

# Eculizumab for treating atypical haemolytic uraemic syndrome

Highly specialised technologies guidance

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## Your responsibility

The recommendations in this guidance represent the view of NICE, arrived at after careful consideration of the evidence available. When exercising their judgement, health professionals are expected to take this guidance fully into account, alongside the individual needs, preferences and values of their patients. The application of the recommendations in this guidance is at the discretion of health professionals and their individual patients and do not override the responsibility of healthcare professionals to make decisions appropriate to the circumstances of the individual patient, in consultation with the patient and/or their carer or guardian.

All problems (adverse events) related to a medicine or medical device used for treatment or in a procedure should be reported to the Medicines and Healthcare products Regulatory Agency using the [Yellow Card Scheme](#).

Commissioners and/or providers have a responsibility to provide the funding required to enable the guidance to be applied when individual health professionals and their patients wish to use it, in accordance with the NHS Constitution. They should do so in light of their duties to have due regard to the need to eliminate unlawful discrimination, to advance equality of opportunity and to reduce health inequalities.

Commissioners and providers have a responsibility to promote an environmentally sustainable health and care system and should [assess and reduce the environmental impact of implementing NICE recommendations](#) wherever possible.

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# 1 Guidance

- 1.1 Eculizumab, within its marketing authorisation, is recommended for funding for treating atypical haemolytic uraemic syndrome, only if **all** the following arrangements are in place:
- coordination of eculizumab use through an expert centre
  - monitoring systems to record the number of people with a diagnosis of atypical haemolytic uraemic syndrome and the number who have eculizumab, and the dose and duration of treatment
  - a national protocol for starting and stopping eculizumab for clinical reasons
  - a research programme with robust methods to evaluate when stopping treatment or dose adjustment might occur.
- 1.2 The long-term budget impact of eculizumab for treating atypical haemolytic uraemic syndrome is uncertain but will be considerable. NHS England and the company (Alexion Pharma UK) should consider what opportunities might exist to reduce the cost of eculizumab to the NHS.

## 2 The condition

- 2.1 Atypical haemolytic uraemic syndrome (aHUS) is a chronic, rare, progressive condition that causes severe inflammation of blood vessels and the formation of blood clots in small blood vessels throughout the body, a process known as systemic thrombotic microangiopathy. In around 70% of patients, aHUS is associated with an underlying genetic or acquired abnormality of the proteins of the complement system, which is part of the body's defence against infection. The prognosis for people with aHUS is poor. Patients are at constant risk of sudden and progressive damage, and failure of vital organs. Mortality rates range from 10–15% in the acute phase of the disease and, within a year of diagnosis, up to 70% of patients progress to end-stage renal failure and need dialysis or die. One patient in 5 has aHUS affecting organs other than the kidneys, most commonly the brain or heart.
- 2.2 aHUS can occur at any age. Onset occurs in childhood more frequently than in adulthood (around 60% and 40% of all cases respectively). Most children (70%) who develop aHUS will experience the disease for the first time before the age of 2 years. The true incidence and prevalence of aHUS in England is uncertain because some patients remain undiagnosed. Worldwide, the prevalence of aHUS ranges from 2.7–5.5 per million population, with an incidence of about 0.40 per million population.
- 2.3 Before eculizumab became available, plasma therapy was traditionally the first-line treatment for aHUS. Guidelines published by the British Committee for Standards in Haematology and the British Transplantation Society (2009; before the availability of eculizumab) recommend offering all patients with aHUS a trial of plasma exchange and/or plasma infusion. However, response to plasma therapy is variable, and up to 40% of patients may die or progress to end-stage renal failure and need dialysis with the first clinical aHUS manifestation, despite the use of plasma therapy. Some patients may be eligible for a kidney or combined kidney–liver transplantation; however, there is a high risk of organ rejection after recurrent disease.

### 3 The technology

3.1 Eculizumab (Soliris, Alexion Pharma UK) is a human monoclonal antibody that binds to complement C5 and blocks prothrombotic and pro-inflammatory processes. It is produced from murine myeloma cells by recombinant DNA technology. Eculizumab has a marketing authorisation in the UK 'in adults and children for the treatment of patients with atypical haemolytic uraemic syndrome (aHUS)'. It is also licensed for use in people with paroxysmal nocturnal haemoglobinuria.

3.2 Eculizumab is currently commissioned, through an interim commissioning policy, by NHS England in line with the [Clinical Commissioning Policy Statement: Eculizumab for atypical haemolytic uraemic syndrome](#) for:

- new patients with aHUS (defined to include those with a functioning kidney), and
- existing patients who are on dialysis and are suitable for a kidney transplant.

The policy is currently administered through an interim national aHUS service at the Newcastle Upon Tyne Hospitals NHS Foundation Trust. An evidence submission from NHS England was provided to the Committee, which described the policy in detail.

3.3 In adults and adolescents (people aged 12–17 years), the most common adverse reactions with eculizumab are headache and leukopenia. The most common adverse reactions in paediatric patients (children aged 2 months to 11 years) are diarrhoea, vomiting, pyrexia, upper respiratory tract infection and headache. Eculizumab use is associated with an increased risk of meningococcal infection. All patients are vaccinated against meningococcal infection before starting treatment with eculizumab and are revaccinated in accordance with guidelines. Patients are informed of the signs and symptoms of meningococcal infection and are provided with a safety card. For full details of adverse reactions and contraindications, see the summary of product characteristics and the European public assessment report.

3.4 Eculizumab is given intravenously in adults as initial treatment at a dose of 900 mg for 4 weeks, then as maintenance treatment at a dose of 1200 mg on week 5 and then every 12–16 days. The summary of product characteristics for eculizumab states that 'treatment is recommended to continue for a patient's lifetime, unless discontinuation of treatment is clinically indicated'. Patients under 18 years with a body weight of 40 kg or more are treated in line with the adult dosing recommendations. Paediatric patients with a body weight below 40 kg have their dose adjusted by body weight. Eculizumab costs £3150 per 30 ml (10 mg/ml) vial (excluding VAT; British national formulary, online July 2014). The total cost of eculizumab per adult is estimated to be about £340,200 (initial and maintenance treatment) in the first year of treatment and about £327,600 for 1 year of treatment on the recommended maintenance dose.

## 4 Evidence submissions

The Evaluation Committee ([section 9](#) considered evidence submitted by the company who owns eculizumab, a review of the company's submission by the Evidence Review Group (ERG; [section 10](#)) and evidence submitted by clinical and patient experts and NHS England.

### Nature of the condition

4.1 Evidence submitted by patient experts included a survey that was conducted in 2013 with the intention of better understanding the impact of atypical haemolytic uraemic syndrome (aHUS) on patients and their families. The survey was completed by 37 patients and highlighted that:

- aHUS has a substantial impact on patients' productivity and may impact on patients' education.
- aHUS may have a substantial impact on patients' day-to-day activities and participation in leisure activities.
- Some patients (and their families) have to move house so that they can live closer to a specialist centre or are closer to a carer.
- Patients may need up to 4 hours of travel time each week for hospital visits or medical appointments related to the management of their condition. When the patient is a child, a parent or carer usually must provide transportation and accompany them, adding to the burden.
- Patients may need both formal and informal care. The average time a carer spends looking after a patient with aHUS is 44 hours per week.
- aHUS can cause financial problems for patients and their families. Often parents of a patient with aHUS, or other family members, have to stop working to be able to provide care.

4.2 Evidence from patient and clinical experts highlighted that patients with aHUS have a greatly impaired quality of life, from both the frequent and severe



symptoms they experience and the burden of treatment with dialysis and plasma therapy. Families and carers of patients with aHUS also experience substantial burden, and often have to reduce their work or daily activities to provide the necessary care.

