Highly Specialised Technology Evaluation

Eculizumab for the treatment of atypical haemolytic uraemic syndrome (aHUS)

Committee Papers

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Highly Specialised Technologies

Eculizumab for treating atypical haemolytic uraemic syndrome (aHUS)

The following documents are made available to the consultees and commentators:

1. **Response to consultee, commentator and public comments on the Evaluation Consultation Document (ECD) 2**

2. **Consultee and commentator comments on the Evaluation Consultation Document 2 from:**
   - Alexion Pharma UK
   - aHUS UK
   - AHUS Action
   - NHS England
   - Royal College of Physicians and the Renal Association (*joint submission*)

Please note we received notification of no comments from the Royal College of Nursing and the Royal College of Paediatrics and Child Health

Any information supplied to NICE which has been marked as confidential has been redacted. All personal information has also been redacted.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Highly Specialised Technology Evaluation

Eculizumab for treating atypical haemolytic uraemic syndrome (aHUS)

Response to consultee, commentator and public comments on the 2nd Evaluation Consultation Document (ECD)

Definitions:

Consultees – Organisations that accept an invitation to participate in the appraisal including the manufacturer or sponsor of the technology, national professional organisations, national patient organisations, the Department of Health and relevant NHS organisations in England. Consultee organisations are invited to submit evidence and/or statements and respond to consultations. They are also have right to appeal against the Final Evaluation Determination (FED). Consultee organisations representing patients/carers and professionals can nominate clinical specialists and patient experts to present their personal views to the Evaluation Committee.

Clinical specialists and patient experts – Nominated specialists/experts have the opportunity to make comments on the ECD separately from the organisations that nominated them. They do not have the right of appeal against the FED other than through the nominating organisation.

Commentators – Organisations that engage in the evaluation process but that are not asked to prepare an evidence submission or statement. They are invited to respond to consultations but, unlike consultees, they do not have the right of appeal against the FED. These organisations include manufacturers of comparator technologies, Welsh Government, Healthcare Improvement Scotland, the relevant National Collaborating Centre (a group commissioned by the Institute to develop clinical guidelines), other related research groups where appropriate (for example, the Medical Research Council); other groups (for example, the NHS Confederation, and the *British National Formulary*).

Public – Members of the public have the opportunity to comment on the ECD when it is posted on the Institute's web site 5 days after it is sent to consultees and commentators. These comments are usually presented to the evaluation committee in full, but may be summarised by the Institute secretariat – for example when many letters, emails and web site comments are received and recurring themes can be identified.

Please note: Comments received in the course of consultations carried out by NICE are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the submissions that NICE has received, and are not endorsed by NICE, its officers or advisory committees.

Comments received from consultees

Consultee	Comment	Response
aHUS UK	**INTRODUCTION** aHUSUK and its members welcome the change in the recommendation made by the Evaluation Committee and appreciate the reasoning that led to that change. aHUSUK's response to Evaluation Consultation Document 2 follows. • **Has all of the relevant evidence been taken into account?** Yes, all needed for this recommendation. • **Are the summaries of the criteria considered by the Committee and the clinical and economic considerations reasonable interpretations of the evidence?** Yes • **Are the provisional recommendations sound and a suitable basis for guidance on the use of eculizumab for the treatment of aHUS in the context of national commissioning by NHS England?** Yes. • **Are there any aspects of the recommendations that need particular consideration to ensure that they avoid unlawful discrimination against any group of people on the grounds of gender, disability, religion, sexual orientation, age, gender reassignment or pregnancy or maternity?** Yes, whilst nothing in these guidelines excludes those who may knowingly risk aHUS when pregnant from receiving eculizumab if a rescue is needed (because pregnancy is known to be a trigger), aHUSUK has concerns that pregnancy and maternity may become a potential "particular consideration" for indirect discrimination in practice. • **Given the requirement for relevant health bodies (clinical commissioning groups, NHS England and local authorities) to provide funding to ensure that the health technology is available within 3 months, from the date the recommendation is published by NICE (see section 5.1), is an extension to this normal period appropriate because any of the following circumstances apply?**	Comments noted. Comment noted. 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,

Consultee	Comment	Response
	- **The health technology cannot be appropriately administered until training is in place?** - **The health technology cannot be appropriately administered until certain health service infrastructure requirements including goods, materials or other facilities are in place?** - **The health technology cannot be appropriately administered until other appropriate health services resources, including staff, are in place?** - **The specific conditions in the guidance warrant a longer implementation time?** - **If so, please specify the reasons and an estimate of the time period within which the recommendation can be complied with.** No comment.	there was no need to alter them (please see section 5.21 in the FED). Comment noted.
	EVALUATION COMMITTEE's PRELIMINARY RECOMMENDATION Agreed, and whilst there is considerable uncertainty, aHUSUK's expectation is that the cost can be much less. (1.1, 1.2) **THE CONDITION** No further comment. (2) **CLINICAL EVIDENCE** No further comment. (3) **EVIDENCE SUBMISSIONS** No further comment. (4)	Comments noted.
	CONSIDERATION OF EVIDENCE Understandably, as yet, no robust evidence about the withdrawal of the drug is available. aHUSUK would not wish to see patients being taken off eculizumab in a piecemeal fashion, nor according to some arbitrary set time limit, because the risks are evident and patients need to have confidence that they will get the best possible clinical management. (5.4) A clear distinction needs to be made between those few patients for whom eculizumab does not work, and those for whom eculizumab has worked, but for whom it may no longer be needed to do the job it has done. aHUSUK believes that Clinicians need to have advice based on robust evidence, and that patients need to	Comment noted. The clinical experts reassured the Committee that, in clinical practice, this was explored on a case-by-case basis using clinical judgement. 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

