≥ 1 complement gene mutation and/or factor H autoantibody, n/N (%)	13/17 (76)	14/20 (70)	NR	NR
Time from diagnosis of aHUS to screening, months, median (range)	9.7 (0.3 to 235.9)	48.3 (0.7 to 285.8)	0.6 (0.03 to 191)	Range: 0.5 to 1.5
Time from current clinical presentation of aHUS to screening, months, median (range)	0.8 (0.2 to 3.7)	8.6 (1.2 to 45.0)	NR	NR
Received PT (PE/PI) within 1 week before eculizumab initiation, n (%)	17 (100)	20 (100)	10 (45)	10 (100%)
Duration of PE/PI, months, median (range)	0.7 (0.1 to 3.2)	10.1 (2.4 to 47.0)	NR	0.5
On dialysis before the first dose of eculizumab, n/N (%)	6/17 (35)	2/20 (10)	11 (50)	8 (80)
≥ 1 Prior kidney transplant, n/N (%)	7/17 (41)	8/20 (40)	2 (9)	NR
Platelet count, × 10^9/L, median (range)	118 (62 to 161)	218 (105 to 421)	Mean (SD): 87.5 (42.3)	Range: 16 to 87
Patients with platelet count < 150 × 10^9/L, n (%)	15 (88)	3 (15)	22 (100)	10 (100)

Parameter	C08-002[34] (N = 17)	C08-003[35] (N = 20)	C10-003[30-32] (N = 22)	Baskin et al.[33] (N = 10)[a]
LDH level, U/L, median (range)	269 (134 to 634)	200 (151 to 391)	Mean (SD): 1,943.7 (1,824.4)	Range: 985 to 2,416
LDH > ULN, n (%)	10 (59)	4 (20)	19 (86.4)	NR
Hemoglobin level, g/L, median (range)	87 (67 to 126)	108 (79 to 131)	Mean (SD): 80.2 (15.3)	Range: 5.8 to 10.5
Serum creatinine, µmol/L, median (range)	256 (124 to 787)	234 (106 to 893)	Mean (SD): 154.5 (116.4)	Range: 125 to 539
eGFR, mL/min per 1.73 m^2				Anuria –63.2
Mean (SD)	23 (15)	31 (19)	32.7 (30.37)	NR
Median	19	28	NR	NR
Range	5 to 59	6 to 72	NR	NR
CKD stage, n (%)			NR	NR
1–2	0	2 (10)	NR	NR
3	5 (29)	8 (40)	NR	NR
4	5 (29)	6 (30)	NR	NR
5	7 (41)	4 (20)	NR	NR
EQ-5D score, median (range)	0.8 (0.3 to 1.0)	0.9 (0.2 to 1.0)	NR	NR

aHUS = atypical hemolytic uremic syndrome; CKD = chronic kidney disease; eGFR = estimated glomerular filtration rate; EQ-5D = EuroQol 5-Dimension Questionnaire; LDH = lactate dehydrogenase; n = number of patients with event; N = total number of patients; NR = not reported; PE = plasma exchange; PI = plasma infusion; PT = plasma therapy; SD = standard deviation; TMA = thrombotic microangiopathy; U/L = upper/lower; ULN = upper limit of normal.

[a] Among the 10 patients, 5 were PE/PI resistant and five were PE/PI dependent. Laboratory data in study by Baskin were the data at time to switch from PT to eculizumab for treatment of aHUS.

[B] Reported as the age when aHUS was diagnosed.

Source: Licht et al.[35] Table 1, p. 4.

4.3 Efficacy

The main efficacy outcomes are presented in Table 6 and Table 7.

4.3.1 Pediatric patients

In Study C10-003, 14 patients (64%) and 15 (68%) achieved a complete TMA response at week 26, and sustained this response up to one year. Platelet levels and eGFR increased significantly from baseline through the 26-week study period and were maintained or further improved at one year. Nine of 11 patients (82%) on dialysis at baseline discontinued dialysis, and all remained dialysis-free at one year. Eleven patients not on dialysis at baseline also remained dialysis-free at one year. Quality of life improved. At week 26, the Pediatric Functional Assessment of Chronic Illness Therapy – Fatigue (Peds-FACIT-F) least squares mean change from baseline to data cut-off was 19.7 (range: 15.6 to 23.7), which was statistically significant ($P < 0.0001$).[30] The author concluded that long-term analysis at one year demonstrated the safety and efficacy of ongoing eculizumab therapy in pediatric patients with aHUS. It is interesting to note that renal function, as represented by eGFR, further increased between week 26 and one year, which suggested the need to pursue eculizumab treatment over the longer term.

In the case series report by Baskin et al.,[33] it was reported that full recovery of hematologic parameters and renal function was obtained in all patients. The time from first eculizumab 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.

4.3.2 Adolescent and adult patients

a) Mortality

During the two-year study period, one patient required new dialysis (days 695 to 696) during hospitalization for an intestinal hemorrhage and subsequently died as a result of this complication.

b) Plasma infusion or plasma exchange–free status

In C08-002 and C08-003, all except two patients in Study C08-002 were able to discontinue PT after the start of eculizumab treatment at week 26. However, PI/PE–free status was not clearly reported during the two-year extension phase.

c) Dialysis-free status

Over two years of study, discontinuation of dialysis was observed in both studies. In Study C08-002, four out of the five patients (80%) on dialysis at baseline discontinued use, including one who discontinued before the first dose of eculizumab, and three who discontinued at a mean of 7.7 days after the treatment was initiated. Two patients (11.8%) were on chronic dialysis at the two-year cut-off. In Study C08-003, of the two patients who required dialysis at baseline, one continued dialysis at the two-year cut-off and the other received dialysis until renal transplantation occurred in the seventh month.

d) Health-related quality of life

Eculizumab significantly improved health-related quality of life (HRQoL), as measured by changes from baseline on the EuroQol 5-Dimensions Questionnaire (EQ-5D). Improvement began after week 1 in Study C08-002 ($P = 0.0398$) and week 3 in Study C08-003 ($P = 0.0013$), and was maintained over two years of treatment ($P < 0.05$ compared with baseline).[36]

e) Thrombotic microangiopathy

Thrombotic microangiopathy event-free status

In Study C08-002, 15 patients (88%) achieved TMA event-free status by 26 weeks and the two-year cut-off. In Study C08-003, TMA event-free status was achieved by 16 patients (80%) at week 26, and 19 patients (95%) by the two-year cut-off. Hematologic normalization was achieved by 18 patients (90%) at all-time points.

