Scottish Medicines Consortium
Providing advice about the status of all newly licensed medicines
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eculizumab 300mg concentrate for solution for infusion (Soliris®)

SMC No. (767/12)

Alexion Pharma UK Ltd.

8 January, 2016

The Scottish Medicines Consortium (SMC) has completed its assessment of the above product and advises NHS Boards and Area Drug and Therapeutic Committees (ADTCs) on its use in NHS Scotland. The advice is summarised as follows:

ADVICE: following a full submission assessed under the ultra-orphan process

eculizumab (Soliris®) is not recommended for use within NHS Scotland.

Indication under review: in adults and children for the treatment of patients with atypical haemolytic uraemic syndrome (aHUS).

Four phase II, open-label, single-arm studies demonstrated the beneficial treatment effect of eculizumab on haematological parameters, renal function and thrombotic microangiopathy events.

The submitting company did not present a sufficiently robust economic analysis and in addition their justification of the treatment's cost in relation to its health benefits was not sufficient to gain acceptance by SMC.

This advice takes account of the views from a Patient and Clinician Engagement (PACE) meeting.

Overleaf is the detailed advice on this product

Chairman,
Scottish Medicines Consortium

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Indication

In adults and children for the treatment of patients with atypical haemolytic uraemic syndrome (aHUS).

Dosing Information

For adult patients (≥18 years of age), the dosing regimen consists of a four-week initial phase followed by a maintenance phase:

• Initial phase: eculizumab 900mg by intravenous (IV) infusion over 25 to 45 minutes every week for the first four weeks.

• Maintenance phase: eculizumab 1,200mg by IV infusion over 25 to 45 minutes for the fifth week, followed by 1,200 mg every 14 ± 2 days.

Paediatric patients with a body weight of at least 40kg are treated with the adult dose. The summary of product characteristics (SPC) gives details of dosing recommendations for paediatric patients with a body weight below 40kg.

Supplementary dosing of eculizumab is required in the setting of concomitant plasmapheresis, plasma exchange or fresh frozen plasma infusion. Refer to the SPC.

Eculizumab treatment is recommended to continue for the patient's lifetime, unless discontinuation is clinically indicated.

Eculizumab must be administered by a healthcare professional and under the supervision of a physician experienced in the management of patients with haematological and/or renal disorders.

Product availability date

24 November 2011. Eculizumab meets SMC ultra-orphan criteria.

Summary of evidence on comparative efficacy

Atypical haemolytic uraemic syndrome (aHUS) is a very rare disease which develops due to dysregulations of the alternative complement pathway resulting in uncontrolled complement activation. It can occur in adults and children and, in approximately half of patients, mutations in complement regulatory genes and/or the presence of neutralising antibodies have been identified. The estimated incidence of aHUS is 1 to 2 patients per million population per annum. The disease is characterised by a chronic thrombotic and inflammatory state resulting from platelet and endothelial cell activation which increases the risk of sudden blood clotting, renal insufficiency with ensuing dialysis, and other severe complications of thrombotic microangiopathy (TMA) which frequently lead to premature mortality.[1]

Eculizumab is a monoclonal antibody which inhibits terminal complement activation. It is also licensed for the treatment of paroxysmal nocturnal haemoglobinuria and SMC is currently assessing a resubmission for use in this indication.[2]

The key evidence to support the use of eculizumab in the treatment of aHUS comes from two similar published studies: C08-002 (n=17) and C08-003 (n=20).[1,3] Both were open-label, single-arm, phase II studies in adults and adolescents and comprised several phases: a screening period, an eight-week observation period (study C08-003 only), a 26-week treatment period, a long-term extension period

and an eight-week follow-up period if eculizumab was discontinued. Eligible patients were adults (≥18 years) and adolescents (12 to 18 years, weighing ≥40kg) with a diagnosis of aHUS, evidence of haemolysis (eg lactate dehydrogenase [LDH] levels of at least the upper limit of the normal range, haptoglobin level less than the lower limit of the normal range or presence of schistocytes) and evidence of renal impairment (creatinine level of at least the upper limit of the normal range). In study C08-002, patients also had evidence of progressive TMA after at least four sessions of plasma exchange or infusion in the previous week. In study C08-003, patients also had no decrease in platelet count of >25% in at least the previous eight weeks and were receiving plasma exchange or infusion at least once every two weeks to three times per week. All patients received eculizumab 900mg by intravenous (IV) infusion once weekly for four weeks, then 1,200mg one week later, followed by a maintenance dose of 1,200mg every two weeks. During both study periods, patients were not to receive plasma therapy unless there was compelling medical need.[1]