Consultee	Comment	Response
	be properly and fully informed before a decision is made. It is vital that they are assured of a return to eculizumab if there a recurrent episode. (5.4) Preserving as much kidney function as possible from the acute episode of aHUS is important; this may take time as recovery continues, albeit at a slowing rate. The potential for gaining function may be influenced by the time taken between onset and diagnosis and the drug being prescribed. Whilst the Committee has focussed on the technology and protocol for starting treatment with eculizumab, the speed of diagnosis and the commencement of eculizumab are crucial, including the results of necessary lab tests. It is very clear that the faster patients access eculizumab, the less damage is done. The less damage done, the less recovery is needed and the sooner exiting the drug may be considered. (5.4) However, underpinning the successful withdrawal of the drug is the need for patients to be assured that their complement activity has returned to a state prior to the triggering event and that the triggering event has passed. (5.4)	the importance of investigating this under a research programme with robust methodology. 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 clinical experts also stated that restarting treatment with eculizumab has been successful in restoring renal function in patients whose disease has recurred (please see sections 5.4 and 5.5 in the FED).
	aHUSUK notes new evidence about the actual numbers receiving eculizumab and accepts that its baseline number in the cost estimates given in its response to ECD 1 was significantly over stated. Consequently aHUSUK's projected five year spend will be just over £30m less, and so will increase the already significant difference between its estimates and the NICE illustrative "upper range". (5.8) aHUSUK recognises the uncertainties in constructing a budget and, indeed, was told by a representative from NICE, following its first meeting, how impossible the task might be (but that this would not be detrimental to aHUS patients). aHUSUK notes the Committee's assurance about likely budgets not being the "sole basis" for a decision. Nevertheless it is also not clear what, in the context of NHS England, constitutes a very high budget. (5.8) Whilst noting that the Committee has reaffirmed its acceptance of the supplier's assertion about the considerable value of their drug, aHUSUK is disappointed that the Evaluation Committee has not, as yet, found the answers it sought so that the unit price of eculizumab is shown to be justifiable. aHUSUK would have preferred that there was no doubt about the price, particularly if the Committee had also taken into account distribution/after sales support as a key part of the business infrastructure needed for a drug to made available in a safe and sustainable way. aHUSUK, however, is of the opinion that a justification can be made from well regulated information in the public domain. Furthermore, the tolerances established within the governance arrangements of the Department of Health's Prescription	The Committee noted the revised estimates. The Committee maintained 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 (please see section 5.9 in the FED). Response from NICE about the Pharmaceutical Price Regulation Scheme 2014 to follow.

Consultee	Comment	Response
	Pricing Regulatory Scheme gives aHUSUK further cause to be assured. (5.10, 5.17) aHUS is a complex disease arising from the coming together of a variable combination of genetic and environmental risk factors, and it results in a spectrum of patient experiences. Within that spectrum some patients may need full doses at two-week intervals for life but some may not. aHUSUK supports research to understand the underlying risks so that treatment can be managed with the certainty of a safe outcome. aHUSUK is confident that putting the findings of this research into practice will make a considerable difference to overall affordability whilst fully protecting aHUS patients. (5.18) Furthermore, aHUSUK supports the idea that the supplier and the NHS will explore further ways to improve cost effectiveness. With a little thought and flexibility waste can be reduced, perhaps for example, unless production processes make it impossible, an intermediate vial size could, through better tailoring to patients' weight changes, improve treatment safety and avoid using some of the drug unnecessarily. (5.18)	Comment noted. 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. The Committee restated the importance of investigating this under a research programme with robust methodology (please see sections 5.4 and 5.5 in the FED). Comment noted.
	IMPLEMENTATION aHUSUK appreciates the way in which it has been engaged in both AGNSS and NICE evaluation processes, even though it was very unhappy about the nine month gap before the two were linked. Although it will not be NICE's job to do so, aHUSUK hopes that it will continue to be consulted by those implementing the recommendations, when the time comes.	Comment noted.
	PROPOSED RECOMMENDATIONS FOR FURTHER RESEARCH aHUSUK fully supports the need for an expert centre, patient registries, clear clinical protocols and further research about treatment in practice, including examining simple and reliable self testing as well as establishing a clear, assured and sustainable care network pathway during the process of withdrawal.	Comment noted.
	GUIDANCE No comment	Comment noted.
	PROPOSAL FOR REVIEW Whilst understanding that the review periods may be fixed at a specific level for all NICE guidelines, aHUSUK believes that the exceptional duration of the appraisal process to which aHUS patients have been subjected, as well as the uncertainties surrounding projected patient numbers, should be taken into account and would suggest that a review should be conducted after the end of the fifth financial year of	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