## Clinical evidence

- 4.3 The key clinical evidence came from 2 published (C08-002A/B and C08-003A/B) and 2 unpublished (interim data from C10-003 and C10-004) prospective studies, and 1 retrospective observational study (C09-001r). No randomised controlled trials were identified. All prospective studies were phase 2, open-label, non-randomised, single-arm studies that included patients with different clinical baseline characteristics. The prospective studies lasted 26 weeks; however, patients were allowed to continue treatment with eculizumab in a long-term extension study.
- 4.4 Study C08-002A/B included adolescent and adult patients (n=17) in the early phase of aHUS (median time from diagnosis to screening was 9.7 months) who were resistant to plasma therapy (that is, with evidence of progressive thrombotic microangiopathy after 4 or more sessions of plasma therapy in the week before starting the study treatment) and impaired kidney function. Before starting treatment with eculizumab, 94% (n=16) of patients had plasma therapy and 29% (n=5) were on dialysis. The primary endpoint of the study was reduction in thrombotic microangiopathy activity (measured by change in platelet count from baseline).
- 4.5 Study C08-003A/B included adolescent and adult patients (n=20) with longer-term aHUS (median time from diagnosis to screening was 48 months) who had chronic renal impairment without evidence of clinical thrombotic microangiopathy and who were having plasma therapy for a median of 10 months before study entry (that is, they were sensitive to plasma therapy). All patients had plasma therapy and 10% of patients (n=2) were on dialysis before they were given eculizumab. The primary endpoint of the study was reduction in thrombotic microangiopathy activity measured by thrombotic microangiopathy activity event-free status (defined as no more than a 25% decrease in platelet count and no plasma therapy or new dialysis for at least 12 consecutive weeks).

- 4.6 Study C10-003 included patients aged 1 month to 17 years (n=22) with aHUS who had thrombocytopenia, haemolysis and elevated serum creatinine. Patients who had had plasma therapy more than 5 weeks before enrolment or who were on chronic dialysis were excluded. Before having eculizumab, 45% (n=10) of patients had had plasma therapy and 50% (n=11) were on dialysis. The primary endpoint of the study was complete thrombotic microangiopathy activity response (determined by haematological normalisation and at least a 25% improvement in serum creatinine from baseline) confirmed by 2 consecutive measurements taken at least 4 weeks apart.
- 4.7 Study C10-004 included adults (n=41) with aHUS who had thrombocytopenia, haemolysis and elevated serum creatinine. There was no requirement for plasma therapy or dialysis before starting eculizumab therapy. Patients on chronic dialysis were excluded from the study. Before having eculizumab, 85% (n=35) of patients had had plasma therapy and 59% (n=24) were on dialysis. The primary endpoint of the study was thrombotic microangiopathy activity response (determined by haematological normalisation and less than 25% worsening in serum creatinine from baseline) confirmed by 2 consecutive measurements taken at least 4 weeks apart.
- 4.8 Study C09-001r was a retrospective chart review of 30 patients, including infants, children, adolescents and adults (median age 12 years [0.17–51.40 years]), who had been diagnosed with aHUS and had had at least 1 dose of eculizumab between 2007 and 2009, outside any company-sponsored study. Before having eculizumab, 80% of patients (n=24) had had plasma therapy and 37% (n=11) were on dialysis.
- 4.9 Two ongoing observational studies were also identified: C11-003, a follow-up study designed to assess the long-term efficacy of eculizumab in patients with aHUS who had previously been in an eculizumab study; and M11-001, a global aHUS registry initiated in April 2012 to prospectively collect data every 6 months from patients with aHUS, regardless of treatment. Limited information from the ongoing studies was provided.
- 4.10 Efficacy and safety data for eculizumab are limited for patients under 18 years. Results from the prospective studies showed that, compared with baseline, treatment with eculizumab improved systemic thrombotic microangiopathy

activity and led to clinically significant improvements in kidney function and gains in quality of life by 26 weeks. Further results from extension studies (median 114 weeks in C08-002A/B and C08-003A/B) showed that the benefits of eculizumab were sustained.

- 4.11 In C08-002A/B, dialysis was stopped in 80% (n=4) of patients who had needed dialysis at the time of starting eculizumab, and these patients remained free from dialysis throughout eculizumab treatment. Similar results were seen in C10-003 and C10-004, with 82% (n=9/11) and 83% (n=20/24) of patients respectively who were on dialysis at baseline no longer needing dialysis during eculizumab treatment.
- 4.12 In the retrospective C09-001r study, improvements were seen in all measured endpoints by 26 weeks. A subgroup analysis of 19 paediatric patients (under 2 years [n=5]; 2–11 years [n=10]; 12–17 years [n=4]) in the study showed that treatment with eculizumab reduced thrombotic microangiopathy activity (as demonstrated by platelet count normalisation) in 89% (n=17) of paediatric patients. In 47% (n=9) of paediatric patients, kidney function improved, and 50% (n=4) of paediatric patients who previously needed dialysis were able to stop dialysis during treatment with eculizumab. Thrombotic microangiopathy activity event-free status (defined as no plasma therapy, no new dialysis and no more than a 25% decrease in platelet count from baseline for 12 weeks or more) was seen in 68% (n=13) of paediatric patients. Efficacy outcomes were similar in another subgroup analysis of 15 paediatric patients aged under 12 years: kidney function improved in 53% (n=8) of patients and thrombotic microangiopathy activity event-free status was seen in 73% (n=11) of patients.
- 4.13 Most patients reported at least 1 adverse reaction in studies C08-002A/B (n=17) and C08-003A/B (n=20), but only 43% (16/37) of these patients had an adverse reaction that was considered by study investigators to be related to the use of eculizumab. Leukopenia, nausea, vomiting and accelerated hypertension were the most common treatment-related adverse reactions in study C08-002A/B, whereas headache, leukopenia and lymphoma were the most commonly reported reactions in study C08-003A/B. No deaths were reported in the 26-week study period in either study. Additional data from the extension study period (a 2-year data update) provided a similar adverse events profile. One death, which was not considered by the study investigators to be related to eculizumab use, was

reported in the extension period.

- 4.14 Limited safety information from the unpublished prospective studies (C10-003 and C10-004) is available; however, no deaths were reported in either study. In the retrospective C09-001r study, 73% (n=22) of patients reported at least 1 adverse reaction. Two (7%) deaths (due to a cerebrovascular accident and a fatal carotid artery dissection), which were considered to be unrelated to eculizumab, were reported.
- 4.15 Five patients stopped eculizumab therapy in the C08-002A/B (n=4) and C08-003A/B (n=1) studies (1 because of an exclusion criterion, 1 because of an adverse event unrelated to eculizumab treatment and 3 because they chose not to continue treatment with eculizumab after completing the 26-week treatment period). Thirteen patients stopped treatment in the retrospective C09-001r study. After stopping eculizumab, there were 7 severe thrombotic microangiopathy activity complications reported, including graft failure needing haemodialysis, renal insufficiency, end-stage renal failure and respiratory distress needing intubation. No patients in the prospective studies developed neutralising antibodies to eculizumab. There were no reported meningococcal infections in the C08-002A/B and C08-003A/B studies. One meningococcal infection was reported in C09-001r after the data cut-off point, and it was noted that the patient fully recovered without sequelae and remained on eculizumab.
- 4.16 Five registry sources for patients with aHUS having standard care (plasma therapy or transplantation) were identified. Two of the registries (Fremeaux-Bacchi 2013 and Norris 2010) included patients with a confirmed clinical diagnosis of aHUS. Results from these 2 registries showed that 45% of patients had end-stage renal failure at 3 years, and the average length of survival was estimated to be between 3 (Norris) and 5 (Fremeaux-Bacchi) years. Comparison between the registries at individual time points was not possible because the times selected for analysis differed between the registries.
- 4.17 At the Committee meeting, a clinical expert highlighted an Italian study (Ardissino et al. 2014), which included a cohort of 10 patients with aHUS. In this study, disease relapsed in 3 patients after stopping eculizumab; all had identifiable genetic mutations that would preclude stopping eculizumab under current national practice. Patients were closely monitored using home urine tests so that

recurrence could be identified early and eculizumab reintroduced immediately if needed, allowing renal function to return to the level it was before treatment was stopped.