Both studies had two primary outcomes, assessed at 26 weeks, one of which was the proportion of patients with hematologic normalisation (defined as platelet count normalisation (≥150 x 10^9/L) and LDH level sustained for at least two consecutive measurements over at least four weeks). In study C08-002, the other primary outcome was inhibition of complement-mediated TMA, measured as the change in platelet count from baseline to week 26. In C08-003, the other primary outcome was TMA event-free status (defined as an absence of all of the following for at least 12 consecutive weeks: a decrease in platelet count of >25%; plasma exchange/infusion; new dialysis). There were significant improvements from baseline in these primary outcomes in both studies. Secondary outcomes assessed additional TMA outcomes, renal outcomes and quality of life, and the results are presented in table 1 below.

Further evidence is available from two closed , open-label, single-arm, phase II studies which have not yet been published in full; C10-003 (in 22 paediatric and adolescent patients) and C10-004 (in 41 adult patients).[2,4-7] Patients were treated with the licensed dose of eculizumab and the primary outcome was the proportion of patients with complete TMA response at week 26 (defined as normalisation of haematological parameters [platelet count and LDH] and ≥25% improvement (reduction) in serum creatinine from baseline [C10-003] or <25% increase in serum creatinine from baseline [C10-004] sustained for at least two consecutive measurements at least four weeks apart). The results of primary and key secondary outcomes are presented in table 1 below.

Table 1: Key outcomes at 26 weeks from four prospective studies of eculizumab in aHUS

	C08-002 (n=17)[1,2,3]	**C08-003 (n=20) [1,2,3]**	**C10-003 (n=22)[2,4,5]**	**C10-004 (n=41) [2,6,7]**
Platelet count normalisation (n/N) (%)	14/17 (82%)	18/20 (90%)[†]	21/22 (96%)	40/41 (98%)
Change in platelet count (mean)	**73 x 10^9/L**	5 x 10^9/L	-	111 x 10^9/L
TMA event-free status (n/N) (%)	15/17 (88%)	**16/20 (80%)**	21/22 (96%)	37/41 (90%)
Haematological normalisation (n/N) (%)	**13/17 (76%)**	**18/20 (90%)**	18/22 (82%)	36/41(88%)
Complete TMA response (n/N) (%)	11/17 (65%)	5/20 (25%)	**14/22 (64%)**	**30/41 (73%)**
eGFR improvement ≥15mL/min/1.73m^2 (n/N) (%)	8/17 (47%)	1/20 (5.0%)	19/22 (86%)	22/41 (54%)
Chronic kidney disease improvement by ≥one stage (n/N) (%)	10/17 (59%)	7/20 (35%)	17/20 (85%)	26/41 (63%)
Dialysis discontinued* (n/N) (%)	4/5 (80%)	-	9/11 (82%)	20/24 (83%)
Mean change in EQ-5D	0.32	0.10	-	

Primary outcomes are highlighted in **bold**.

[†] only three patients had platelet count <150×10^9/L at baseline and of these 33% (1/3) had platelet count normalisation at week 26.