Consultee	Comment	Response
	the budget estimate period so that a full comparison can be made with the estimates used in this evaluation.	technology should be reviewed based on information gathered by NICE, and in consultation with consultees and commentators (please see section 9.1 in the FED).
	CONCLUDING COMMENT aHUSUK did not wish to be subjected to a full evaluation by NICE after having been through the AGNSS appraisal with a positive recommendation. Nevertheless, throughout the process it has found the way in which those at NICE have engaged with its trustees, to be both professional and helpful. Our patient organisation has, because of unique circumstances, been part of the passage of highly specialised technology appraisals from one established decision making organisation to another. It has witnessed an emerging approach to this task, which is being designed and developed with a vision and commitment to produce something for those who seek equity of access to such technologies for treatment of their severe rare diseases. aHUSUK recognises that this has not been easy to do, as it has been hard for aHUS patients to handle the uncertainties of what has been an exceptionally prolonged process. aHUSUK hopes that, from now on, the process is straight forward and that, at last, aHUS patients can have assured access to an effective treatment when they need it for as long as it is needed.	Comments noted.
Alexion Pharma UK	Alexion is pleased that the Evaluation Committee has issued a provisional positive recommendation for national commissioning of eculizumab for the treatment of aHUS patients in England. We agree with the Committee's recommendation, and firmly believe that the details of implementation should be left to the discretion of treating physicians in the context of their management of individual patients with aHUS. Below we provide our responses and comments to the questions posed by the Committee in its second ECD. As always, Alexion remains committed to working with NICE, NHS England, and the treating physicians to ensure that all patients in England with aHUS in need have continued access to eculizumab in a timely and appropriate manner. Below, we provide responses to the Committee's questions	Comments noted. 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 when clinicians consider it appropriate in a structured manner so that approaches in clinical practice could be coordinated and underpinned by research (please see section 5.5 in the FED).
	Committee's Question 1: Has all of the relevant evidence been taken into account? As in the first ECD, all clinical studies of eculizumab in the treatment of aHUS have been considered by the Committee in the second ECD. Alexion would, however, like to make sure that the Committee has reviewed all information submitted on the	Comment noted. Comment noted. The Committee took into account all information presented by the company, clinical experts and patient organisations. The Committee Papers for all meetings are available on the NICE website. The Committee's deliberations on possible

Consultee	Comment	Response
	"Nature of the Condition" and not just the two journal articles mentioned in Section 4.16 of the second ECD as well as evidence from clinical specialists and aHUSUK. Alexion also submitted evidence—in our initial submission and response to the first ECD—regarding the natural history of disease and the unpredictable life-long risks associated with chronic, complement-mediated TMA that should be taken into account by the Committee. It is not clear that the EC has adequately evaluated the submitted evidence regarding the consequences of treatment withdrawal, exposing patients to the same thrombotic microangiopathy (TMA)-mediated disease process that led to their initial clinical presentation and treatment.	dose adjustment and the option of stopping treatment are outlined in sections 5.4 and 5.5 in the FED.
	Committee's Question 2: Are the summaries of the criteria considered by the Committee and the clinical and economic considerations reasonable interpretations of the evidence? Overall, the clinical and economic summaries provided by the Committee are reasonable interpretations of the evidence Alexion provided in its various submissions to NICE. The technical issues for which Alexion disagrees with the Committee or NICE's interpretation of the evidence have already been outlined in detail in our various submissions. [1] Alexion would, however, like to clarify two points made by the Committee in the second ECD: 1) In the second ECD the Committee comments on the comparison of the annual treatment cost and lifetime QALY benefit between specialised medicines that Alexion provided to NICE. Specifically, in Section 5.11 of the ECD, the Committee states 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." The analysis undertaken by Alexion considered two scenarios: the cost of treating a child (15Kg) and that of an adult (75kg). In both scenarios the weight was assumed to be the same for all therapies. Under these scenarios, the analysis demonstrated that eculizumab is not the most expensive specialised medicine—4 of the other 10 drugs were more expensive in both of the scenarios. The Committee seems to be suggesting that for adults, the average weight is likely to differ between diseases, but no data were presented to support this suggestion. No systematic review of average weight data across ultra-orphan diseases is available, and therefore such a	Comments noted. 1) Comment noted. 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 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 (please see section 5.12 in the FED).

[1] Alexion submissions thus far include: 1) Initial submission on (date); 2) Response to ERG on (date); and 3) Response to first ECD on (date).