## Economic evidence

- 4.18 The company developed a de novo cost–consequence model that used a Markov structure to estimate the costs and consequences for a population of 28-year-olds over a lifetime horizon, discounted at a rate of 1.5%. The model simulated the experience of patients with aHUS having eculizumab or standard care in terms of progression of kidney damage (defined as severity of chronic kidney disease) and its impact in terms of costs, health-related quality of life and survival. Five mutually exclusive health states were included in the model: 3 health states reflected the patient's level of kidney function (based on the National Kidney Foundation Outcomes Quality Initiative, determined by estimated glomerular filtration rate and the level of kidney damage); 1 was a temporary health state for patients who had had a kidney transplant; and 1 was for death. The transition probabilities between the 3 chronic kidney disease health states were taken from the C08-002A/B and C08-003A/B prospective studies for the eculizumab group, and from a retrospective analysis of available pre-treatment data for the standard care group. Results from the other available studies were not used to inform the model parameters. Additional transition probabilities for the transplant health state and for mortality risks were taken from the wider literature. For the eculizumab group, transitions to better or worse health states were possible in any model cycle. In the standard care group, only transitions to worse health states were possible, except when transplantation was assumed to be successful. Transitions to the transplant health state were assumed to apply only to the standard care group. Costs of treatment, including administration costs, were estimated from standard sources.
- 4.19 Health utility values were estimated from EQ-5D data collected within the C08-002A/B and C08-003A/B studies from 37 patients. The weighted improvement in mean utility score from baseline to week 64 across both studies was 0.208. This value was applied as a disutility to all chronic kidney disease health states in the standard care group (to characterise the difference between health-related quality of life for patients having standard care and for those

having eculizumab).

- 4.20 At a discount rate of 1.5%, eculizumab was estimated to produce 24.08 additional years of life and 25.22 additional quality-adjusted life years (QALYs) per patient compared with standard care. The discounted incremental cost of eculizumab compared with standard care presented in their evidence submission has been designated confidential by the company because they consider this information relates to their commercial interests. The company also conducted a probabilistic sensitivity analysis that showed that eculizumab is consistently expected to produce large incremental QALY gains and higher incremental costs compared with standard care. Other sensitivity analyses from the company showed that the estimates of incremental health benefit and incremental cost are particularly sensitive to assumptions about a patient's age at the start of eculizumab treatment and the use of discounting in the model.
- 4.21 The company also developed a budget impact model to estimate the total costs to the NHS of the assumed uptake of eculizumab in England from 2013 to 2017. The company designated all results from their analysis as confidential because they consider these relate to their commercial interests. The company's model predicted a steady increase in the number of patients in England who would be treated with eculizumab for the treatment of aHUS over the 5-year period (specific patient numbers by year are confidential). The company considered that its budget impact of eculizumab was likely to be overestimated because the budget impact of health utility improvements was excluded from the analysis. In addition, indirect costs (which the company considered would be reduced by eculizumab) were also not included.
- 4.22 To estimate the impact of eculizumab beyond direct health benefits the company used: lost productivity and government benefits and tax revenues for patients and carers; and cost savings associated with personal expenses for patients and carers, such as transportation and housing, and other carer costs.

## Evidence Review Group review

- 4.23 The ERG reviewed the company's submission. It considered that the company had included all relevant studies in its evidence submission. The ERG expressed

some concern about several limitations and uncertainties in the evidence base and, in particular, considered that the optimal dose and duration of treatment with eculizumab was unclear. While the summary of product characteristics recommends lifelong treatment with eculizumab unless stopping treatment is clinically indicated, evidence-submissions from patient organisations noted the need for well-controlled prospective studies to define the optimal length of treatment for eculizumab and to determine whether all patients need to continue long-term therapy.

- 4.24 To explore the suitability and robustness of the company's model, the ERG made amendments and conducted exploratory analyses to assess the impact of different assumptions. Most assumptions made by the company were retained within the ERG's exploratory analysis; however, the prognosis of standard care was estimated using published aHUS registry data, rather than pre-treatment data from the C08-002A/B and C08-003A/B studies. The changes made by the ERG resulted in a better prognosis for patients having standard care compared with the predictions of the company's model.
- 4.25 Results from the ERG's exploratory analyses suggested that, at a discount rate of 3.5%, eculizumab is expected to produce 10.14 additional QALYs compared with standard care. Incremental costs from the analysis were higher than those estimated in the company's analysis, and are designated confidential by the company. The ERG highlighted that the estimates of overall survival for the standard care group were considerably higher in the ERG's exploratory analysis (ERG's exploratory analysis, 35.47 undiscounted life years; company's model, 9.97 undiscounted life years). These differences in survival, together with different transition probabilities assumed for the chronic kidney disease states and lower transplant rates assumed for the standard care patients, led to lower estimates of incremental QALYs gained between the treatment groups within the ERG's exploratory analysis.
- 4.26 The ERG considered that the estimates for uptake of eculizumab in the company's budget impact analysis were low. It presented results from a range of uptakes up to 100%. Results from the analysis are designated confidential by the company.
- 4.27 Full details of all the evidence are in the submissions received for this evaluation,

and in the ERG report, which are all available in the [committee papers](#).



## 5 Consideration of the evidence

The Evaluation Committee reviewed the data available on the benefits and costs of eculizumab, having considered evidence on the nature of atypical haemolytic uraemic syndrome (aHUS) and the value placed on the benefits of eculizumab by people with the condition, those who represent them and clinical experts. It also took into account the value of eculizumab and the effective use of resources for specialised commissioning.

### Nature of the condition

5.1 The Committee heard from the clinical experts that aHUS is a heterogeneous disease, with a wide variation in its natural history and in how it responds to treatment. It noted that aHUS is very rare; 20–30 new patients are diagnosed with the condition each year in England. The Committee considered the findings from the survey submitted by the patient experts and agreed that patients with aHUS have a greatly impaired quality of life, from both the severe symptoms they experience and the burden of treatment with dialysis and plasma therapy, and that the families and carers of patients with aHUS also experience substantial burden.

### Impact of the new technology

5.2 The Committee acknowledged that, until eculizumab became available and the NHS England clinical commissioning policy was developed, plasma therapy and dialysis were the main treatment options for aHUS, both of which had limited impact on disease morbidity and mortality but a substantial negative effect on a patient's quality of life. The Committee heard from the patient experts that the impact of eculizumab is influenced by the severity of the disease and the stage of life when a patient becomes affected. For patients with aHUS who have kidney failure, eculizumab offers them the potential for a kidney transplant and an opportunity to restore their health and have a life free from the restrictions of dialysis and the need for frequent plasma therapy. For patients with active disease, eculizumab offers them the possibility of avoiding end-stage renal failure, dialysis and kidney transplantation, as well as other organ damage. It also

offers patients the chance to have restored kidney function or retain their residual kidney function without the need for further dialysis treatment. The Committee heard from the clinical experts that they considered eculizumab to be a step change in the management of aHUS, and the Committee agreed with this.

5.3 The Committee considered the clinical-effectiveness evidence for eculizumab presented by the company. It acknowledged that there were limitations in the evidence base, particularly the lack of randomised trial evidence. However, it noted that, in all of the studies, treatment with eculizumab led to substantial decreases in thrombotic microangiopathy activity, and an improvement in kidney function and quality of life in most patients. The Committee heard from the clinical experts that, since they began prescribing eculizumab, the benefits seen in their patients have been greater than they had originally anticipated. They remarked that many patients were able to stop dialysis after starting treatment with eculizumab, and that there were also non-renal benefits such as improvements in gastrointestinal symptoms. The Committee noted the comments from the Evidence Review Group (ERG) and the patient experts that long-term data on the optimal dose and duration of treatment with eculizumab are lacking. It acknowledged that, although there are ongoing studies that will capture longer-term data, this information will not be available for some time. The Committee also heard from the clinical experts that an international aHUS registry has been established by the company as a commitment towards ensuring that long-term data are collected for all patients with aHUS. The Committee also acknowledged that there are limited data available on the effectiveness of eculizumab in children and adolescents, but concluded that there was no reason to expect a different effect in this group compared with the adult population. Overall, the Committee concluded that eculizumab is a very effective treatment option for patients with aHUS.