TMA event-free status: defined as an absence of all of the following for at least 12 consecutive weeks: a decrease in platelet count of >25%; plasma exchange/infusion; new dialysis.
Haematological normalisation: defined as platelet count normalisation (≥150 x 10^9/L) and LDH level sustained for at least two consecutive measurements over at least four weeks.
Complete TMA response: defined as haematologic normalisation plus improvement in renal function (25% reduction in serum creatinine from baseline in two consecutive measurements for ≥four weeks).
* percentage of patients on dialysis at baseline who discontinued by 26 weeks. In study C10-004, two patients not on dialysis at baseline started and continued to week 26.
EQ-5D: EuroQoL-5D questionnaire (range 0 to 1; 0.06 is a clinically meaningful threshold).[1]

The majority of patients continued eculizumab treatment in longer term extensions to these studies and results indicate that the treatment effects were generally maintained or improved from week 26 to up to two years in studies C08-002 and C08-003, and up to one year in studies C10-003 and C10-004.[8-10]

A retrospective, single-arm, observational study (C09-001r) was performed in 30 patients of any age who had received at least one dose of eculizumab outside of a company-sponsored, controlled, clinical study. This provided additional data on paediatric patients (n=15, aged 2 months to 12 years) and results were consistent with those of the C08-002 and C08-003 studies.[2,11]

Summary of evidence on comparative safety

Since the studies were single-arm, there are no comparative safety data. The majority of patients reported adverse events during treatment with eculizumab and the most frequently reported were diarrhoea, vomiting, nausea, abdominal pain, headache, anaemia, leukopenia, hypertension, nasopharyngitis, upper respiratory tract infection and insomnia.[1] Refer to the summary of product characteristics (SPC) for details.[2]

Due to its mechanism of action, treatment with eculizumab increases a patient's susceptibility to meningococcal infection. In studies C08-002, C08-003 and C10-003, there were no reported cases of meningococcal infection.[3,5,9] However, in study C10-004, two of the 41 adult patients had meningococcal infection during the first 26 weeks of treatment, one of whom continued eculizumab.[7,10]

Summary of clinical effectiveness issues

Eculizumab is the only medicine licensed for the treatment of aHUS. Alternative treatment options include supportive care, dialysis, and plasma infusion or plasma exchange therapy. The efficacy of plasma therapy has not been formally studied in a clinical trial. However, a recent commentary accompanying the two-year follow-up of C08-002 and C08-003 noted that plasma therapy is reasonably effective at normalising haematologic parameters of TMA but is not uniformly effective at preventing the progression of renal disease. Progression to end stage renal failure or premature death frequently occurs despite plasma therapy.[12] Eculizumab meets SMC ultra orphan criteria. Clinical experts consulted by SMC considered that there is unmet need in this therapeutic area.

Data from the two published studies (C08-002 and C08-003) demonstrated the treatment effect of eculizumab on haematological parameters, renal function, TMA events and the reduced use of dialysis and plasma therapy. All patients in study C08-003 discontinued plasma therapy, as did 88% of patients in study C08-002. However, there were differences between the two study populations. Patients in the C08-002 study had disease of a short duration (median of 9.7 months) and were considered by the European Medicines Agency (EMA) as refractory to plasma therapies, defined as not having responded to, insufficiently responded to, or intolerant to aggressive plasma therapy.

Seventy percent of patients had CKD stage 4 or 5. The EMA considered that results in patients in this study, who lack alternative treatment options, were robust.[1] Patients in the C08-003 study had disease of a longer duration (median of 48 months) and were considered by the EMA as having less severe disease which was stable on chronic plasma therapy. Half of study patients had CKD stage 4 or 5. In patients in this study, the effects on haematological parameters and TMA events were clear; however, the effects on renal function were less marked.[1,3] The studies were primarily assessed at 26 weeks but results from extended treatment, up to two years, indicate that the treatment effect was maintained or improved. The results of C08-002 and C08-003 are supported by as yet unpublished studies C10-003 in paediatrics and adolescents, and C10-004 in adults.

The quality of the available evidence is limited due to a lack of randomised, controlled studies. All four prospective studies were of open-label, single-arm design. There are no comparative data with other supportive treatments or plasma therapy. Due to the rare nature of the disease, the studies have been performed in small patient numbers and data on paediatric patients are limited.