Complete thrombotic microangiopathy response

In Study C08-002, complete TMA response was achieved by 11 patients (65%) at week 26 and by 13 patients (76%) at the two-year cut-off. In Study C08-003, complete TMA response was achieved by five patients (25%) at 26 weeks and by 11 patients (55%) at the two-year cut-off.

f) Hematologic outcomes

Platelet count

In Study C08-002, eculizumab treatment was associated with a significant increase in platelet count from baseline at week 26 ($P < 0.001$) and sustained to the two-year cut-off ($P < 0.001$), indicating the inhibition of complement-mediated TMA throughout treatment. Platelet count was normalized in 14 patients (82%) at 26 weeks and in 15 patients (88%) at the two-year cut-off. Hematologic normalization was reported in 13 patients (76%) at week 26 and by 15 patients (88%) at the two-year cut-off. The two patients who did not achieve hematologic normalization withdrew from the study within the initial 26-

week treatment period. In Study C08-003, 18 patients achieved normal platelet counts at the two-year cut-off.

Lactate dehydrogenase

In Study C08-002, LDH normalization was achieved by 14 patients (82%) at 26 weeks and by 15 patients (88%) at two years. In Study C08-003, 19 patients (95%) achieved normal LDH levels at week 26 and sustained at the two-year cut-off.

g) Renal outcomes

Improvements in eGFR from baseline levels that were observed at week 26 and were maintained to the two-year cut-offs of eculizumab treatment in both studies C08-002 and C08-003. Mean changes from baseline in eGFR at week 26 and the two-year cut-off are shown in Table 6.

In Study C08-002, the number of patients who had kidney transplants did not change between baseline and the two-year cut-off, and no patient lost an existing renal graft. In Study C08-003, one patient received a renal transplant on study day 217. No patient underwent renal transplantation or lost an existing renal graft between years 1 and 2 of the study.

In addition, the three years' observation of studies C08-002[43] and C08-003[17] indicated that long-term treatment with eculizumab over three years led to improvements in hematologic and renal outcomes in patients with aHUS and progressing TMA,[43] as well as in patients with aHUS and long disease duration and chronic kidney disease.[17] There were no unexpected adverse events and no cases of meningococcal disease with long-term eculizumab therapy.[17,43]

TABLE 6: EFFICACY OUTCOMES

Parameter	Study C08-002				Study C08-003				Study C10-003		Baskin et al.[33]
	26 Weeks (N = 17)	1 Year (N = 17)	2 Years (N = 17)	3 Years (N = 17)	26 Weeks (N = 20)	1 Year (N = 20)	2 Years (N = 20)	3 Years (N = 20)	26 Weeks (N = 22)	1-Year Analysis (N = 22)	23 Months[a] (N = 10)
Mean change from BL in platelet count, × 10^9/L (95% CI)	73 (40 to 105)	91 (67 to 116)	75 (54 to 96)	NE	5 (–17 to 28)	NA	NA	NE	Mean (SD) 200 (111)	Mean (SD) 175 (59)	Range[b] 172 to 476
Normalization of platelet count, n/N (%)	14/17 (82)	15/17 (88)	15/17 (88)	NE	18/20 (90)	18/20 (90)	18/20 (90)	NE	21	21	NR
TMA event-free status, n/N (%)	15/17 (88)	15/17 (88)	15/17 (88)	15 /17 (88)	16/20 (80)	17/20 (85)	19/20 (95)	NR	–	–	NR
Hematologic normalization, n/N (%)	13/17 (76)	15/17 (88)	15/17 (88)	15 /17 (88)	18/20 (90)	18/20 (90)	18/20 (90)	NR	18/22 (81)	20/22 (90)	NR
Complete TMA response, n/N (%)	11/17 (65)	13/17 (76)	13/17 (76)	NE	5/20 (25)	7/20 (35)	11/20 (55)	NE	14	15	10 (100)
LDH ≤ ULN, n/N (%)	14/17 (82)	15/17 (88)	15/17 (88)	NE	19/20 (95)	19/20 (95)	19/20 (95)	NE	18/22	20/22	Range:[b] 146 to 379
Increase in Hb ≥ 20 g/L from BL, n/N (%)	11/17 (65)	13/17 (76)	13/17 (76)	NE	9/20 (45)	10/20 (50)	13/20 (65)	NE	–	–	Range:[b] 11.4 to 13.6
Mean change in haptoglobin level from BL, g/L (SD)	0.5 (0.44)	0.6 (0.41)	0.9 (0.38)	NE	–0.1 (0.52)	0.3 (0.61)	0.5 (0.64)	NE	–	–	NR
Renal Outcomes											
eGFR increased from BL, mL/min per 1.73 m^2, n/N	NR	NR	NR	NE	NR	NR	NR	NE	Mean (SD) 66.9 (41.4)	Mean (SD) 79.9	Range:[b] 86 to 113

Parameter	Study C08-002				Study C08-003				Study C10-003		Baskin et al.[33]
	26 Weeks (N = 17)	1 Year (N = 17)	2 Years (N = 17)	3 Years (N = 17)	26 Weeks (N = 20)	1 Year (N = 20)	2 Years (N = 20)	3 Years (N = 20)	26 Weeks (N = 22)	1-Year Analysis (N = 22)	23 Months[a] (N = 10)
(%)										(11)	
Increase in eGFR of ≥ 15 mL/min per 1.73 m^2, n/N (%)	8/17 (47)	9/17 (53)	10/17 (59)	59%	1/20 (5)	3/20 (15)	8/20 (40)	40%	19/22 (86.4)	19/22 (86.4)	NR
Decrease in SCr level of ≥ 25%, n/N (%)	11/17 (65)	13/17 (76)	13/17 (76)	76%	3/20 (15)	7/20 (35)	11/20 (55)	55%	16/22 (72.7)	16/22 (72.7)	Range:[b] 35 to 90
Improvement in proteinuria by ≥ 1 grade, n/N (%)	12/16 (75)	13/16 (81)	14/16 (88)	NE	6/11 (55)	7/11 (64)	9/11 (82)	NE	–	–	NR
Improvement in CKD by ≥ 1 stage, n/N (%)	10/17 (59)	11/17 (65)	12/17 (71)	76%	7/20 (35)	9/20 (45)	12/20 (60)	60%	17/20 (85)	17/20 (85)	NR

BL = baseline; CDR = CADTH Common Drug Review; CI = confidence interval; CKD = chronic kidney disease; eGFR = estimated glomerular filtration rate; Hb = hemoglobin; LDH = lactate dehydrogenase; n = number of patients with event; N = total number of patients; NA = not applicable; NE = not extractable, because data were presented in figures; NR= not reported; SCr = serum creatinine; SD = standard deviation; TMA = thrombotic microangiopathy; ULN = upper limit of normal range.

[a] Median follow-up time: 23 months (range: 20 to 38)

[b] The data indicated range of level at the end of treatment.