Consultee	Comment	Response
	comparison is currently difficult to make, which is why Alexion chose to use a simplifying assumption. The cost difference, however, seen in the analysis for two products, idursulfase and galsulfase, was twice that of eculizumab in adults. For eculizumab to be more expensive than these agents would require adult patients being treated with these drugs to weigh less than half the weight of an aHUS patient, which in the opinion of Alexion clinical experts is unlikely. Furthermore, the published clinical trials of the other highly specialised technologies for very rare diseases also indicate that this may not be the case. For example, the average age of patients enrolled in the idursulfase trial is 14.8 years, and the average patient weight was 37kg at baseline.[2] The age range in this trial was 5.4–30.9; so it is likely that some proportion of the trial patients were at or over 75kg. 2) Also in the second ECD, the Committee states that the budget impact of eculizumab for treating aHUS is "uncertain but will be considerable". Although all budget estimates are technically uncertain since the future cannot be predicted with certainty, Alexion has confidence in the budget estimates provided to the Committee are reasonable and as accurate as current disease and market understanding allow. Additional details clarifying our assumptions are provided in our response for the first ECD submitted on (date).	2) Comment noted. The Committee considered that there was uncertainty around the range of budget impact estimates it had been presented with. The clinical expert advised the Committee that the incidence of new cases was possibly greater than previously thought. 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 (please see section 5.9 in the FED).
	Committee's Question 3: Are the provisional recommendations sound and a suitable basis for guidance on the use of eculizumab for the treatment of atypical haemolytic uraemic syndrome in the context of national commissioning by NHS England? Alexion agrees with the Committee that the provisional recommendations generally provide a sound and suitable basis for guidance on the use of eculizumab for the treatment of aHUS in England. Specifically, Alexion agrees with the Committee's preliminary recommendation that funding of eculizumab for the treatment of aHUS	Comments noted.

[2] Muenzer, Joseph, et al. "A phase II/III clinical study of enzyme replacement therapy with idursulfase in mucopolysaccharidosis II (Hunter syndrome)."Genetics in Medicine 8.8 (2006): 465-473.

Consultee	Comment	Response
	via national commissioning by NHS England should be granted. With regard to the conditions set forth in the second ECD, however, Alexion's comments are as follows: <u>Coordination of the use of eculizumab through an expert centre</u> Alexion agrees that coordination on the use of eculizumab for aHUS should be done through an expert centre or centres throughout England. <u>Monitoring systems to record the number of people with a diagnosis of atypical haemolytic uraemic syndrome, the number of people who receive eculizumab, and the dose and duration of treatment for these people</u> Alexion is supportive of collecting data to monitor the usage of eculizumab and the outcomes of patients with aHUS. Alexion already facilitates the collection of data on aHUS patients—both those treated with eculizumab and those who are not—globally through the aHUS global registry. Data from this registry are available to researchers at the expert centres in England as a repository through which to collect and analyse the patient information. <u>National protocol for starting and stopping eculizumab for clinical reasons</u> As stated previously, Alexion believes that patients with aHUS should be treated in accordance with the EMA-approved Statement of Product Characteristics (SPC). While there is not always such a statement for therapies approved by the EMA to treat patients with ultra-rare disorders, in the case of the approval of eculizumab for treatment of patients with aHUS, Section 4.2 of the SPC affirmatively states: "Soliris treatment is recommended to continue for the patient's lifetime, unless the discontinuation of Soliris is clinically indicated (see section 4.4)." As outlined in the SPC, and Alexion's submission and response to the first ECD, significant negative patient health outcomes may occur if treatment with eculizumab is stopped; hence, the reason for the statement in Section 4.2 of the SPC. As such, any decision to withdraw eculizumab treatment for aHUS patients should be based upon the treating physician's expert clinical assessment in the context of an individual patient's clinical condition and the evaluation of whether the patient is suffering an adverse reaction as described in Section 4.4 of the approved SPC entitled "Special warnings and precautions for use." Although Alexion does not agree that development of a protocol is a necessary or	Comment noted. Comment noted. Comments noted. 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 and that this is 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 the accumulation of experience in clinical practice. 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