The SPC recommends that eculizumab treatment should be continued for the patient's lifetime, unless discontinuation is clinically indicated.[2] However, there appears to be some uncertainty over the optimal duration of therapy for all patients. If eculizumab is discontinued, patients should be monitored closely for signs or symptoms of severe TMA. The SPC also recommends that patients should be monitored for TMA by measuring platelet counts, serum LDH and serum creatinine and that dose adjustment may be required within the recommended 14±2 days during the maintenance phase (up to every 12 days).[2]

To reduce the risk of meningococcal infection, all patients must be vaccinated against meningococcus at least two weeks before starting treatment.[2,13,14] The eculizumab SPC advises that if it is started less than two weeks after vaccination, appropriate prophylactic antibiotics must be given for at least two weeks.[2] Guidance issued by the aHUS Rare Disease Group recommends that prophylactic antibiotics should be given for the duration of treatment with eculizumab.[13,14] Eculizumab-treated patients should be monitored for early signs of meningococcal infection, evaluated immediately if infection is suspected and treated with appropriate antibiotics if necessary. Patients may also have increased susceptibility to other infections and should be provided with information from the package leaflet to increase their awareness of potential serious infections and their signs and symptoms.[2]

The SPC states that infrequent antibody responses have been detected in eculizumab-treated patients across all clinical studies. In placebo controlled studies, low antibody responses have been reported with a frequency (3.4%) similar to that of placebo (4.8%). In patients with aHUS treated with eculizumab, antibodies to eculizumab were detected in 3% (3/100) by the ECL bridging format assay. Only 1/100 (1%) aHUS patients had low positive values for neutralising antibodies. There has been no observed correlation of antibody development to clinical response or adverse events.[1,2]

The introduction of eculizumab would offer an active treatment for patients with aHUS who are otherwise managed by supportive therapy, dialysis and plasma therapy, with the potential to improve haematological and renal parameters, reduce TMA events and reduce the need for plasma therapy and dialysis. Clinical experts consulted by SMC considered that eculizumab is a therapeutic advancement.

Summary of patient and clinician engagement

A patient and clinician engagement (PACE) meeting with patient group representatives and clinical specialists was held to consider the added value of eculizumab, as an ultra-orphan medicine, in the context of treatments currently available in NHS Scotland, specifically in the treatment of adults and children with atypical haemolytic uraemic syndrome (aHUS).

The key points expressed by the group were:

- aHUS is a very rare life-threatening condition that can occur at any age but generally presents in young patients, impacting on their ability to work and/or care for their families
- While the organ primarily affected is the kidney, it is a multi-system disease and the cardiovascular, neurological and gastroenterological systems can also become affected
- Eculizumab is the only treatment option available that addresses the underlying cause of aHUS by blocking activation of the complement system to prevent or reverse a decline in renal and cardiac function
- As eculizumab can be given at home or in an out-patient setting it causes less disruption to family life than more invasive supportive treatments such as dialysis or plasma exchange
- If eculizumab is initiated early enough it may reduce morbidity in the acute phase. Additionally, it may reverse or prevent a decline in renal function, providing an opportunity to avoid the need for long term dialysis with its significant impact on both patients and their families
- For those patients with aHUS induced end stage renal failure on dialysis, eculizumab may allow a kidney transplant and the opportunity for increased life expectancy and improved quality of life without dialysis
- As eculizumab is available in other parts of the United Kingdom, PACE participants highlighted a potential equity issue if it is not accepted for use in NHS Scotland.

Summary of ultra-orphan decision making framework

Eculizumab has been considered by SMC using its decision-making framework for the assessment of ultra-orphan medicines. Relevant factors under each of the criteria are summarised below:

Nature of condition
aHUS is a very rare life-threatening condition that can occur at any age. It generally presents with intravascular haemolysis due to uncontrolled activation of the complement system leading to local tissue damage throughout the body. The organ primarily affected is the kidney but it is a multi-system disease and the cardiovascular, neurological and gastroenterological systems can also become affected.

Patients with end stage renal failure (ESRF) caused by aHUS face a lifetime on dialysis with its associated burden because they are considered unsuitable for transplantation in view of the potential for a transplanted kidney to fail.

Impact of new technology
Eculizumab is the only treatment option available that addresses the underlying cause of aHUS by blocking activation of the complement system to prevent or reverse a decline in renal and cardiac function.