Source: Two full-text publications[34,35] and 5 abstracts[36-38,44,45] plus 7 more abstracts[30,31,39-41,43,46] (total 12 abstracts) based on the 2 studies (Study C08-002 and Study C08-003) that were already included in the original CDR clinical review report. For studies C08-002 and C08-003, the data for week 26, 1 year, and 2 years are extracted from the CDR review, Licht et al.,[35] and Legendre et al.[34] ; the data for the 3-year analysis were extracted from Sheerin et al.[43] and Delmas et al.[17] for studies C08-002 and C08-003, respectively. Study C10-003[30-32,44]

TABLE 7: MEAN CHANGE FROM BASELINE IN EGFR IN STUDIES C08-002 AND C08-003

Time Point	Change From Bl In Egfr (Ml/Min/ 1.73 M^2)	*P* Value		
		Compared With BL Egfr	Compared With Change From BL At Week 26	Compared With Change From BL At 1 Year
Study C08-002[34,35]				
Week 26 (n = 15)				
Mean (SD)	33 (33)	0.0018		
Median (range)	20 (–1 to 98)			
Year 1 (n = 12)				
Mean (SD)	25 (30)	0.0164	0.6299	
Median (range)	15 (–8 to 82)			
Year 2 (n = 9)				
Mean (SD)	37 (30)	0.0062	0.2099	0.0285
Median (range)	29 (3 to 82)			
Study C08-003[34,35]				
Week 26 (n = 20)				
Mean (SD)	6 (6)	0.0003		
Median (range)	5 (–1 to 20)			
Year 1 (n = 17)				
Mean (SD)	7 (10)	0.0057	0.5264	
Median (range)	5 (–14 to 23)			
Year 2 (n = 15)				
Mean (SD)	8 (17)	0.0959	0.8689	0.7700
Median (range)	11 (–42 to 30)			

BL = baseline; eGFR = estimated glomerular filtration rate; SD = standard deviation.
Source: Licht et al.[35]

4.4 Harms

A summary of the adverse events reported for the four included studies is presented in Table 8.

4.4.1 Pediatric patients

It was reported that eculizumab was well tolerated and there were no meningococcal infections or deaths during the 26-week study period.

Twenty of 22 patients enrolled (91%) reported at least one treatment-emergent adverse event (TEAE). None of the infection-related TEAEs were considered severe. Thirteen of 22 patients (59%) reported at least one serious TEAE. One patient discontinued due to agitation, a serious TEAE. No systemic complications related to eculizumab were reported in the case series by Baskin et al.[33] No safety information was reported.

4.4.2 Adolescent and adult patients

a) Serious adverse events

Through the two-year data cut-off, 17 patients (100%) in Study C08-002 and 12 patients (60%) in Study C08-003 reported serious adverse events (SAEs). However, SAEs considered possibly, probably, or

definitely associated with eculizumab, as identified by the investigator, through two years of treatment were reported in four patients in each of the two studies.

b) Adverse events

All 17 patients enrolled in Study C08-002 and 20 patients enrolled in Study C08-003 reported one or more adverse events (AEs). The most common possible eculizumab-related AEs were hypertension, headache, leukopenia, and vomiting. AEs were reported with less frequency over time from week 26 to the two-year update.

a) Withdrawal due to adverse events

Only one patient in Study C08-002 discontinued the treatment due to AEs.

TABLE 8: SUMMARY OF HARMS REPORTED FOR THE THREE INCLUDED STUDIES

Adverse Event	Study C08-002 (N = 17)		Study C08-003 (N = 20)		Study C10-003 (N = 22)
	n (%)		n (%)		n (%)
	At 2 years[a]	At 3 years	At 2 years	At 3 years	At week 26[30]
Death	0	0	1	0	0
SAE[b]		NR			
Accelerated hypertension	2 (12)	NR	NR	NR	NR
Asymptomatic bacteriuria	1 (6)	NR	NR	NR	NR
Hypertension	1 (6)	NR	NR	NR	NR
Influenza	NR	NR	1 (5)	NR	NR
Peritonitis	NR	NR	1 (5)	2(10)	NR
Venous sclerosis at infusion site	NR	NR	2 (10)	2(10)	NR
Patients with ≥ 1 TESAE n (%)	NR	NR	NR	NR	13 (59)
Patients with TESAE (occurring in ≥ 2 patients), n (%)	NR	NR	NR	NR	NR
Fever	NR	NR	NR	NR	2 (9)
Gastroenteritis, viral	NR	NR	NR	NR	2 (9)
Upper respiratory tract infection	NR	NR	NR	NR	2 (9)
Hypertension	NR	NR	NR	NR	2 (9)
Adverse events					
Abnormal blood clotting	NR	NR	1 (5)	1 (5)	NR
Alopecia	NR	NR	1 (5)	1 (5)	NR
Anemia	NR	NR	1 (5)	1 (5)	
Asthenia	1 (6)	NR	NR	NR	NR

Adverse Event	Study C08-002 (N = 17)		Study C08-003 (N = 20)		Study C10-003 (N = 22)
	n (%)		n (%)		n (%)
	At 2 years[a]	At 3 years	At 2 years	At 3 years	At week 26[30]
Chest discomfort	NR	NR	1 (5)	1 (5)	NR
Cough or productive cough	NR	NR	2 (10)	2 (10)	NR
Deafness, bilateral	NR	NR	1 (5)	1 (5)	NR
Dermatitis	1 (6)	NR	NR	NR	NR
Diarrhea	1 (6)	NR	NR	NR	NR
Erythema	1 (6)	NR	NR	NR	NR
Extravasation	NR	NR	1 (5)	1 (5)	NR
Fatigue	1 (6)	NR	NR	NR	NR
Headache	1 (6)	NR	3 (15)	3 (15)	NR
Hematocrit, decreased	1 (6)	NR	NR	NR	NR
Hematuria	(6)	NR	NR	NR	NR
Hemoglobin, decreased	1 (6)	NR	NR	NR	NR
Herpes zoster	1 (6)	NR	NR	NR	NR
Human polyomavirus (BK) infection	NR	NR	1 (5)	1 (5)	NR
Hypotension	NR	NR	1 (5)	1 (5)	NR
Impetigo	1 (6)	NR	NR	NR	NR
Leukopenia	2 (12)	NR	2 (10)	2 (10)	NR
Lymphopenia	NR	NR	2 (10)	2 (10)	NR
Menorrhagia	NR	NR	1 (5)	1 (5)	NR
Nasal congestion	NR	NR	1 (5)	1 (5)	NR
Nasopharyngitis	NR	NR	1 (5)	1 (5)	NR
Nausea	2 (12)	NR	NR	NR	NR
Pharyngolaryngeal pain	NR	NR	1 (5)	1 (5)	NR
Pruritus	NR	NR	1 (5)	1 (5)	NR
Pyrexia	1 (6)	NR	NR	NR	NR
Q fever	NR	NR	1 (5)	1 (5)	NR
Rhinorrhea	NR	NR	1 (5)	1 (5)	NR
Tremor	1 (6)	NR	NR	NR	NR
Urinary tract infection	1 (6)	NR	NR	NR	NR
Vertigo	NR	NR	NR	NR	NR
Vomiting	3 (18)	NR	NR	NR	
Patients with ≥ 1 TEAE, n (%)	NR	NR	NR	NR	20 (91)
Patients with TEAEs (frequency ≥ 20%), n (%)	NR	NR	NR	NR	NR