5.4 The Committee heard that current use of eculizumab is being continually reviewed, with the aim of achieving optimal dosing and treatment duration for each patient. The Committee noted from the evidence submitted by clinical experts that very specific criteria are followed when starting treatment with eculizumab, and circumstances in which eculizumab treatment should be stopped have been defined. The Committee heard from the clinical experts that all patients have treatment with eculizumab for the first 8 weeks until results of their genetic tests are available. Treatment is then adjusted or stopped based on

the test results. After consultation, the company stated that there is currently no robust evidence available to support dose adjustment or stopping treatment, and that considerable negative health outcomes may occur, such as recurrence of thrombotic microangiopathy, if treatment with eculizumab is stopped. The Committee acknowledged that the summary of product characteristics for eculizumab states that 'treatment is recommended to continue for the patient's lifetime, unless the discontinuation of eculizumab is clinically indicated'. However, the Committee noted comments from a professional organisation that there is no scientific or ethical imperative to continue lifelong treatment in all patients. The Committee heard from the clinical experts that there are clinical indications for which long-term treatment with eculizumab may not be considered necessary, for example, in patients whose disease has responded to eculizumab and in whom renal function has returned to normal. The clinical experts also stated that restarting treatment with eculizumab has been successful in restoring renal function in patients whose disease has recurred. However, the company stated that rescue therapy could not be relied on. The Committee queried whether more up-to-date evidence on stopping treatment had become available since the marketing authorisation was granted. The company stated that, as part of its international aHUS registry, there is evidence that stopping and restarting treatment resulted in poor patient outcomes. The Committee heard from a clinical expert that the evidence is evolving and that, so far, the largest study investigating stopping treatment has been the study by Ardissino et al. (2014), which included a cohort of 10 patients with aHUS. In this study, disease relapsed in 3 patients after stopping eculizumab; all had identifiable genetic mutations that would preclude stopping eculizumab under current national practice. Patients were closely monitored using home urine tests so that recurrence could be identified early and eculizumab reintroduced immediately if needed, allowing renal function to return to the level it was before treatment was stopped. The company emphasised that the decision to stop treatment should lie with clinicians. The clinical experts reassured the Committee that, in clinical practice, this was explored on a case-by-case basis using clinical judgement. The Committee considered that this was not contrary to the specifications in the summary of products characteristics of eculizumab for aHUS, and was also supported by accumulation of experience in clinical practice. The clinical experts also emphasised that there was considerable enthusiasm in UK clinical practice to explore dose adjustment and the option of stopping eculizumab early. Comments received during consultation also supported this. The Committee

considered that, with any treatment, the evidence base inevitably improves as clinical experience accumulates, and that this is particularly relevant in the context of highly specialised technologies for treating very rare lifelong conditions. The Committee concluded that there is a need to further investigate possible dose adjustment and the option of stopping treatment when clinicians consider it appropriate.

- 5.5 The Committee understood that patients welcome treatment with eculizumab because it gives them the opportunity to return to a life free from the disease (see section 5.2). However, the Committee noted that treatment with eculizumab involves repeated treatment infusions, which is burdensome for patients. It therefore considered that the opportunity to stop treatment, if clinically appropriate, would be far less burdensome for patients particularly because some types of monitoring, such as simple urine tests, can be self-administered at home. The Committee noted comments from patient organisations pointing out that it is very important to reassure patients they will be able to restart treatment with eculizumab if clinically indicated. The Committee heard from a clinical expert that stopping eculizumab treatment involves strict monitoring for early signs of disease relapse so that eculizumab can be suitably reintroduced. The Committee also noted that, in response to consultation, patient organisations expressed their support for conducting research to improve the understanding of the underlying risks of aHUS, so that treatment can be managed with the increased chance of a safe outcome. The Committee confirmed that its recommendations did not imply that patients should be taken off treatment against clinical judgement. Instead, its recommendations encouraged exploring the possibility of stopping treatment with eculizumab in a structured manner when clinicians consider it appropriate, so that approaches in clinical practice could be coordinated and underpinned by research. The Committee restated the importance of investigating this under a research programme with robust methodology.
- 5.6 The Committee considered the adverse reactions associated with treatment with eculizumab. It noted from the clinical trials that eculizumab was generally well tolerated and, although most patients reported adverse reactions, only a few were considered to be specifically related to eculizumab use. The Committee also recognised that eculizumab is associated with an increased risk of meningococcal infection. The Committee understood that regulatory requirements around the risks associated with eculizumab are outlined in the

summary of products characteristics and the European public assessment report for eculizumab.

- 5.7 The Committee noted advice from NICE to its advisory bodies that states that, in cases when treatment restores people who would otherwise die or have a very severely impaired life to full or near-full health, and when this is sustained over a very long period (normally at least 30 years), a discount rate of 1.5% for costs and benefits may be considered. This advice can only be implemented if it is highly likely that, on the basis of the evidence presented, the long-term health benefits are likely to be achieved. Having referred to this advice, the Committee considered that substantial restoration of health for a very long period is achieved with ongoing treatment with eculizumab. The Committee heard from the clinical experts that the underlying complement disorder is essentially reversed with eculizumab treatment and that there is emerging evidence that benefits are sustained over time. The Committee concluded that there was a case for applying a discount rate of 1.5%.

## Cost to the NHS and Personal Social Services

- 5.8 The Committee considered the budget impact analysis submitted by the company, as well as the exploratory analyses by the ERG. All assumptions and results in these analyses are deemed commercial in confidence by the company. Despite multiple requests from NICE, the company refused to make this information publically available, including the likely proportion of patients with aHUS that will be children. To allow consultees and commentators to properly engage in the consultation process, the Institute prepared an illustration of the possible budget impact of eculizumab for aHUS, using information available in the public domain. This was based on a treatment cost of £340,200 per adult patient in the first year (based on the acquisition cost of the drug and the recommended dosing for an adult), and assumed a patient cohort of 170, as estimated by NHS England in its interim commissioning policy. If it is assumed that all of these adult patients with aHUS are treated with eculizumab, the budget impact for the first year would be £57.8 million. If an additional 20 new patients are treated the following year (based on a worldwide incidence of 0.4 million; see [section 2.2](#)), the budget impact would rise to £62.5 million in year 2, assuming all new patients are treated and all existing patients continue to be treated at the maintenance

cost of £327,600 per year. Using the same assumptions, the budget impact would rise to £69 million in year 3 (190 existing and 20 new patients), £75 million in year 4 (210 existing and 20 new patients) and £82 million in year 5 (230 existing and 20 new patients). After consultation on the evaluation consultation document, the company stated that this budget analysis was flawed and overestimated the budget impact of eculizumab for treating aHUS. The Committee understood that an estimate based on publically available sources was necessary because of the large amount of data the company had marked as confidential. The Committee was clear that this analysis was not the sole basis for its decision-making and was only used to illustrate the potential upper range of the budget impact.

- 5.9 The company's budget impact analysis, which at the moment is confidential and cannot be shared beyond those stakeholders who have signed a confidentiality agreement, was based on different assumptions for uptake and also included both paediatric and adult patients. The Committee heard from the clinical experts that, if eculizumab is recommended for use in line with its marketing authorisation, uptake is likely to be higher than the company's estimates. In addition, considering the substantial health gains associated with eculizumab treatment compared with standard care, the Committee considered that the company's analyses may have underestimated the true rate of uptake of eculizumab. The Committee also noted that, after consultation, a patient organisation provided alternative estimates of the possible budget impact of eculizumab for aHUS. It assumed a patient cohort of 111 in the base case, of which 74 patients were assumed to need a 1200 mg dose and 37 to need a 600 mg dose of eculizumab. The budget impact for the first year was estimated to be £36 million. If it was assumed that an additional 25 new patients would be treated in the following year, the budget impact was estimated to rise to £45 million in year 2 and up to £68 million in year 5. The Committee considered that uncertainty remained about the number of patients who would be considered for treatment with eculizumab for aHUS. However, it heard from a clinical expert that 56 people currently have eculizumab for aHUS as part of the NHS England interim commissioning policy, and understood that taking this number into account would lower the estimates provided by the patient organisation. After consultation on the second evaluation consultation document, the patient organisation stated that, taking into account the actual number of people having eculizumab, their estimation for year 5 would be £30 million lower.