Treatment with eculizumab has been shown in four phase II, open-label, single-arm studies to have a beneficial treatment effect on haematological parameters, renal function and thrombotic microangiopathy events

At the PACE meeting, participants shared their experiences of eculizumab and noted that if it is initiated early enough, it may reduce the morbidity associated with the acute phase and provide an opportunity to avoid the need for long term dialysis. In addition, for those patients with aHUS induced ESRF on dialysis, eculizumab may be life changing because it provides an opportunity to be considered for transplantation.

Value for money
The company submitted a cost-consequence analysis comparing eculizumab with best supportive care (BSC) for the treatment of children and adults with aHUS. BSC included plasma exchange/plasma infusion (PE/PI), dialysis, and renal transplantation. SMC clinical experts have confirmed that BSC is the appropriate comparator.

A quality-adjusted life-year (QALY) based cost-consequence analysis was conducted using a Markov model structure. Although the analysis is described as a cost-consequence analysis, it is very similar to a cost-utility analysis but stops short of combining the incremental costs and QALYs gained to produce an incremental cost-effectiveness ratio. Patients progressed through the model according to three stages of CKD (CKD 0-2, CKD 3a-4, and CKD 5/ ESRF). The model also included a temporary health state for transplant (but note that only patients in the BSC arm were at risk of transplant) and a death state. The model focused on the effects of aHUS on patients' renal function as a result of complement-mediated TMA. Progression through CKD stages in the model was based on statistical modelling of eGFR deterioration using data from the eculizumab clinical studies. The non-renal effects of TMA were not specifically modelled separately because of a lack of data, but the model did account for additional quality of life and mortality benefits with eculizumab beyond the impact on renal function. A lifetime horizon was used and the company justified this on the basis that aHUS is a chronic condition which requires a lifetime horizon to capture costs and benefits of treatment. Patients were said to be aged 28 at the start of the model and the time horizon was just under 100 years.

The clinical data used for the eculizumab arm of the model were based on the C08-002 and C08-003 studies. In the economic model, 7 separate transition probability matrices were derived using patient-level data relating to patients' CKD stage distribution showing the changes from baseline to week 26, week 26-52, week 52-78, week 78-104, week 104-130, week 130-156, and week 156-182. This average transition probability matrix was used for the duration of the model transitions for eculizumab effectively assuming the benefits of treatment are stable over time. This resulted in the probability of an improvement in at least 1 CKD stage per 6 months for eculizumab-treated patients of between 14.3% (for patients in CKD stage 1) and 34.8% (for patients in CKD stage 3a). The efficacy of BSC was estimated using the pre-treatment data from the C08-002 and C08-003 studies based on the period from diagnosis to baseline. The relationship between eGFR and days since diagnosis was estimated using regression analysis. A fixed effects model was used which resulted in a 6-month transition probability of moving to a worse CKD stage of 0.367 (i.e. 36.7% chance of declining by 1 CKD stage). It was not possible for any patients to experience an improvement in renal function with BSC.

Transitions from CKD 5/ESRF to death were estimated using data from the UK Renal Registry, which noted a one-year survival rate of 89.8%. This was applied in the model for both BSC and eculizumab

patients using a 6-month mortality rate of 5.1%. The company stated that eculizumab had an impact on non-renal outcomes and this was included in the model by assuming an excess mortality rate of 4% per 6 months applied in the BSC arm only based on data from a TMA registry in France. No increased mortality rate was included in the eculizumab arm thus assuming the mortality risk associated with non-renal complications of aHUS was removed with eculizumab treatment.

The utility values for the eculizumab arm were based on the EQ-5D data collected in the studies. The weighted average change in utility from baseline to week 64 was estimated to be 0.208. The utility values at year 1 were used to represent eculizumab-treated patients and a utility decrement of 0.208 was applied to each health state to generate the BSC values. This resulted in utility values of 1, 0.87 and 0.867 applied to the three CKD health states in the eculizumab arm, and utility values of 0.792, 0.662, and 0.659 for the same three CKD health states in the BSC arm.