Adverse Event	Study C08-002 (N = 17)		Study C08-003 (N = 20)		Study C10-003 (N = 22)
	n (%)		n (%)		n (%)
	At 2 years[a]	At 3 years	At 2 years	At 3 years	At week 26[30]
Fever	NR	NR	NR	NR	11 (50)
Cough	NR	NR	NR	NR	8 (36)
Abdominal pain	NR	NR	NR	NR	7 (32)
Diarrhea	NR	NR	NR	NR	7 (32)
Upper respiratory tract infection	NR	NR	NR	NR	7 (32)
Vomiting	NR	NR	NR	NR	6 (27)
Nasopharyngitis	NR	NR	NR	NR	6 (27)

AE = adverse event; n = the number of patients with event; NR = not reported, SAE = serious adverse event; TEAE = treatment-emergent adverse event; TESAE = treatment-emergent serious adverse event; WDAE = withdrawal due to adverse event.
[a] AEs reported at 2 years in this table are the AEs considered possibly, probably, or definitely associated with eculizumab treatment, as identified by the investigator.
[b] An SAE was defined as any event that results in death, is immediately life-threatening, requires hospitalization or prolongation of existing hospitalization, results in persistent or significant disability or incapacity, or is a congenital anomaly or birth defect.
Source: Licht et al.[35] Greenbaum et al.[30]

5. DISCUSSION

5.1 Summary of New Evidence

Two included studies were conducted in pediatric patients with aHUS. One study (C10-003) was identified that was conducted in patients with aHUS younger than 18 years. Patients met all three proposed diagnostic criteria. Of the 22 patients who participated in the study, 19 completed at 26 weeks and at one year. The results were presented in three conference abstracts.[30-32] Dosing was based on weight cohorts, and the regimen was designed in collaboration with investigators and regulatory agencies, but no detailed information on the study design or dosage regimen was provided.[30-32] It was reported that 64% and 68% of patients achieved complete TMA response at week 26 and at one year, respectively. Platelet levels and eGFR increased significantly from baseline through the 26-week study period and were maintained or further improved at one year. Nine of 11 patients (82%) on dialysis at baseline discontinued dialysis, and all remained dialysis-free at one year. Quality of life was reportedly significantly improved. However, it is not clear whether the observed improvement was clinically meaningful, as no minimal clinically important difference was identified. The other study, a retrospective study, included 10 children treated with eculizumab. Five of the 10 patients were PE/PI resistant and five were PE/PI dependent. Full recovery of hematological parameters and renal functions was observed after switching from PE/PI to treatment with eculizumab.

The new evidence for adolescent and adult patients was derived from two studies (C08-002 and C08-003). In both studies, patients received 900 mg weekly for four weeks, followed by 1,200 mg at week 5, and 1,200 mg every two weeks thereafter. The duration of the study was 26 weeks[34,35] and was extended to two years.[35] Patients were predominantly adult women from Europe and North America. The percentage of patients experiencing their first aHUS attack was 41% and 25% in studies C08-002 and C08-003, respectively, while the percentage of patients with a previous kidney transplant was approximately 40% in both studies. Of the two studies, the clinical efficacy and safety results at week 26 were already included in the original CDR review. The two-year analyses of two trials 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 addition, the three years' observation of the two studies indicated that long-term treatment with eculizumab over three years led to improvements in hematologic and renal outcomes in patients with aHUS and progressing TMA.[17,43]

5.2 Interpretation of the Results

The clinical studies included in this report presented data for a total of 59 aHUS patients who were resistant to PE/PI treatment and had aHUS confirmed using all of the diagnostic criteria that underlie the proposed reimbursement criteria. Most pediatric and adult patients experienced improvements in hematological and renal outcomes while receiving eculizumab, and most patients were able to discontinue PI/PE. The available data indicate that the aforementioned improvements were maintained for up to three years. These data represent additional clinical evidence that eculizumab may provide the subset of patients who meet the proposed reimbursement criteria with some meaningful clinical benefit that was not available at the time that the previous CDR report was prepared. However, while the additional evidence provide data for a larger number of patients than at the time of the CDEC Recommendation, the quality of the clinical evidence is not better than that included in the previous report. Indeed, the inclusion in the current report of any available evidence (from an appropriate population), irrespective of study design, resulted in the inclusion of some evidence that is of poorer

quality than that considered previously (e.g., conference abstracts that could not be verified). Nevertheless, it is acknowledged that given the rarity of the disease, and the life-threatening nature of the disease if not treated optimally, it is unlikely that a high-quality RCT is feasible in this population. Therefore, the actual magnitude of the clinical effect of eculizumab in aHUS patients remains unclear and will likely remain so in future.

5.3 Funding Criteria in Other Agencies

Some international jurisdictions, namely PBAC in Australia and NICE in the UK, have proceeded to develop criteria that will allow for the public funding of eculizumab treatment in a subpopulation of aHUS patients. PBAC had concerns similar to those noted by CDEC regarding the available evidence;[47] however, when considering the unmet need and the input of clinicians and patients, PBAC decided to allow for public funding of eculizumab for aHUS patients who meet specific diagnostic criteria (see APPENDIX 4). NICE has also endorsed funding of eculizumab for aHUS with a national protocol to develop initiation and discontinuation criteria.[48] NICE noted several specific concerns with PT/PE for aHUS, including the variability of responses and the fact that, despite the use of PT/PE, up to 40% of patients may die or progress to end-stage renal failure and need dialysis with the first clinical aHUS manifestations. Nevertheless, they felt compelled by the available evidence to consider funding for a defined group of patients, which they will define publicly some time in 2015.

A major consideration for reimbursement of eculizumab in other jurisdictions, specifically in Australia and the UK, has been the argument that eculizumab fulfills an unmet medical need for aHUS patients who do not respond to conventional therapy with PI/PE. CDR consulted a Canadian clinical expert who confirmed that such an unmet need exists also in Canada, because PI/PE provides modest symptomatic relief but has limited long-term efficacy. The clinical expert indicated that the diagnostic criteria that underlie the proposed reimbursement criteria are appropriate to ensure that patients with other types of TMA (such as thrombotic thrombocytopenic purpura, Shiga-toxin HUS, or other secondary TMAs that most likely would respond to PE/PI) who do not reflect the unmet need would not be treated with eculizumab. Regarding the evidence available to support the efficacy of eculizumab in aHUS patients who reflect the unmet need due to the inadequacy of PI/PE, the data presented in this report include some new evidence that eculizumab does provide some clinical benefit, which persists for up to three years, in patients who are resistant to PE/PI treatment.