Consultee	Comment	Response
	appropriate condition of eculizumab national commissioning, we feel strongly that any aHUS treatment protocol should be developed by the expert clinicians who are most familiar with the disease, and use of eculizumab to treat aHUS and should be consistent with the SPC. Alexion recognizes that a protocol has already been developed by the UK Renal Association and is in use at the aHUS expert centre at Newcastle upon Tyne Hospital's NHS Foundation Trust. However, Alexion does not endorse the implementation of this protocol with the reservations that it is counter to the SPC safety statement on discontinuation, and that it lacks medical evidence of safety upon treatment withdrawal. <u>Research programme with robust methods to evaluate when stopping treatment or dose adjustment might occur</u> The nature of the research programme envisaged by the Committee is not explained in the second ECD, which has limited Alexion's ability to respond in consultation. However, while Alexion would be greatly concerned by the ethical implications of any clinical trial that required treatment withdrawal or dose adjustment on any basis, we are willing to work with expert centres in the UK to assist in the continued collection and analysis of observational data through the monitoring systems (described above) to better understand the course of aHUS and the therapeutic benefit of eculizumab.	when clinicians consider it appropriate. 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 when clinicians consider it appropriate in a structured manner 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 (please see sections 5.4 and 5.5 in the FED). The Committee is unable to dictate the design of any research studies it recommends but the questions to be answered are clearly laid out in the FED (please see sections 1.1, 7.1 and 7.2 in the FED).
	Committee's Question 4: Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of race, gender, disability, religion or belief, sexual orientation, age, gender reassignment, or pregnancy and maternity? Alexion does not think that any aspects of the recommendation need particular consideration to avoid unlawful discrimination against any group of people on the grounds of race, gender, disability, religion or belief, sexual orientation, age, gender reassignment, or pregnancy and maternity. The recommendations can be applied to all patients with aHUS equally.	Comment noted.
	Committee's Question 5: Given the requirement for relevant health bodies (clinical commissioning groups, NHS England and local authorities) to provide funding to ensure that the health technology is available within 3 months, from the date the recommendation is published by NICE (see section 5.1), is an extension to this normal period appropriate because any of the following circumstances apply?	Comments noted.

Consultee	Comment	Response
	Question 5a: The health technology cannot be appropriately administered until training is in place? No additional training is needed to appropriately administer eculizumab as it is administered via a standard intravenous infusion. **Question 5b: The health technology cannot be appropriately administered until certain health service infrastructure requirements including goods, materials or other facilities are in place?** No additional infrastructure requirements are needed to appropriately administer eculizumab. **Question 5c: The health technology cannot be appropriately administered until other appropriate health services resources, including staff, are in place?** No additional health services resources are needed to administer eculizumab. **Question 5d: The specific conditions in the guidance warrant a longer implementation time?** No additional time is needed for implementation. While the details of implementing the preliminary recommendations are being discussed with the relevant clinical experts, access for aHUS patients in need of eculizumab should continue to be made available under the interim commissioning policy already in place. **Question 5e: If so, please specify the reasons and an estimate of the time period within which the recommendation can be complied with.** No additional comments.	
Royal College of Physicians and Renal Association	We welcome the recommendation of the committee that eculizumab should be available for use in aHUS subject to certain conditions (addressed below). We believe this to be the right decision for patients with aHUS and those yet undiagnosed who will experience significant health benefit from eculizumab. We are pleased that the culmination of years of successful medical research has been translated into an effective treatment, and that patients will now benefit from this. We believe that all relevant evidence has been taken into account and that the summaries of the criteria considered by the Committee and the clinical and	Comments noted.

Consultee	Comment	Response
	economic considerations are reasonable interpretations of the evidence.	
	Our experts note the robust defence of costs by the manufacturer and feel that the main areas of contention now appear to rest within the remit of health economics. We do, however, wish to respond with regard to two outstanding clinical issues, as below: • The main clinical issue is that of dosage and interval, and whether the drug can be withdrawn. We note that the manufacturer firmly rejects the proposal that the drug can ever be withdrawn, and our experts are uncomfortable with this stance. The manufacturer quotes previous EMA recommendation for lifelong treatment. However, this ignores the fact that the evidence base will inevitably improve as studies are carried out and that there is no scientific or ethical imperative to continue lifelong treatment in all patients. The manufacturer also states that lifelong complement inhibition is necessary in those with a complement gene abnormality. This is theoretical and we do not currently understand either the nature of second hits required for disease relapses or the adverse consequences of long-term complement inhibition. • Our experts believe that the cost analysis provided by the manufacturer, compared to other ultra-rare disease therapies, is a compelling set of calculations to justify its use. Our only comment here is that this would only hold true if a similar number of patients were being treated with each of the drugs being compared, across the UK. If Eculizumab is being used (or will be used) in a significantly higher number of patients (particularly as it is or has been evaluated for several other conditions) then the cost to the NHS will be far higher, and the comparison with other ultra-rare disease therapies is less relevant.	Comment noted. 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 concluded that there is a need to further investigate possible dose adjustment and the option of stopping treatment when clinicians consider it appropriate. The Committee restated the importance of investigating this under a research programme with robust methodology (please see sections 5.4 and 5.5 in the FED). 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 (please see section 5.12 in the FED).
	The recommendation of eculizumab by the committee is subject to a number of conditions, considered below: • We agree that use of eculizumab should be co-ordinated through an expert centre. We strongly propose that eculizumab should be delivered locally with local expertise but recognise the value of the resource provided by an expert centre or specialised service, including diagnostic and management support. • We agree with the recommendation that the number of people with aHUS and the number receiving eculizumab should be monitored and information collected about dosing and duration. There is great value in collecting this independently of the manufacturer-sponsored registry and would be best achieved by having an expert centre or specialised service.	Comments noted.