The analysis included the drug acquisition and administration costs of eculizumab. For administration costs, the company assumed 80% of patients would be enrolled in the company-funded homecare program which covers the cost of administration. The administration cost for 80% of patients was therefore excluded. For the remaining 20%, it was assumed 13 administrations are required per 6 month period. The company confirmed that it is their intention to continue to fund the homecare program. An additional cost for a meningococcal vaccine was also included, as specified in the SPC. No additional monitoring costs were included for eculizumab-treated patients.

No costs were included to account for adverse events. The company justified this assumption on the basis that adverse events associated with eculizumab are generally mild to moderate in severity and there was a lack of data to use to estimate the cost of adverse events for the BSC arm. Dialysis costs were included for patients in the ESRF health state according to mode of dialysis. The costs of plasma therapy were included for BSC patients. Kidney transplant and maintenance costs were included in the BSC arm only. CKD health state specific costs were also included.

The company estimated a lifetime QALY gain of 15.3 with eculizumab compared to BSC and a life year gain of 14. The outcome of dialysis days avoided with eculizumab treatment over a lifetime horizon was estimated to be 890 days (2.44 years). SMC would also wish to present the lifetime incremental cost of eculizumab but owing to commercial in confidence concerns raised by the submitting company, SMC is unable to publish this information. Please note that the annual medicine cost per patient per year is presented in the cost table below.

The results were most sensitive to assuming a 0% discount rate for health benefits, which resulted in the QALY gain increasing to 36. Results were also sensitive to reducing the additional mortality rate applied to the BSC arm (QALY gain reduced to 14.6) and increasing the starting age of patients to 45 (QALY gain reduced to 11.7).

In addition to the high incremental costs relative to the QALY gains, the following limitations were noted:

- The clinical data used to inform the economic analysis have a number of important limitations. The estimates for treatment effect are based on non-comparative data for 37 patients, followed up for a maximum of three years. Therefore, there is uncertainty in the results from a lifetime analysis based on extrapolation of the available data.
- The drug cost of eculizumab may have been underestimated. The patients were aged 28 at the start of the model and would therefore receive the dose for patients >40kg, but the drug cost has been estimated assuming a proportion of patients were receiving lower than the adult dose. The company noted that the starting age of patients in the model represented the average patient at baseline in the studies and therefore the costs should be calculated using a distribution of patient weight. However, all patients in the C08-002 and C08-003 studies were

aged ≥12 years and would therefore receive dose for patients >40kg. Sensitivity analysis was provided assuming all patients receive the full adult dose and this increased the incremental cost.

- The efficacy of BSC was based on the pre-treatment phase of the C08-002 and C08-003 studies but there is evidence from other published registry data sources that the mortality rate on BSC has been overestimated. An analysis was provided which removed the excess mortality rate applied to the BSC arm and this resulted in an increased incremental cost and a QALY gain of 13.53.
- The transition probabilities applied over the model time horizon are likely to overestimate the maintenance benefits of eculizumab as they are based on the improvements in CKD stage from baseline up to year 3 (with small patient numbers for the latest data points). Given the improvements in CKD stage are likely to be greatest in the initial phases of treatment, it would seem more appropriate to base the extrapolation phase on the data from, for example, year 2 onwards. This is likely to be more representative of the 'steady state' efficacy of eculizumab. The company provided sensitivity analysis using more conservative transition probabilities over the longer term whereby the probability of improving by 1 CKD stage was reduced by 30%. This resulted in an increased incremental cost and a QALY gain of 14.34.
- The utility values were included in the model according to health state but patients in the eculizumab arm were assumed to experience a quality of life of 1 (i.e. full health) in the CKD0-2 health state, whereas the utility value for the same health state in the BSC arm is 0.792. The eculizumab arm utility values are higher than population norm values and even for patients with ESRF the utility value only decreased to 0.87. The company was asked to provide sensitivity analysis assuming the BSC utility values in both arms of the model. The results were sensitive to this with the QALY gain reducing by around 30% to 10.83.
- The model structure is possibly too simplistic. The CKD stages were grouped resulting in only 2 health states before ESRF in the model, which may be too simplistic as it is likely patients' quality of life and resource use will be different within these health states. For example, the difference in quality of life observed in the eculizumab studies between baseline and year 1 may reflect more patients being in better CKD stages within the same health state. In addition, a single transition probability matrix was used for the eculizumab arm instead of using patient-level data over time. However, the company argued using patient-level data would not have had a big impact on the results and sensitivity analysis subsequently provided by the company provides some support to this assumption.
- The model assumed a large mortality benefit with eculizumab such that patients experience almost a normal life expectancy, but given the limitations with the clinical data the extrapolation period is particularly uncertain. Survival at 50 years was estimated to be 48% and at 60 years was 18%. Reducing the time horizon to 30 and 40 years only had a relatively small impact on the overall results given the drug cost and mortality benefits would both be truncated with this analysis. Time horizons of 10 and 20 years were also provided and resulted in reduced incremental costs and QALY gains of 2.97 and 7.92 respectively. However, these analyses are exploratory and do not reflect the recommended lifetime treatment duration of eculizumab.