The PBAC funding criteria consist of initiation and continuation criteria for those patients who are considered to be responders,[47] and the PBAC criteria resemble the proposed reimbursement criteria of the public plans in Canada who participate in the CDR process, as documented in Section 2 (Request for Advice). However, a notable difference between the PBAC reimbursement criteria and those proposed in Section 2 of this report is that PBAC does not require patients to have been treated previously with plasmapheresis. Similarly, the NICE guidance document does not specify that patients must have undergone plasmapheresis. By contrast, the proposed Canadian reimbursement criteria require patients to have had a minimum of four PEs over four successive days (see Section 2). Although the clinical evidence that CDR included in the current report required that patients have ongoing TMA despite plasmapheresis, there is one study of eculizumab that included patients with acute aHUS who had not undergone plasmapheresis (Study C10-004), for which relevant data have been presented in two abstracts.[2,18] Study C10-004 included 44 adult patients, 41 of whom received eculizumab, and 38 (92.7%) of whom completed 26 weeks of treatment. The patients had a two-week median interval between disease onset and initiation of eculizumab treatment. Of the 24 patients on dialysis at baseline, 20 (83.3%) discontinued dialysis before week 26 and remained dialysis-free at one year. One of the four patients who continued dialysis at week 26 discontinued dialysis by one year. Of the four patients with

no baseline dialysis and who initiated new dialysis, two discontinued dialysis by week 26. At the one-year update, mean (SD) exposure to eculizumab was 13.2 (7.1) months. It was reported that the outcomes at the one-year update suggested that eculizumab continued to inhibit TMA and maintain the clinical gains observed after 26 weeks of therapy. Three patients withdrew during the 26-week study period (one due to a SAE of meningococcal meningitis, one due to lack of efficacy, and one due to pregnancy). No unexpected safety signals were observed at the one-year update. Based on the short (two-week) duration between diagnosis of aHUS and treatment with eculizumab, the authors concluded that these findings support the recommendation that eculizumab therapy be initiated immediately once a diagnosis of aHUS is made. However, because the diagnosis of aHUS in this study was not confirmed by evidence of ongoing active TMA, as defined by laboratory test abnormalities despite plasmapheresis, it is unclear whether these patients had TMAs other than aHUS.

5.4 Clinical Expert Input

Three Canadian nephrologists with clinical expertise in the diagnosis and management of aHUS (one pediatric nephrologist) were consulted by CDR to provide feedback on the diagnostic criteria that underlie the proposed reimbursement criteria. All three experts agreed there is a need to fund the eculizumab treatment for aHUS, and based this opinion on both the clinical evidence available and the unmet medical need of aHUS patients. However, all of the experts agreed that given the difficulty in definitively diagnosing aHUS and the high cost of eculizumab, there is a need to establish reimbursement criteria, based on diagnostic criteria, that will allow for the selection of patients with confirmed aHUS; not only would these patients be most likely to benefit from eculizumab treatment, but diagnostic criteria allow for differentiation of appropriate patients from those patients with more common forms of TMA. All of the clinical experts agreed in principle with each of the three proposed reimbursement criteria, although two experts provided some suggestions to further refine the wording of the criteria (see Table 9). However, two experts noted that the value of a Shiga-toxin test in patients (particularly adults) without a history of exposure or a clinical history of colitis or bloody diarrhea is unclear. One expert stated that the proposed criteria should be validated clinically prior to being implemented broadly. One expert suggested adding an additional requirement to criterion 1, specifically that an alternative diagnosis of conditions that are unlikely to respond to PE/PI or eculizumab treatment should be ruled out (see criterion 1c in Table 9). The experts suggested that potential conditions to be ruled out include disseminated intravascular coagulation, disseminated malignancy, malignant hypertension, malignant hypertension, antiphospholipid antibody syndrome, lupus, scleroderma, and HIV.

One expert provided additional criteria that would capture an additional subgroup of aHUS patients, and these were endorsed by the other experts (see criterion 4 in Table 9). Specifically, the additional criteria would address the subset of patients who have lost their kidney function and/or are awaiting a kidney transplant and are either known to have aHUS or are at a high risk of developing aHUS. The additional criteria propose that in such patients, as well as in patients with a low risk of relapse who develop a TMA after a renal transplant, eculizumab should be administered prophylactically as per the UK Renal Association Clinical Practice Guidelines.[49] Patients potentially eligible under this criterion are proposed to be considered for a case-by-case review of eligibility for reimbursement of eculizumab treatment after being recommended for eculizumab therapy by a nephrologist or hematologist.

In support of the aforementioned criteria for renal transplant patients, there is unpublished evidence to suggest that the use of prophylactic eculizumab therapy in such patients improved outcomes by reducing the rate of graft loss from 40% to less than 5% (based on personal communication between one of the clinical experts and a member of the UK aHUS transplant registry). CDR reviewers noted that the population of patients represented by the clinical evidence presented in this report included patients who had undergone a kidney transplant; therefore, there is evidence available to suggest that this subpopulation would respond to eculizumab in a manner similar to other aHUS patients.

TABLE 9: SUMMARY OF THE CLINICAL EXPERTS' FEEDBACK ON PROPOSED CRITERIA

Proposed Criteria in the Request for Advice	Feedback From Clinical Experts		
	Expert 1	Expert 2	Expert 3
1. Confirmed diagnosis of aHUS at initial presentation, defined by presence of TMA a) ADAMTS-13 activity ≥ 10% on blood samples taken prior to plasma exchange or plasma infusion (PE/PI), and b) STEC-negative test.	Concurred	Concurred, but noted that the value of the STEC test in the absence of a history of a diarrheal illness is unclear.	Concurred, but noted that: • Confirming diagnosis may take a long time • Taking samples prior to PE/PI is not necessary as low ADAMTS-13 activity persists despite daily PE/PI • STEC test may be appropriate in all children, but not in adults without a history of exposure or clinical history of colitis or bloody diarrhea.
Additional requirement suggested by clinical experts			
c) Absence of an alternative diagnosis (such as DIC, disseminated malignancy, malignant HTN) that is unlikely to respond to PE/PI or eculizumab.	Concurred	Concurred, and suggested additional conditions to rule out, including malignant HTN; APL antibody syndrome; lupus; scleroderma; and HIV.	Concurred
2. Ongoing active TMA, defined by laboratory test abnormalities despite plasmapheresis (minimum of 4 PEs daily required over 4 successive days). Patients must demonstrate: a) Unexplained (not a secondary TMA) thrombocytopenia (platelet count < 150 × 10^9/L); AND hemolysis as indicated by the documentation of 2 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.	Concurred		
3. At least 1 of the following documented clinical features of active organ damage or impairment: • Kidney impairment as demonstrated by one of	Concurred	Concurred, but noted that other presentations — such as pancreatitis, gastric ischemia, and cardiac	Concurred, but noted the populations not covered by this criterion are (a) patients presenting with tissue damage due to other