The clinical expert also advised the Committee that the incidence of new cases was possibly greater than previously thought. The Committee considered that there was uncertainty around the range of budget impact estimates it had been presented with, and acknowledged that the Institute's illustration represented the upper end of the impact on the budget for highly specialised services. The Committee concluded that, taking into account all the evidence, including the various budget impact analyses presented and the estimates of the size of the population, the budget impact of eculizumab for aHUS was very high and likely to increase with the onset of new cases.

5.10 The Committee was made aware of the annual costs of a range of other treatments that are available through nationally commissioned specialised and highly specialised services. However; it was not provided with information that explains the difference between the costs of developing and manufacturing eculizumab for aHUS and those costs for other treatments. The Committee noted that the company had no plans for further clinical studies into the use of eculizumab for the treatment of aHUS. The Committee heard from the company that the cost per patient of treatments for very rare diseases are high because there are only a small number of patients from whom to recover the research, development and manufacturing costs. However, the Committee noted that eculizumab is also licensed for the treatment of paroxysmal nocturnal haemoglobinuria. The size of the combined population is an important consideration in helping to understand the price being asked for a drug for its second and subsequent indications. The Committee concluded that it had not been presented with sufficient justification for the high cost per patient of eculizumab in light of the manufacturing, research and development costs of a medicinal product for the treatment of a very rare condition. It asked the company to provide additional information on the following matters:

- whether there were any clinical or safety requirements during clinical development that might justify the development cost of eculizumab being materially greater than for other treatments for small populations
- the post-marketing research plans, and their costs, for eculizumab for the treatment of aHUS and for other indications
- an explanation of the relationship between the development costs of eculizumab and the price being proposed for the NHS

- any additional information that the company considers will help the Committee reach a conclusion on whether the incremental therapeutic improvement over standard therapy justifies the proposed cost of eculizumab.

5.11 The Committee noted the response from the company stating that research and development costs only explain a small proportion of the cost variance between highly specialised technologies and technologies for treating conditions that affect larger populations. The company stated that, because of a very small number of patients, there is a higher level of financial risk involved in entering the market for very rare diseases, and that there is a need to set up several sites to recruit patients into clinical trials, invest in clinical and patient education, and reinvest resources for new indications. The company also stated that there is a higher risk of failure associated with discovering new treatments for very rare diseases. However, the Committee noted that the company's justification of costs were not exclusive to eculizumab and would apply to all highly specialised technologies for very rare diseases. The Committee also took into account the annual number of patients (adults and children) treated with each of the highly specialised technologies and noted that the number of people treated with eculizumab for aHUS did not represent the smallest patient population compared with other highly specialised technologies. Therefore, the Committee concluded that it had not been presented with a justification of why the overall cost of eculizumab was materially higher than the overall cost of other highly specialised technologies. The company emphasised that the Committee should consider the differential value and benefit from the technology combined with the limited size of the treated population. The Committee stated that the value of eculizumab had been recognised (see sections 5.2 and 5.3), but that this would need to be discussed in the context of the substantial impact eculizumab was expected to have on the budget for highly specialised services.

5.12 The Committee noted that the company also included information on the annual treatment cost per patient of different specialised technologies. The Committee noted that, in this analysis, the annual cost per patient was estimated based on an average weight of 75 kg for adults across conditions. The company highlighted that, based on this analysis, eculizumab was not the most expensive highly specialised technology. However, the Committee heard from a clinical expert and the NHS England representative that the assumption of an average weight of



75 kg for adults in calculating per patient cost for the different drugs was unrealistic because the average weight of adults with most of these conditions was considerably less. Moreover, the average weight varies across conditions. The Committee noted comments from the company stating that there is no evidence on the age-related weight of patients with very rare diseases. The company also stated that the cost difference seen in the analysis for 2 other highly specialised technologies, idursulfase and galsulfase, was twice that of eculizumab in adults. The company stated that eculizumab would only be more expensive than these 2 technologies if adults having these drugs weighed less than half of patients with aHUS, which in the opinion of the company's clinical experts was unlikely. However, based on clinical advice, the Committee considered that it was likely that adults with conditions such as Hunter syndrome, associated with a distinctly smaller stature, would weigh significantly less than adults with aHUS. The Committee heard from the clinical experts that, if the annual treatment cost per patient for adults was adjusted by the average weight of patients for the different indications, eculizumab would be the most expensive treatment. The Committee concluded that the annual cost of eculizumab per patient was considerably higher than the annual cost per patient of other highly specialised technologies for very rare diseases.

## Value for money

- 5.13 The Committee discussed the results of the company's cost-consequence model and the assumptions on which they were based. It heard from the company that they aspired to develop a simple, transparent model informed by the available clinical evidence, and that they considered that their model underestimated the value of eculizumab because they were unable to include the effects of eculizumab on non-renal health states because of the lack of data. The Committee noted that the company assumed a higher health utility in patients having eculizumab to compensate for this and agreed that, even with this, its model was likely to be conservative.
- 5.14 The Committee discussed whether the assessment of the change in health-related quality of life had been adequately captured. It heard from the clinical and patient experts that people who had eculizumab could lead an active and fulfilling life and were able to contribute much more to society. The

Committee accepted that eculizumab is a step change in the management of aHUS and could be considered a significant innovation for a disease with a high unmet clinical need. The Committee acknowledged that the company had attempted to capture the benefits of treatment on extra-renal manifestations in the higher utility value assigned to the health states for those having eculizumab compared with standard care. Even with this, the Committee felt that it was likely that other benefits of a substantial nature had not been adequately captured in the model, and therefore may have led to the underestimation of the overall effectiveness of eculizumab.

5.15 The Committee noted the concerns of the ERG about uncertainties in the company's model and considered the exploratory analyses conducted by the ERG. The Committee was aware that the company considered the ERG's modifications to their model to be unreliable. The Committee noted that, although the incremental quality-adjusted life years (QALYs) estimated in the ERG's analysis were markedly lower than those calculated by the company (10.14 QALYs compared with 25.22 QALYs), both analyses produced substantial QALY gains of a magnitude rarely seen for a new drug treatment. The Committee noted that the company's estimate of the incremental cost of eculizumab compared with standard care was considerable, and that incremental costs estimated by the ERG were even higher (results are designated confidential by the company). The Committee also noted that in the analysis presented by the company in response to the evaluation consultation document, comparing eculizumab with other highly specialised technologies, the company highlighted that eculizumab was associated with the highest QALY gain. The Committee noted that, while there is no specific budget for the provision of highly specialised services in the NHS in England, the resources available for commissioning such services are not unlimited and therefore it remained uncertain on whether the results of the cost-consequence analysis demonstrated good value for money. The Committee therefore sought further information from NHS England on what considerations relating to the management of its specialised commissioning budget it considers should be taken into account when determining a reasonable overall treatment cost for eculizumab. The Committee acknowledged ongoing work initiated by NICE to develop a set of cost reference points for highly specialised treatments compared with other treatments commissioned through specialised services. However, it noted that this work will only be used to inform the future development of methods for evaluating highly specialised technologies. It was

not taken into consideration for this evaluation.