Patient and clinician engagement (PACE)

A PACE meeting was held for this submission. Participants at the PACE meeting indicated a range of potential impacts of the new technology for the patient and families/carers.

Impact beyond direct health benefits and on specialist services

aHUS has a considerable impact on the patient and their family members beyond that described by the health outcomes measured. At the PACE meeting, participants highlighted that many patients are young and may be working and/or looking after children. Family members live with the anxiety of seeing patients on dialysis or at increased risk of cardiac failure or other cardiac events.

Eculizumab may prevent or delay the onset of ESRF and the need for dialysis, which has a significant impact on the quality of life of both patients and their families. Patients on dialysis experience multiple symptoms including pain and fatigue, are often unable to work, face severe dietary and fluid restrictions, and have reduced life-expectancy. The PACE participants shared details of case histories where post-eculizumab treatment and transplant, patients were able to return to work with little or no dependence on carers, reducing the financial impact of the condition on their families and allowing them to fully contribute to society again.

For those patients with aHUS induced ESRF on dialysis, access to eculizumab and the opportunity for a life-changing transplant gives both patients and their families hope for the future.

As eculizumab can be given at home or in an out-patient setting it causes less disruption to family life than more invasive supportive care options such as dialysis or plasma exchange.

Cost to NHS and Personal Social Services
SMC would wish to present the estimated budget impact of eculizumab for NHS Scotland, but owing to commercial in confidence concerns raised by the submitting company SMC is unable to publish this information.

The Committee also considered the benefits of eculizumab in the context of the SMC decision modifiers that can be applied when encountering high cost-effectiveness ratios and agreed that a number of the criteria were satisfied: a substantial improvement in quality of life; the potential to bridge to a definitive therapy; and the absence of other treatments of proven benefit. In addition, as eculizumab is an ultra-orphan medicine, SMC can accept greater uncertainty in the economic case.

After considering all the available evidence and the output from the PACE process, and after application of the appropriate SMC modifiers, the Committee was unable to accept eculizumab for use in NHS Scotland.

*Other data were also assessed but remain commercially confidential.**

Summary of patient and public involvement

The following information reflects the views of the specified Patient Groups.

- Submissions were received from Kidney Research UK and aHUS UK, which are both registered charities.

- Both Kidney Research UK and aHUS UK have received pharmaceutical company funding in the past two years, with both having received funding from the submitting company.

- aHUS is a predominantly genetic, progressive disease whereby the small capillaries in all major organs are at risk of blockage, particularly the kidneys. Onset is sudden and without any warning signs. The acute phase of aHUS is life-threatening. Following the acute phase, most patients do not recover kidney function. Within a year the majority either die, or have ESRF which requires dialysis. Patients describe how aHUS has restricted everything in their lives and how their lives revolve around “just getting through each day”.

- Currently patients are often reliant on plasma exchange which is a specialist service delivered through regional centres. It is not a permanent solution. For those who are too late for plasma exchange, a life-time on dialysis is often the only option. Eculizumab is given by injection every two

weeks, which can be performed at the patient's house. This is minimally intrusive, contrasting with patient's experiences on plasma exchange or dialysis.