Proposed Criteria in the Request for Advice	Feedback From Clinical Experts		
	Expert 1	Expert 2	Expert 3
the following: 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 • Onset of neurological impairment related to TMA.		involvement — should be addressed, as in the Australian guidelines.	diseases without overt hematological manifestations, and (b) patients with tissue damage due to retinal vessel occlusion or stroke where a pathological diagnosis may not be possible.
Additional criterion suggested by clinical experts			
4. 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 kidney transplant due to the development of TMA OR Have proven aHUS and require a kidney transplant	Concurred		

ADAMTS-13 = a disintegrin and metalloproteinase with a thrombospondin type 1 motif, member 13; aHUS = atypical hemolytic uremic syndrome; AE = adverse event; APL = antiphospholipid antibody; DIC = disseminated intravascular coagulation; eGFR = estimated glomerular filtration rate; HRQoL = health-related quality of life; HTN = hypertension; LDH = lactate dehydrogenase; PE = plasma exchange; PI = plasma infusion; PT = plasma therapy; SAE = serious adverse event; SCr = serum creatinine; STEC = Shiga toxin–producing *Escherichia coli*; TMA = thrombotic microangiopathy; ULN = upper limit of normal.

5.5 Patient Input

Two patient groups (aHUS Canada and the Canadian Organization for Rare Disorders [CORD]) provided input for this RFA. Both groups acknowledged that clinical evidence regarding the efficacy and safety of eculizumab in aHUS patients is very limited. However, the patient groups emphasized that there is an unmet medical need for aHUS patients, which could be met by providing access to eculizumab. They also noted that both PBAC and NICE have endorsed funding for eculizumab based on the same evidence base available to CDEC. A summary of the patient input is presented in APPENDIX 3.

6. CONCLUSIONS

CDR identified new clinical evidence regarding the efficacy and harms of eculizumab in aHUS patients resistant to PE/PI treatment that was not available at the time of the original CDR review in 2013. New evidence was derived from two new studies, namely Study C10-003 (a single-arm, open-label prospective trial) and a case series reported by Baskin et al.,[33] as well as the long-term extension phases of two studies (studies C08-002 and C08-003; both single-arm, open-label prospective trials) that were included in the previous CDR review. All patients met the diagnostic criteria that underlie the proposed reimbursement criteria to identify appropriate aHUS patients. Although the quality of the available clinical evidence remains low and precludes any determination of effect size, the available evidence does suggest that most pediatric and adult patients experience improvements in hematological and renal outcomes while receiving treatment with eculizumab, and that these improvements persist for up to three years (the extent of the available follow-up data). Therefore, there does appear to be clinical evidence to support the efficacy of eculizumab in the population of aHUS patients subscribed by the three proposed reimbursement criteria outlined in the RFA. The proposed criteria are broadly aligned with those of PBAC in Australia, except for the requirement for patients to have undergone plasmapheresis. Three clinical experts consulted by CDR endorsed the proposed criteria as a means of providing access to eculizumab for those aHUS patents most likely to benefit from treatment. In addition to the proposed criteria, the clinical experts suggested an additional requirement to rule out alternative diagnoses and to allow coverage for a subpopulation of renal transplant patients with aHUS. These criteria should allow for aHUS patients with the greatest unmet medical need to be treated with eculizumab, which is in line with the wishes of representative patient groups.

APPENDIX 1: CDEC RECOMMENDATION FOR ATYPICAL HEMOLYTIC UREMIC SYNDROME (2013)[1]

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).

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, multi-centre, 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 end point 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 decrease of ≥ 25% in serum creatinine level; and 47%, 5% and 37% of patients (respectively) improved by ≥ 15 mL/minute/1.73 m^2 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.

APPENDIX 2: LITERATURE SEARCH METHODS

Literature Search Methods

The literature search was performed by an information specialist using a peer-reviewed search strategy.

Published literature was identified by searching the following bibliographic databases: MEDLINE (1946–) with in-process records and daily updates via Ovid; Embase (1974–) via Ovid; and PubMed. The search strategy consisted of both controlled vocabulary, such as the National Library of Medicine's MeSH (Medical Subject Headings), and keywords. The main search concepts were Soliris (eculizumab) and hemolytic uremic syndrome.

No filters were applied to limit retrieval by study type. Where possible, retrieval was limited to the human population. Retrieval was not limited by publication year or by language.

The initial search was completed on February 25, 2015. Regular alerts were established to update the search until the meeting of the Canadian Drug Expert Committee (CDEC) on May 20, 2015. Regular search updates were performed on databases that do not provide alert services.

Grey literature (literature that is not commercially published) was identified by searching relevant websites from the following sections of the Grey Matters checklist (http://www.cadth.ca/en/resources/finding-evidence-is/grey-matters): guidelines, drug regulatory approvals, and supplemental Google search. These searches were supplemented by reviewing the bibliographies of key papers and through contacts with appropriate experts.

APPENDIX 3: PATIENT INPUT

This section was summarized by CADTH Common Drug Review (CDR) staff, based on the input provided by patient groups. It has not been systematically reviewed.

1. Brief Description of Patient Group(s) Supplying Input

One patient group, aHUS Canada, submitted input regarding the eculizumab atypical hemolytic uremic syndrome (aHUS) Request for Advice. Another group, the Canadian Organization for Rare Disorders (CORD), provided comments on both Australia's Pharmaceutical Benefits Advisory Committee (PBAC) funding criteria (August 24, 2014) and the final, highly specialized technical guidance (January 28, 2015) by NICE.

aHUS Canada is a nationwide group with the mission of supporting patients and families living with aHUS. In addition to providing support to patients and caregivers, aHUS Canada strives to connect those affected by the condition to establish a Canadian aHUS community, build public awareness and understanding of this very rare and potentially fatal disease, and advocate for the best possible care and treatment for patients. aHUS Canada has received an unrestricted educational grant from Alexion. There are no other conflicts of interest with respect to corporate members, sponsorship, or funding arrangements.