- 5.16 The Committee noted the response to consultation from NHS England stating that, if all patients with aHUS were treated with eculizumab, the cost associated with commissioning eculizumab would add considerable pressure to the budget available for specialised commissioning. The Committee queried the reasoning behind NHS England's decision to commission eculizumab through an interim commissioning policy. It heard that there were potential irreversible implications for patients with aHUS if they did not have eculizumab treatment while waiting for the outcome of the NICE evaluation of eculizumab for aHUS. The budget needed to support the interim commissioning of eculizumab had already been identified. Acknowledging the substantial impact eculizumab would have on the budget, the Committee discussed how the budget available for highly specialised commissioning is distributed. It understood that the budget covers the commissioning of both services and medicines and is not ring fenced, but noted the comment from NHS England that the budget allocated for highly specialised services in 2013–14 was £544 million, of which the spend on high-cost drugs was £156 million. The Committee heard that, if eculizumab was to be recommended, it would need to be included in the budget planning for the next few years in the context of flat-term funding, and therefore other services may be affected. The Committee also considered that, if recommended, the use of eculizumab for aHUS would be expected to increase. The Committee heard that so far commissioning had not been stopped for any highly specialised services, but the approach was to incorporate very clear start and stop criteria developed in collaboration with a small group of clinicians. For example, eculizumab for paroxysmal nocturnal haemoglobinuria is funded for only 100 of the 300 symptomatic patients with the most severe form of disease. The Committee considered that this was important for its considerations, particularly in light of its considerations on dose adjustment and stopping treatment discussed in sections 5.4 and 5.5.

## Impact of the technology beyond direct health benefits and on the delivery of the specialised service

5.17 The Committee acknowledged the potential wider societal benefits of eculizumab treatment proposed by the company and patient experts, including the ability to contribute to society or continue education, and cost savings from personal expenses for patients and carers for transportation and housing. It acknowledged the concerns from the ERG that the company's analysis of these non-health benefits did not consider the expected cost savings due to the displacement of other technologies and services to fund eculizumab. However, on balance, the Committee was persuaded that the non-health effects were likely to be substantial but proportionate to the health effects. The Committee also considered the impact of eculizumab on the delivery of the highly specialised service, and acknowledged statements from clinical experts that showed that, because eculizumab is already available through an interim national aHUS service, all of the components necessary to deliver eculizumab within a national specialised service are already in place and functioning. The Committee was therefore satisfied that no significant additional staffing and infrastructure requirements will be needed in centres where patients with aHUS are currently treated.

## Conclusion

5.18 After considering all available evidence and the opinions of the clinical and patient experts, the Committee agreed that eculizumab represents an important treatment option and effectively decreases thrombotic microangiopathy activity and improves kidney function in most patients with aHUS. The Committee noted that the use of eculizumab would be of significant value to patients with aHUS, but it was aware of its need to consider the extent to which the cost to the NHS of doing so was reasonable. The Committee still considered that it had not been presented with enough justification for the high cost per patient of eculizumab, or for the overall cost of eculizumab with reference to what could be expected to be reasonable in the context of a highly specialised service.

5.19 The Committee considered that the budget impact of recommending eculizumab for aHUS in relation to the substantial benefits it offered to patients, families and carers would be lower if the potential for dose adjustment and stopping treatment was taken into account. However, the Committee was aware of the limited evidence about stopping treatment, despite the significant clinical interest in investigating this possibility. It recalled its considerations on the appropriateness of further investigating possible dose adjustments and the option of stopping treatment when clinicians consider it appropriate, the accumulation of experience in clinical practice and the importance of coordinating clinical practice on the basis of robust research (see [sections 5.4 and 5.5](#)). The Committee also took into account NHS England's current approach to commissioning technologies for very rare diseases on the basis of clear stop and start criteria. Based on these considerations, the Committee concluded that eculizumab, within its marketing authorisation, could be recommended for funding for treating aHUS, only if **all** the following arrangements are in place:

- coordination of eculizumab use through an expert centre
- monitoring systems to record the number of people with a diagnosis of aHUS and the number who have eculizumab, and the dose and duration of treatment
- a national protocol for starting and stopping eculizumab for clinical reasons
- a research programme with robust methods to evaluate when stopping treatment or dose adjustment might occur.

The long-term budget impact of eculizumab for treating aHUS is uncertain but will be considerable. NHS England and the company (Alexion Pharma UK) should consider what opportunities might exist to reduce the cost of eculizumab to the NHS.

5.20 The Committee noted the company's concerns that the Committee was stepping beyond its remit in asking for a justification for whether eculizumab represents a reasonable cost to the NHS. However, the Committee was clear that it is within its remit to take into account the total budget for specialised services and how it is allocated, as well as the scale of the investment in comparable areas of medicine. The Committee will also take into account what could be considered a reasonable cost for the medicine in the context of recouping manufacturing, research and

development costs from sales to a limited number of patients.

- 5.21 The Committee noted the potential equality issue raised by a patient organisation stating that, although the recommendations do not exclude anyone from having rescue therapy with eculizumab if needed, there is a concern for people who risk disease recurrence through pregnancy. The Committee heard from the patient expert that more research should be conducted on the use of eculizumab before or during pregnancy. The Committee heard from a clinical expert that people who became pregnant are intensively monitored and continue to be offered treatment with eculizumab. The clinical expert also noted that more research is being conducted on the underlying risk of pregnancy and aHUS, and on the use of eculizumab during pregnancy, and the Committee supported this. The Committee concluded that, because its recommendations do not restrict access to eculizumab during pregnancy, there was no need to alter them.

## Summary of Evaluation Committee's key conclusions

HST1	Evaluation title: Eculizumab for treating atypical haemolytic uraemic syndrome	Section
<b>Key conclusion</b>		
	The Committee agreed that eculizumab represents an important treatment option of significant value to patients with atypical haemolytic uraemic syndrome (aHUS). However, it was concerned about the substantial impact eculizumab is expected to have on the budget for highly specialised services. The Committee considered that it had not been presented with enough justification for the high cost per patient of eculizumab, or for the overall cost of eculizumab with reference to what could be expected to be reasonable in the context of a highly specialised service.	5.9, 5.18
	The Committee concluded that there is a need to further investigate possible dose adjustment and the option of stopping treatment when clinicians consider it appropriate, under a research programme with robust methodology.	5.4, 5.5

<p>The Committee considered that the budget impact of recommending eculizumab for aHUS in relation to the substantial benefits it offered to patients, families and carers would be lower if the potential for dose adjustment and stopping treatment is taken into account.</p>		5.19
<p>Eculizumab, within its marketing authorisation, is recommended for funding for treating aHUS, only if all the following arrangements are in place:</p> <ul style="list-style-type: none"> <li>• coordination of eculizumab use through an expert centre</li> <li>• monitoring systems to record the number of people with a diagnosis of aHUS and the number who have eculizumab, and the dose and duration of treatment</li> <li>• a national protocol for starting and stopping eculizumab for clinical reasons</li> <li>• a research programme with robust methods to evaluate when stopping treatment or dose adjustment might occur.</li> </ul>		1.1
<p>The long-term budget impact of eculizumab for treating aHUS is uncertain but will be considerable. NHS England and the company (Alexion Pharma UK) should consider what opportunities might exist to reduce the cost of eculizumab to the NHS.</p>		1.2
<p><b>Current practice</b></p>		
<p>Nature of the condition, including availability of other treatment options</p>	<p>aHUS is a very rare condition; 20–30 new patients are diagnosed with aHUS each year in England. The Committee agreed that patients with aHUS have a greatly impaired quality of life, from both the severe symptoms they experience and the burden of treatment with dialysis and plasma therapy, and that the families and carers of patients with aHUS also experience substantial burden.</p>	5.1
	<p>Until eculizumab became available, plasma therapy and dialysis were the main treatment options for aHUS, both of which have limited impact on disease morbidity and mortality but a substantial negative effect on a patient's quality of life.</p>	5.2
<p><b>The technology</b></p>		