- Eculizumab would improve patients' quality of life by improving control of their disease, reducing hospital attendances and reducing invasive procedures that carry potential risks and complications. It would also significantly reduce the stress and anxiety of patients and their families.

Additional information: guidelines and protocols

Clinical practice guidelines for the management of aHUS in the United Kingdom were published in 2010 by a working party from the Renal Association, the British Committee for Standards in Haematology and the British Transplantation Society.[15] It is recommended that:

- All patients presenting with aHUS should be offered a trial of plasma exchange and/or plasma infusions. (Strength of recommendation: weak; quality of recommendation: low).
- Renal transplantation alone is not recommended in patients known to have a factor H or factor I mutation. Patients carrying an CD46 mutation, but no additional mutation in factor H, factor I, factor B and C3 or an anti-factor H autoantibody can be informed that the risk of recurrence post transplantation is low. Patients known to have a C3 or factor B mutation should be informed that current evidence suggests that there is a significant risk of disease recurrence post transplantation. Patients known to have an anti-factor H autoantibody should be treated to minimise the antibody titre before proceeding to renal transplantation. Living related renal transplantation alone should be avoided in aHUS. (strong, moderate).
- In aHUS patients with a known mutation in either factor H or factor I consideration should be given to either an isolated liver or a combined liver/kidney transplant as part of an internationally coordinated clinical trial. Within the UK an advisory panel should be established to consider all patients prior to listing. Within the UK liver transplantation alone or in combination with a kidney transplant should only be undertaken in a limited number of centres with appropriate expertise. (weak, low).

Since these guidelines predate the availability of eculizumab for aHUS, no recommendations are made in relation to its use.

The aHUS Rare Disease Group has produced clinician information on aHUS which provides recommendations on diagnosis, treatment with eculizumab and monitoring.[16]

Additional information: comparators

No other medicines are licensed for use in the treatment of aHUS and patients are generally managed by supportive care, dialysis and plasma infusion or plasma exchange therapy.

Cost of relevant comparators

Drug	Dose Regimen	Cost per year (£)
Eculizumab	**900mg by IV infusion once weekly for four weeks, then 1,200mg one week later and then a maintenance dose of 1,200mg every two weeks.**	**340,200**

Costs from eMIMs October 2015. The cost is based on the above dose which is recommended for adults ≥18 years and paediatric patients weighing >40kg. In subsequent years, the annual cost would be £327,600 which excludes the initial five week phase.

Additional information: budget impact

SMC is unable to present the estimated budget impact of eculizumab for NHS Scotland as the submitting company has indicated that this information is commercial in confidence.

*Other data were also assessed but remain commercially confidential.**

References

The undernoted references were supplied with the submission. Those shaded in grey are additional to those supplied with the submission.

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This assessment is based on data submitted by the applicant company up to and including 13 November, 2015.

*Agreement between the Association of the British Pharmaceutical Industry (ABPI) and the SMC on guidelines for the release of company data into the public domain during a health technology appraisal: http://www.scottishmedicines.org.uk/About_SMC/Policy_statements/Policy_Statements

Drug prices are those available at the time the papers were issued to SMC for consideration. SMC is aware that for some hospital-only products national or local contracts may be in place for comparator products that can significantly reduce the acquisition cost to Health Boards. These contract prices are commercial in confidence and cannot be put in the public domain, including via the SMC Detailed Advice Document. Area Drug and Therapeutics Committees and NHS Boards are therefore asked to consider contract pricing when reviewing advice on medicines accepted by SMC.

Advice context:

No part of this advice may be used without the whole of the advice being quoted in full.

This advice represents the view of the Scottish Medicines Consortium and was arrived at after careful consideration and evaluation of the available evidence. It is provided to inform the considerations of Area Drug & Therapeutics Committees and NHS Boards in Scotland in determining medicines for local use or local formulary inclusion. This advice does not override the individual responsibility of health professionals to make decisions in the exercise of their clinical judgement in the circumstances of the individual patient, in consultation with the patient and/or guardian or carer.