Consultee	Comment	Response
	• We propose that a national protocol for starting and stopping eculizumab should be developed, but that this should be informed by well-conducted clinical trials. We do not think that any aspects of the recommendations pose a risk of unlawful discrimination. The provisional recommendations are sound and provide clear guidance on the use of eculizumab in aHUS and are a suitable basis for guidance on the use of eculizumab for the treatment of aHUS in the context of national commissioning by NHS England. Since an interim national aHUS service is already in place we believe that the health technology will be available within three months of the publication of the recommendation.	
aHUS Action	aHUS Action welcomes the advice of the NICE Highly Specialised Technologies Committee in recommending Eculizumab for the treatment of aHUS. The Committee has rightly recognised that Eculizumab marks a step change for the treatment of aHUS and this initial recommendation provides much needed hope for patients after many years of uncertainty. aHUS Action is committed to supporting the development of a national treatment protocol, as requested by NICE, to ensure the cost effective use of Eculizumab in the NHS, and that all patients who are proven to clinically benefit from Eculizumab receive it. Further to the recommendations, aHUS Action seeks clarification from NHS England on whether an NHS Highly-Specialised National Service is required to implement the recommendations or an Expert Centre is sufficient.	Comment noted.
NHS England	1. NHS England is grateful for the opportunity to comment on this document. 2. We believe that all of the relevant evidence has been taken into account. 3. We believe that the summaries of the criteria considered by the Committee and the clinical and economic considerations are reasonable interpretations of the evidence. 4. We believe that the provisional recommendations are sound and a suitable basis for guidance on the use of eculizumab for the treatment of atypical haemolytic uraemic syndrome in the context of national commissioning by NHS England.	Comments noted.

Consultee	Comment	Response
	5. We do not think that any aspects of the recommendations need particular consideration to avoid unlawful discrimination against any group of people on the grounds of race, gender, disability, religion or belief, sexual orientation, age, gender reassignment, or pregnancy and maternity. 6. We believe that we can make the health technology available within 3 months, subject to a proviso on the research programme. 7. The Committee has set the following conditions for the use of eculizumab in aHUS: • coordination of the use of eculizumab through an expert centre; • monitoring systems to record the number of people with a diagnosis of atypical haemolytic uraemic syndrome, the number of people who receive eculizumab, and the dose and duration of treatment for these people • 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 first three requirements are straightforward to implement. A research programme will take longer to establish. Ideally this should be multi centre and international so as to recruit large numbers of patients: we understand that the UK clinical experts are applying for European funding. If that proposal fails, we will work with the National Institute for Health Research to set up an England-only trial. Agreeing the protocol, securing ethical consent and clearing research governance procedures is likely to take 12 – 18 months.	

The Royal College of Nursing and the Royal College of Paediatrics and Child Health noted that they did not have any comments on the 2nd ECD

September 25, 2014

[redacted]
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Re: Alexion response to the second Evaluation Consultation Document (ECD) for eculizumab in atypical haemolytic uraemic syndrome (aHUS)

[redacted]

Alexion is pleased that the Evaluation Committee has issued a provisional positive recommendation for national commissioning of eculizumab for the treatment of aHUS patients in England. We agree with the Committee's recommendation, and firmly believe that the details of implementation should be left to the discretion of treating physicians in the context of their management of individual patients with aHUS. Below we provide our responses and comments to the questions posed by the Committee in its second ECD.

As always, Alexion remains committed to working with NICE, NHS England, and the treating physicians to ensure that all patients in England with aHUS in need have continued access to eculizumab in a timely and appropriate manner.

Yours Sincerely,

[redacted]
Global Government Affairs

Cc: [redacted]

I. Introduction

In the pages that follow, Alexion responds to the second Evaluation Consultation Document (ECD) and addresses the questions outlined by the Evaluation Committee (the Committee) in the second ECD. Specifically, the Committee has asked to receive comments on the following:

- Has all of the relevant evidence been taken into account?
- Are the summaries of the criteria considered by the Committee and the clinical and economic considerations reasonable interpretations of the evidence?
- Are the provisional recommendations sound and a suitable basis for guidance on the use of eculizumab for the treatment of atypical haemolytic uraemic syndrome in the context of national commissioning by NHS England?
- Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of race, gender, disability, religion or belief, sexual orientation, age, gender reassignment, or pregnancy and maternity?
- Given the requirement for relevant health bodies (clinical commissioning groups, NHS England and local authorities) to provide funding to ensure that the health technology is available within 3 months, from the date the recommendation is published by NICE (see section 5.1), is an extension to this normal period appropriate because any of the following circumstances apply?
    - The health technology cannot be appropriately administered until training is in place?
    - The health technology cannot be appropriately administered until certain health service infrastructure requirements including goods, materials or other facilities are in place?
    - The health technology cannot be appropriately administered until other appropriate health services resources, including staff, are in place?
    - The specific conditions in the guidance warrant a longer implementation time?
    - If so, please specify the reasons and an estimate of the time period within which the recommendation can be complied with.