<p>Proposed benefits of the technology</p> <p>How innovative is the technology in its potential to make a significant and substantial impact on health-related benefits?</p>	<p>The Committee accepted that eculizumab represents a step change in the treatment of patients with aHUS and could be considered a significant innovation for a disease with a high unmet clinical need.</p> <p>For patients with aHUS who have kidney failure, eculizumab offers them the potential for a kidney transplant and an opportunity to restore their health and have a life free from the restrictions of dialysis and the need for frequent plasma therapy. For patients with active disease, eculizumab offers them the possibility of avoiding end-stage renal failure, dialysis and kidney transplantation, as well as other organ damage. It also offers patients the chance to have restored kidney function or to keep their residual kidney function without the need for further dialysis treatment.</p>	<p>5.2, 5.14</p>
<p>Adverse reactions</p>	<p>The Committee noted from the clinical trials that eculizumab was generally well tolerated, and that, although most patients reported adverse reactions, only a few were considered to be specifically related to eculizumab use. The Committee also recognised that eculizumab is associated with an increased risk of meningococcal infection. The Committee understood that details on adverse reactions and risks associated with eculizumab are stated in the summary of products characteristics and the European public assessment report.</p>	<p>5.6</p>
<p><b>Clinical evidence</b></p>		
<p>Availability, nature and quality of evidence</p>	<p>No randomised controlled trials were identified. The key clinical evidence came from 2 published (C08-002A/B and C08-003A/B) and 2 unpublished (interim data from C10-003 and C10-004) prospective studies, and 1 retrospective observational study (C09-001r).</p>	<p>4.3</p>
<p>Uncertainties generated by the evidence</p>	<p>There were limitations in the evidence base, particularly because of the lack of randomised trial evidence.</p>	<p>5.3</p>



	<p>Long-term data on the optimal dose and duration of treatment with eculizumab are lacking. However, the Committee considered that investigating this was not contrary to the specifications in the summary of product characteristics of eculizumab for aHUS, and was also supported by the accumulation of experience in clinical practice. The Committee concluded that there is a need to further investigate possible dose adjustment and the option of stopping treatment when clinicians consider it appropriate.</p>	5.3, 5.4
	<p>The Committee acknowledged that there are limited data available on the effectiveness of eculizumab in children and adolescents, but concluded that there was no reason to expect a different effect in this group compared with the adult population.</p>	5.3
Impact of the technology	<p>In all of the studies, treatment with eculizumab led to a substantial reduction in thrombotic microangiopathy activity, and improvement in kidney function and quality of life in most patients. The clinical experts remarked that, since they began prescribing eculizumab, the benefits seen in their patients have been better than originally anticipated. Many patients were able to stop dialysis after starting treatment with eculizumab, and there were also non-renal benefits such as improvements in gastrointestinal symptoms.</p> <p>Overall, the Committee concluded that eculizumab is a very effective treatment option for patients with aHUS.</p>	5.3
<b>Cost evidence</b>		
Availability and nature of evidence	<p>The company submitted a budget impact analysis and a de novo cost–consequence model.</p>	4.18, 4.21

<p>Uncertainties around and plausibility of assumptions and inputs in the economic model and budget impact analysis</p>	<p>Considering the substantial health gains associated with eculizumab treatment compared with standard care, the Committee considered that the company's budget impact analyses may have underestimated the true rate of uptake of eculizumab. The Committee considered that there was uncertainty around the range of budget impact estimates it had been presented with and acknowledged that the Institute's illustration represented the upper end of the impact on the budget for highly specialised services. The Committee concluded that, taking into account all the evidence, including the various budget impact analyses presented and the estimates of the size of the population, the budget impact of eculizumab for aHUS was very high and likely to increase with the onset of new cases.</p>	<p>5.9</p>
	<p>The Committee noted the concerns of the Evidence Review Group (ERG) about uncertainties in the company's model, and considered the exploratory analyses conducted by the ERG. The Committee was also aware that the company considered the modifications made by the ERG to the model were unreliable</p>	<p>5.15</p>

<p>Incorporation of health-related quality-of-life benefits and utility values</p> <p>Have any potential significant and substantial health-related benefits been identified that were not included in the economic model, and how have they been considered?</p>	<p>The Committee acknowledged that the company had attempted to capture the benefits of treatment on extra-renal manifestations in the higher utility value assigned to the health states for those having eculizumab compared with standard care. Even with this, the Committee felt that it was likely that other benefits of a substantial nature had not been adequately captured in the model, and therefore may have led to the underestimation of the effectiveness of eculizumab.</p>	<p>5.14</p>
<p>Cost to the NHS and PSS</p>	<p>Despite multiple requests from NICE, the company refused to make its budget impact information publically available. To allow consultees and commentators to properly engage in the consultation process, the Institute has prepared an illustration of the possible budget impact of eculizumab for aHUS using information that is available in the public domain. This illustration showed the budget impact could range from £57.8 million in the first year to £82 million by year 5. The Committee was clear that this analysis was not the sole basis for its decision-making and was only used to illustrate the potential upper range of the budget impact.</p>	<p>5.8</p>

	<p>After consultation, a patient organisation had provided alternative estimates of the possible budget impact of eculizumab for aHUS, indicating a budget impact ranging from £36 million in the first year to £68 million in year 5. After consultation on the second evaluation consultation document, the patient organisation stated that, taking into account the actual number of people having eculizumab, their estimation for year 5 would be £30 million lower. The Committee was made aware of the annual costs of a range of other treatments that are available through nationally commissioned specialised and highly specialised services. The Committee concluded that, taking into account all the evidence, including the various budget impact analyses presented and the estimates of the size of the population, the budget impact of eculizumab for aHUS was very high and likely to increase with the onset of new cases.</p>	5.9
	<p>The Committee noted that the company's justification of costs were not exclusive to eculizumab and would apply to all highly specialised technologies for very rare diseases. Therefore, the Committee concluded that it had not been presented with a justification of why the overall cost of eculizumab was materially higher than the overall cost of other highly specialised technologies.</p>	5.11
Value for money	<p>Although the incremental quality-adjusted life years (QALYs) estimated in the ERG's analysis were markedly lower than those calculated by the company (10.14 QALYs compared with 25.22 QALYs), both analyses produced substantial QALY gains of a magnitude that is rarely seen for any new drug treatment. The Committee acknowledged that the company's estimate of the incremental cost of eculizumab compared with standard care was considerable and that incremental costs estimated by the ERG were even higher (results are designated confidential by the company).</p>	5.15

	<p>The Committee noted the response to consultation from NHS England stating that if all patients with aHUS were treated with eculizumab, the cost associated with commissioning eculizumab would add considerable pressure to the budget available for specialised commissioning. The Committee heard that so far commissioning had not been stopped for any highly specialised services, but the approach was to incorporate very clear start and stop criteria developed in collaboration with a small group of clinicians. The Committee considered that the budget impact of recommending eculizumab for aHUS in relation to the substantial benefits it offered to patients, families and carers would be lower if the potential for dose adjustment and stopping treatment was taken into account.</p>	<p>5.16, 5.19</p>
<p>Impact beyond direct health benefits and on the delivery of the specialised service</p>	<p>The Committee was persuaded that the non-health effects were likely to be substantial but proportionate to the health effects.</p> <p>The Committee was satisfied that no significant additional staffing and infrastructure requirements will be needed in specialist centres where patients with aHUS are currently treated.</p>	<p>5.17</p>
<p><b>Additional factors taken into account</b></p>		
<p>Access agreements</p>	<p>Not applicable</p>	<p>-</p>

<p>Equalities considerations and social value judgements</p>	<p>The Committee noted the potential equality issue raised by a patient organisation stating that, although the recommendations do not exclude anyone from having rescue therapy with eculizumab if needed, there was a concern for people who risk disease recurrence through pregnancy. The Committee heard from the clinical expert that more research is being done on the underlying risk of pregnancy and aHUS and on the use of eculizumab during pregnancy, and the Committee supported this. The Committee concluded that because its recommendations do not restrict access to eculizumab during pregnancy, there was no need to alter them.</p>	<p>5.21</p>
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## 6 Implementation

- 6.1 Section 7(6) of the National Institute for Health and Care Excellence (Constitution and Functions) and the Health and Social Care Information Centre (Functions) Regulations 2013 requires clinical commissioning groups, NHS England and, with respect to their public health functions, local authorities to comply with the recommendations in this evaluation within 3 months of its date of publication.
- 6.2 NHS England has stated that it is able to meet all the conditions for reimbursement within 90 days with the exception of the research programme which will require longer to establish. It is expected that a national protocol for starting and stopping eculizumab for clinical reasons will be developed within 3 months of publication of this Guidance, on the basis of current evidence and practice, and subsequently updated as results from the research programme are available. No extension to the normal period was required.
- 6.3 NICE has not developed implementation tools but will work with NHS England to ensure implementation of the recommendations is monitored.