CORD is Canada's national network for organizations representing all those with rare disorders. CORD provides a strong common voice to advocate for health policy and a health care system that works for those with rare disorders. CORD works with governments, researchers, clinicians, and industry to promote research, diagnosis, treatment, and services for all rare disorders in Canada. CORD declared the following sources of support: AbbVie Canada, Actelion Pharmaceuticals, Aegerion Pharmaceuticals, Alexion Pharmaceuticals, Amgen Canada, Amicus Therapeutics Inc., ApoPharma, Bayer, Bayshore Home Health, BioMarin Pharmaceutical, BIOTECanada, Rx&D: Canada's Research-Based Pharmaceutical Companies, Celgene, CSL Behring Canada, Genzyme Canada, Gilead Sciences Canada, GSK, Hoffmann-La Roche, Ikaria, Janssen, MK&A, Medunik Canada, Merck Frosst Canada, Novartis Pharmaceuticals Canada, Pfizer Canada, PTC Therapeutics, Rare Disease Therapeutics, Sanofi Canada, SHIRE Human Genetic Therapies, Sigma-Tau Pharmaceuticals Inc., Valeo Pharmaceuticals Inc., and ViroPharma.

2. Condition and Current Therapy-Related Information

This information was obtained through one-on-one conversation with a variety of patients with aHUS and their caregivers.

A patient's life can be broken into two phases, acute and maintenance. In the acute phase, the primary clinical symptoms are the most threatening and difficult to control: anemia, low platelet count, and acute renal failure. Patients describe their initial symptoms as flu-like, with feelings of general "unwellness" accompanied by extreme fatigue and edema. These initial symptoms eventually prompted all of the patients surveyed to go to their local emergency room, where they were admitted straight to the intensive care unit (ICU). All but one of the patients surveyed required dialysis immediately. There is a very short timeline from the patient initially not feeling well to being admitted to the ICU. At the onset, the kidney is the first vital organ to be stricken. Continual uncontrolled systemic thrombosis leads to the beginning of failure of other organs. In one case, a patient's thrombosis was so severe that an arm and leg were amputated; the patient also had a colectomy. Patients cannot attend work or school

during the acute phase. The length of hospital stay is anywhere from 10 days to a couple of months, depending upon the severity of the symptoms and the number of organs affected.

The maintenance phase can be further subdivided, into those in kidney failure and those who maintain their original kidneys. Most patients go from the acute phase straight to dialysis in the maintenance phase. Generally, plasma therapy (PT) is not required while on dialysis, except for patients who have maintained their original kidneys or those who are re-entering the acute phase. Some patients are able to work or attend school on a limited basis while in the maintenance phase. The quality of their lives is limited by dialysis schedules, central lines, extreme fatigue, a variety of adverse events, dietary restrictions, the need to avoid common infections that may trigger re-entry to the acute phase, social isolation, and anxiety. These difficulties are exacerbated as many patients are young children.

PT is described as "virtually ineffective" in the acute phase for stopping systemic clotting or controlling systemic thrombosis. It also does not address the underlying cause of aHUS and carries serious — sometimes fatal — risks. Prior to infusions, patients must be pre-medicated to prevent or reduce allergic reactions. aHUS patients must also take other supportive therapy, including vitamins, phosphate binders, iron therapy, hormones to stimulate red blood cell production, and blood pressure medication. All infusion patients reported increased fatigue, confused thinking, and nausea post-treatment, and experienced high total protein levels, increased blood pressure, and headaches. Similar side effects are described in patients on chronic dialysis. A variety of central lines are used for PT, including fistulas and portacaths. These patients therefore have to undergo multiple surgeries and suffer the associated risks. Despite some level of tolerance in patients, all adverse effects compound over time and contribute to the progression of the disease, increasing the likelihood of a relapse. Eventually, the native kidneys of the few patients who undergo PT to maintain them fail as well.

Because PT is available only in major hospitals, many patients must travel, increasing time and financial burdens on families. Parents of patients receiving PT estimated that their children miss 30% to 40% of their school year, with the parents' absenteeism from work at 20% to 40%. Some families have lost their life-savings, been forced to sell their businesses, required one parent to cease work entirely to dedicate themselves to care, and/or had to move and find new employment closer to a treatment centre when their child was diagnosed. Additionally, because PT and dialysis do not control the underlying complement activity of aHUS and merely buy time before the onset of end-stage renal disease, patients are not eligible for kidney transplant, and thus have no hope for improvement in their quality of life. Patients on dialysis experience similar hardships. Hemodialysis requires at least four hours, three days per week. Extra time is spent travelling to and from dialysis. If dialysis is done at home, then there is extra, significant burden on the patient's family. In these cases, up to 10 hours, six days per week are required. Both school and work are severely affected, with most patients on dialysis unable to maintain full-time employment, both because of the time commitment and the inherent detrimental effects on health and well-being.

As aHUS is often caused by a genetic mutation, parents often suffer from guilt or marital stress due to one parent having passed on the mutation. Additionally, people who are genetically predisposed toward aHUS, and their loved ones, live in fear of unknown triggers that might cause the affliction.

The high amounts of emotional, psychological, financial, and responsibility-related stress on patients and their families lead to feelings of isolation, fear, hopelessness, anxiety, and depression, all of which are compounded by the lack of available governmental and community support services due to the relative rarity of aHUS.

3. Related Information About the Drug Being Reviewed

Patients expect a dramatic improvement with the availability of eculizumab. The minority of patients on maintenance PT expect that the first, most easily measured improvement will be the gift of time. For patients on dialysis, eculizumab literally provides hope for the future by giving them the potential to receive "the gift of life" in the form of a kidney transplant.

Instead of travelling to a major hospital and attending weekly or biweekly plasma infusions that last upward of seven hours, eculizumab can be infused intravenously over 45 minutes in a clinic or at home, with the help of a registered nurse. Central lines are not required and pre-medication is limited.

Eculizumab controls the systematic clotting that occurs throughout the body, increasing the odds of survival and allowing a patient's kidneys to be saved even in the acute phase. Eculizumab clearly controls complement activity better than PT, which becomes ineffective over time.

Most patients felt that any eculizumab side effects could not be any worse than those they were currently experiencing. Patients on dialysis in particular stated that they "could put up with" quite a few side effects if it meant a chance at a normal life again. One patient on PT indicated that since her diagnosis, she had *never* attended school for five days consecutively, and correspondingly, one of her parents had not been able to attend work. In addition, the new treatment would mean that her central line could be removed, along with all of the associated risks. The patient then wondered what it would feel like to not have a portacath.

It is indicated that all patients on eculizumab have noted dramatic improvement. Patients without experience with eculizumab were overwhelmingly willing to experience side effects if they also experienced benefits.