II. Response to the Committee's Questions

Below, we provide responses to the Committee's questions:

<u>Committee's Question 1</u>: Has all of the relevant evidence been taken into account?

As in the first ECD, all clinical studies of eculizumab in the treatment of aHUS have been considered by the Committee in the second ECD. Alexion would, however, like to make sure that the Committee has reviewed ***all*** information submitted on the "Nature of the Condition" and not just the two journal articles mentioned in Section 4.16 of the second ECD as well as evidence from clinical specialists and aHUSUK. Alexion also submitted evidence—in our initial submission and response to the first ECD—regarding the natural history of disease and the unpredictable life-long risks associated with chronic, complement-mediated TMA that should be taken into account by the Committee. It is not clear that the EC has adequately evaluated the submitted evidence regarding the consequences of treatment withdrawal, exposing patients to the same thrombotic microangiopathy (TMA)-mediated disease process that led to their initial clinical presentation and treatment.

<u>Committee's Question 2</u>: Are the summaries of the criteria considered by the Committee and the clinical and economic considerations reasonable interpretations of the evidence?

Overall, the clinical and economic summaries provided by the Committee are reasonable interpretations of the evidence Alexion provided in its various submissions to NICE. The technical issues for which

Alexion disagrees with the Committee or NICE's interpretation of the evidence have already been outlined in detail in our various submissions.[1]

Alexion would, however, like to clarify two points made by the Committee in the second ECD:

1) In the second ECD the Committee comments on the comparison of the annual treatment cost and lifetime QALY benefit between specialised medicines that Alexion provided to NICE. Specifically, in Section 5.11 of the ECD, the Committee states 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."

   The analysis undertaken by Alexion considered two scenarios: the cost of treating a child (15Kg) and that of an adult (75kg). In both scenarios the weight was assumed to be the same for all therapies. Under these scenarios, the analysis demonstrated that eculizumab is not the most expensive specialised medicine—4 of the other 10 drugs were more expensive in both of the scenarios. The Committee seems to be suggesting that for adults, the average weight is likely to differ between diseases, but no data were presented to support this suggestion. No systematic review of average weight data across ultra-orphan diseases is available, and therefore such a comparison is currently difficult to make, which is why Alexion chose to use a simplifying assumption.

   The cost difference, however, seen in the analysis for two products, idursulfase and galsulfase, was twice that of eculizumab in adults. For eculizumab to be more expensive than these agents would require adult patients being treated with these drugs to weigh less than half the weight of an aHUS patient, which in the opinion of Alexion clinical experts is unlikely. Furthermore, the published clinical trials of the other highly specialised technologies for very rare diseases also indicate that this may not be the case. For example, the average age of patients enrolled in the idursulfase trial is 14.8 years, and the average patient weight was 37kg at baseline.[2] The age range in this trial was 5.4–30.9; so it is likely that some proportion of the trial patients were at or over 75kg.

2) Also in the second ECD, the Committee states that the budget impact of eculizumab for treating aHUS is "uncertain but will be considerable". Although all budget estimates are technically uncertain since the future cannot be predicted with certainty, Alexion has confidence in the budget estimates provided to the Committee are reasonable and as accurate as current disease and market understanding allow. Additional details clarifying our assumptions are provided in our response for the first ECD submitted on (date).

<u>Committee's Question 3</u>: Are the provisional recommendations sound and a suitable basis for guidance on the use of eculizumab for the treatment of atypical haemolytic uraemic syndrome in the context of national commissioning by NHS England?

Alexion agrees with the Committee that the provisional recommendations generally provide a sound and suitable basis for guidance on the use of eculizumab for the treatment of aHUS in England. Specifically, Alexion agrees with the Committee's preliminary recommendation that funding of eculizumab for the treatment of aHUS via national commissioning by NHS England should be granted. With regard to the conditions set forth in the second ECD, however, Alexion's comments are as follows:

[1] Alexion submissions thus far include: 1) Initial submission on (date); 2) Response to ERG on (date); and 3) Response to first ECD on (date).

[2] Muenzer, Joseph, et al. "A phase II/III clinical study of enzyme replacement therapy with idursulfase in mucopolysaccharidosis II (Hunter syndrome)."Genetics in Medicine 8.8 (2006): 465-473.

Coordination of the use of eculizumab through an expert centre

Alexion agrees that coordination on the use of eculizumab for aHUS should be done through an expert centre or centres throughout England.

Monitoring systems to record the number of people with a diagnosis of atypical haemolytic uraemic syndrome, the number of people who receive eculizumab, and the dose and duration of treatment for these people

Alexion is supportive of collecting data to monitor the usage of eculizumab and the outcomes of patients with aHUS. Alexion already facilitates the collection of data on aHUS patients—both those treated with eculizumab and those who are not—globally through the aHUS global registry. Data from this registry are available to researchers at the expert centres in England as a repository through which to collect and analyse the patient information.