## 7 Recommendations for further research

7.1 The Committee recommended the use of eculizumab for atypical haemolytic uraemic syndrome (aHUS) only if **all** the following arrangements are in place:

- coordination of eculizumab use through an expert centre
- monitoring systems to record the number of people with a diagnosis of atypical haemolytic uraemic syndrome and the number who have eculizumab, and the dose and duration of treatment
- a national protocol for starting and stopping eculizumab for clinical reasons
- a research programme with robust methods to evaluate when stopping treatment or dose adjustment might occur.

These arrangements include, but are not exclusive to, determining: which patient characteristics allow safe treatment withdrawal after an initial response; whether the patient's disease responds to retreatment with eculizumab if it has relapsed after stopping treatment; and whether the drug dose can be titrated to a marker of response, for example, platelet count, as well as data relating to patient experience of the value offered by eculizumab.

7.2 There is a need for further evidence on the long-term outcomes of treatment with eculizumab, and on the effect of treatment in children, adolescents and during pregnancy. The Committee supports enrolment of patients into the aHUS registry and the collection of high-quality information from these registries periodically to inform treatment decisions.



## 8 Review of guidance

- 8.1 Guidance on this technology will be considered for review 3 years after publication or when sufficient evidence from the research needed on eculizumab for treating atypical haemolytic uraemic syndrome becomes available (whichever date is soonest). The Guidance Executive will decide whether the technology should be reviewed based on information gathered by NICE, and in consultation with consultees and commentators.

Andrew Dillon  
Chief Executive  
January 2015

## 9 Evaluation Committee members and NICE project team

### Evaluation Committee members

The Highly Specialised Technologies Evaluation Committee is a standing advisory committee of NICE. Members are appointed for a 3-year term and a Chair and Vice Chair are also appointed for 3 years. A list of the Committee members who took part in the discussions for this evaluation appears below.

Committee members are asked to declare any interests in the technology being evaluated. If it is considered there is a conflict of interest, the member is excluded from participating further in that evaluation.

The minutes of each Evaluation Committee meeting, which include the names of the members who attended and their declarations of interests, are posted on the NICE website.

#### **Dr Peter Jackson**

Chair of the HST Evaluation Committee, Consultant Physician and Honorary Reader in Clinical Pharmacology

#### **Professor Ron Akehurst**

Professor Emeritus in Health Economics, University of Sheffield and Strategic Director, BresMed Health Solutions Ltd

#### **Mr Sotiris Antoniou**

Consultant Pharmacist, Cardiovascular Medicine, Barts Health NHS Trust.

#### **Mr Steve Brennan**

Chief Finance Officer, NHS North Kirklees Clinical Commissioning Group

#### **Dr Trevor Cole**

Consultant in Clinical and Cancer Genetics and Honorary Reader in Medical Genetics, Clinical Genetics Unit, Birmingham Women's Healthcare NHS Trust

**Dr Jonathan Howell**

Consultant in Public Health with NHS Specialised Services Commissioning and Public Health England

**Mr Jeremy Manuel**

Lay Member

**Mr Francis Pang**

Vice-President, Market Access, Biogen Idec

**Mrs Linn Phipps**

Lay Member

**Dr Mark Sheehan**

Oxford BRC Ethics Fellow, The Ethox Centre, University of Oxford

**Professor Lesley Stewart**

Director, Centre for Reviews and Dissemination, York

**Mrs Sheela Upadhyaya**

Highly Specialised Program of Care Lead (London Region), NHS England

**Dr Anthony Wierzbicki**

Consultant in Metabolic Medicine/Chemical Pathology, Guy's & St Thomas' Hospitals, London

## **NICE project team**

Each highly specialised technology evaluation is assigned to a team consisting of 1 or more technical personnel, a project manager and the Associate Director for the Highly Specialised Technologies Programme.

**Pilar Pinilla-Dominguez**

Technical Lead

**Fiona Pearce/Raisa Sidhu**

Technical Advisers

**Josie Godfrey**

Associate Director – Highly Specialised Technologies

**Jenna Dilkes**

Project Manager

## 10 Sources of evidence considered by the Committee

A. The Evidence Review Group (ERG) report for this evaluation was prepared by the School of Health and Related Research (SchARR), The University of Sheffield:

- Tappenden P, Bessey A, Pandor A, et al. Eculizumab for treating atypical haemolytic uraemic syndrome. Final report to the National Institute for Health and Care Excellence, November 2013

B. The following organisations accepted the invitation to participate in this evaluation as consultees and commentators. They were invited to comment on the draft scope, and the evaluation consultation document. Organisations listed in I, II and III were also invited to make written submissions. Organisations listed in II and III had the opportunity to give their expert views. Organisations listed in I, II and III also have the opportunity to appeal against the final evaluation determination.

I. Company/sponsor:

- Alexion Pharma UK

II. Professional/specialist and patient/carer groups:

- aHUS Action
- aHUS UK
- British Society for Haematology
- Genetic Alliance UK
- Kidney Research UK
- Royal College of Nursing
- Royal College of Paediatric and Child Health
- Royal College of Pathologists

- Royal College of Physicians

III. Other consultees:

- NHS England
- Department of Health

IV. Commentator organisations (did not provide written evidence and without the right of appeal):

- Healthcare Improvement Scotland
- National Institute for Health Research Health Technology Assessment
- Welsh Kidney Patients Association
- Welsh Government

C. The following individuals were selected from clinical and patient expert nominations from the consultees and commentators. They gave their expert personal view on eculizumab by providing oral and written evidence to the Committee.

- Dr Rodney Gilbert, Consultant Paediatric Nephrologist, nominated by Alexion Pharma UK – clinical expert
- Professor Tim Goodship, Professor of Renal Medicine, nominated by aHUS Action and aHUS UK – clinical expert
- Dr Marie Scully, Consultant Haematologist, nominated by the British Society for Haematology and the Royal College of Pathologists – clinical expert
- Elena Lilley, nominated by aHUS UK – patient expert
- Len Woodward, Treasurer, nominated by aHUS UK – patient expert

D. The following individuals were nominated as NHS Commissioning experts by NHS England. They gave their expert/NHS commissioning personal view on eculizumab by providing oral and written evidence to the Committee.

- Barbara Howe, National Programme of Care Director – Highly Specialised, selected by NHS England – NHS Commissioning expert

- Edmund Jessop, Public Health Adviser, selected by NHS England – NHS Commissioning Expert
- Fiona Marley, Assistant Head of Specialised Services, selected by NHS England – NHS Commissioning Expert

E. Representatives from the following company/sponsor attended Committee meetings. They contributed only when asked by the Committee chair to clarify specific issues and comment on factual accuracy.

- Alexion Pharma UK

## About this guidance

This guidance was developed using the NICE [highly specialised technologies guidance](#) process.

It has been incorporated into the NICE pathway on [blood conditions](#) along with other related guidance and products.

We have produced [information for the public explaining this guidance](#). Information about the evidence it is based on are also [available](#).

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### Your responsibility

This guidance represents the views of NICE and was arrived at after careful consideration of the evidence available. Healthcare professionals are expected to take it fully into account when exercising their clinical judgement. However, the guidance does not override the individual responsibility of healthcare professionals to make decisions appropriate to the circumstances of the individual patient, in consultation with the patient and/or guardian or carer.

Implementation of this guidance is the responsibility of commissioners and/or providers. Commissioners and providers are reminded that it is their responsibility to implement the guidance, in their local context, in light of their duties to have due regard to the need to eliminate unlawful discrimination, advance equality of opportunity and foster good relations. Nothing in this guidance should be interpreted in a way that would be inconsistent with compliance with those duties.

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