Patients with experience on eculizumab reported no side effects, and although they initially had concerns about increased susceptibility to illness, none had experienced this. One patient, who had been on PT until it ceased to be effective, had suffered kidney failure. While on dialysis, she received eculizumab as part of a clinical trial. The patient stated that she had "never felt so good" and had even delayed putting her name on the transplant list, just to have a chance to enjoy her newfound life, even while on dialysis. Another patient started receiving eculizumab at diagnosis while in the ICU, suffering from renal failure and uncontrollable internal bleeding. From the first administration, the bleeding stopped and his kidney function was eventually restored. He spent less than a month in the hospital and was able to return to his regular school and sports activities within a week of discharge. He receives eculizumab at home and misses no school (and his parents miss no work) due to treatments. He considers himself "back to normal".

The potential positive effects of eculizumab for patients and their families are almost immeasurable. One parent indicated that with eculizumab, they can now confidently start saving for their child's university education, as their child now has a future.

4. Comments on the Proposed Funding Criteria

CORD is very supportive of the NICE guidance with respect to the premise on which the guidance was made, the process used to arrive at the criteria, and the criteria for access. CORD is particularly impressed with the articulation of the premise upon which the NICE guidance was based. It indicated that the clinical data available to NICE were the same as that provided to CADTH; however, NICE did not "get stuck on" a re-review of the clinical trials and the inherent shortcomings of small patient populations, short clinical trials for life-threatening conditions, and the lack of long-term outcomes. Instead, it went to the actual challenges of the disease, the benefits and risks of the therapy, the lack of other effective therapies, and the ability to manage access.

The NICE guidance makes eculizumab available to all patients with aHUS, with four arrangements in place, as recommended by 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 receive eculizumab, and the dose and duration of treatment; a national protocol for starting and stopping eculizumab for clinical reasons; and a research program with robust methods to evaluate when stopping treatment or dose adjustment might occur. In view of the lack of evidence, the agreement to continue to monitor and to decide whether "remission" for a period of time could warrant discontinuation is not only reasonable but also highly prudent, especially in terms of patient safety.

With regard to Australia's PBAC recommendation, CORD indicated that the overriding concern was the potential budget impact, which, it said, was a very poor starting point for optimal patient care. Moreover, the debate over "stopping" when there appeared to be "remission" at six months, 12 months, and 24 months seemed to be "entirely arbitrary and *not* evidence based." The indicators for remission are not based on clinical evidence but would leave patients at great risk and in need of very close monitoring, with "rescue" therapy undoubtedly required in some or many cases. This would be costly for both the patients and the system.

aHUS Canada indicated that the use of eculizumab is "a step change in the management of aHUS and can be considered a significant innovation for a disease with a high unmet clinical need. Eculizumab offers people with aHUS the possibility of avoiding end-stage renal failure, dialysis, and kidney transplantation, as well as other organ damage."

In summary, both aHUS Canada and CORD acknowledged that clinical evidence is very limited; however, PBAC and NICE have already proposed to fund eculizumab in the treatment of aHUS, based on the same evidence available to CADTH, and the unmet clinical needs. Both groups stated that they expect a revised recommendation from CADTH.

APPENDIX 4: PHARMACEUTICAL BENEFITS SCHEME FUNDING CRITERIA FOR ATYPICAL HEMOLYTIC UREMIC SYNDROME (AUSTRALIA)

Treatment Phase: Initial Treatment 1 — New Patient[50]

Clinical Criteria:

Patient must have active and progressing thrombotic microangiopathy (TMA),
AND
Patient must have ADAMTS-13 (a disintegrin and metalloproteinase with a thrombospondin type 1 motif, member 13) activity of ≥ 10% on a blood sample taken prior to plasma exchange (PE) or infusion (PI); or, if ADAMTS-13 activity was not collected prior to PE/PI, patient must have platelet counts > 30 × 10^9/L and a serum creatinine (SCr) > 150 mol/L,
AND
Patient must have a confirmed negative Shiga toxin–producing *Escherichia coli*) STEC result if the patient has had diarrhea in the preceding 14 days,
AND
Patient must have clinical features of active organ damage or impairment,
AND
Patient must not receive more than four weeks of treatment under this restriction.

Treatment Criteria:

Must be treated by a pediatric nephrologist, a nephrologist, a pediatric hematologist or a hematologist; or, must be in consultation with a pediatric nephrologist, a nephrologist, a pediatric hematologist or a hematologist.

Evidence of active and progressing TMA is defined by the following:
(1) A platelet count of less than 150 x 10^9/L; and evidence of two of the following:
- (a) Presence of schistocytes on blood film;
- (b) Low or absent haptoglobin;
- (c) Lactate dehydrogenase (LDH) above normal range;

OR
(2) Tissue biopsy confirming TMA in patients who don‘t have evidence of platelet consumption and hemolysis;
AND
(3) Evidence of at least one of the following clinical features of active TMA-related organ damage or impairment is defined as below:
- (a) Kidney impairment, as demonstrated by one of the following:
  - (i) A decline in estimated glomerular filtration rate (eGFR) of > 20% in a patient who has pre-existing kidney impairment; and/or
  - (ii) An SCr of greater than the upper limit of normal (ULN) in a patient who has no history of pre-existing kidney impairment; or
  - (iii) An SCr of greater than the age-appropriate ULN in pediatric patients; or
  - (iv) A renal biopsy
- (b) Onset of TMA-related neurological impairment;
- (c) Onset of TMA-related cardiac impairment;
- (d) Onset of TMA-related gastrointestinal impairment;

(e) Onset of TMA-related pulmonary impairment.

The authority application must be in writing and must include:
(1) A completed authority prescription form; and
(2) A completed aHUS eculizumab Authority Application Supporting Information Form — Initial PBS-subsidized eculizumab treatment; and
(3) A signed patient acknowledgement or an acknowledgement signed by a parent or authorized guardian, if applicable; and
(4) A copy of a current Certificate of Vaccination; and
(5) A measurement of body weight at the time of application; and
(6) The result of ADAMTS-13 activity on a blood sample taken prior to PE/PI, the date and time that the sample for the ADAMTS-13 assay was collected, and the dates and times of any PEs or PIs that were undertaken in the two weeks prior to collection of the ADAMTS-13 assay; and
(7) In the case that a sample for ADAMTS-13 assay was not collected prior to PE or PI, measurement of ADAMTS-13 activity must be taken one to two weeks following the last PE or PI. The ADAMTS-13 result must be submitted to the Department of Human Services within 27 days of commencement of eculizumab treatment in order for the patient to be considered as eligible for further PBS-subsidized eculizumab treatment, under initial treatment 1-balance of supply; and
(8) A confirmed negative STEC result if the patient has had diarrhea in the preceding 14 days; and
(9) Evidence of active and progressing TMA, including pathology results where relevant. Evidence of the onset of TMA-related neurological, cardiac, gastrointestinal, or pulmonary impairment requires a supporting statement with clinical evidence in patient records. All tests must have been performed within one month of application; and
(10) For all patients, a recent measurement of eGFR, platelets, and two of either LDH, haptoglobin, or schistocytes of no more than 1 week old at the time of application.

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