National protocol for starting and stopping eculizumab for clinical reasons

As stated previously, Alexion believes that patients with aHUS should be treated in accordance with the EMA-approved Statement of Product Characteristics (SPC). While there is not always such a statement for therapies approved by the EMA to treat patients with ultra-rare disorders, in the case of the approval of eculizumab for treatment of patients with aHUS, Section 4.2 of the SPC affirmatively states: "Soliris treatment is recommended to continue for the patient's lifetime, unless the discontinuation of Soliris is clinically indicated (see section 4.4)." As outlined in the SPC, and Alexion's submission and response to the first ECD, significant negative patient health outcomes may occur if treatment with eculizumab is stopped; hence, the reason for the statement in Section 4.2 of the SPC. As such, any decision to withdraw eculizumab treatment for aHUS patients should be based upon the treating physician's expert clinical assessment in the context of an individual patient's clinical condition and the evaluation of whether the patient is suffering an adverse reaction as described in Section 4.4 of the approved SPC entitled "Special warnings and precautions for use."

Although Alexion does not agree that development of a protocol is a necessary or appropriate condition of eculizumab national commissioning, we feel strongly that any aHUS treatment protocol should be developed by the expert clinicians who are most familiar with the disease, and use of eculizumab to treat aHUS and should be consistent with the SPC. Alexion recognizes that a protocol has already been developed by the UK Renal Association and is in use at the aHUS expert centre at Newcastle upon Tyne Hospital's NHS Foundation Trust. However, Alexion does not endorse the implementation of this protocol with the reservations that it is counter to the SPC safety statement on discontinuation, and that it lacks medical evidence of safety upon treatment withdrawal.

Research programme with robust methods to evaluate when stopping treatment or dose adjustment might occur

The nature of the research programme envisaged by the Committee is not explained in the second ECD, which has limited Alexion's ability to respond in consultation. However, while Alexion would be greatly concerned by the ethical implications of any clinical trial that required treatment withdrawal or dose adjustment on any basis, we are willing to work with expert centres in the UK to assist in the continued collection and analysis of observational data through the monitoring systems (described above) to better understand the course of aHUS and the therapeutic benefit of eculizumab.

Committee's Question 4: Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of race, gender, disability, religion or belief, sexual orientation, age, gender reassignment, or pregnancy and maternity?

Alexion does not think that any aspects of the recommendation need particular consideration to avoid unlawful discrimination against any group of people on the grounds of race, gender, disability, religion or belief, sexual orientation, age, gender reassignment, or pregnancy and maternity. The recommendations can be applied to all patients with aHUS equally.

Committee's Question 5: Given the requirement for relevant health bodies (clinical commissioning groups, NHS England and local authorities) to provide funding to ensure that the health technology is available within 3 months, from the date the recommendation is published by NICE (see section 5.1), is an extension to this normal period appropriate because any of the following circumstances apply?

Question 5a: The health technology cannot be appropriately administered until training is in place?

No additional training is needed to appropriately administer eculizumab as it is administered via a standard intravenous infusion.

Question 5b: The health technology cannot be appropriately administered until certain health service infrastructure requirements including goods, materials or other facilities are in place?

No additional infrastructure requirements are needed to appropriately administer eculizumab.

Question 5c: The health technology cannot be appropriately administered until other appropriate health services resources, including staff, are in place?

No additional health services resources are needed to administer eculizumab.

Question 5d: The specific conditions in the guidance warrant a longer implementation time?

No additional time is needed for implementation. While the details of implementing the preliminary recommendations are being discussed with the relevant clinical experts, access for aHUS patients in need of eculizumab should continue to be made available under the interim commissioning policy already in place.

Question 5e: If so, please specify the reasons and an estimate of the time period within which the recommendation can be complied with.

No additional comments.

aHUSUK's RESPONSE TO EVALUATION CONSULTATION DOCUMENT 2

INTRODUCTION

aHUSUK and its members welcome the change in the recommendation made by the Evaluation Committee and appreciate the reasoning that led to that change. aHUSUK's response to Evaluation Consultation Document 2 follows.

THE NICE QUESTIONS (Preface)

- **Has all of the relevant evidence been taken into account?**

  Yes, all needed for this recommendation.

- **Are the summaries of the criteria considered by the Committee and the clinical and economic considerations reasonable interpretations of the evidence?**

  Yes

- **Are the provisional recommendations sound and a suitable basis for guidance on the use of eculizumab for the treatment of aHUS in the context of national commissioning by NHS England?**

  Yes.

- **Are there any aspects of the recommendations that need particular consideration to ensure that they avoid unlawful discrimination against any group of people on the grounds of gender, disability, religion, sexual orientation, age, gender reassignment or pregnancy or maternity?**

  Yes, whilst nothing in these guidelines excludes those who may knowingly risk aHUS when pregnant from receiving eculizumab if a rescue is needed (because pregnancy is known to be a trigger), aHUSUK has concerns that pregnancy and maternity may become a potential "particular consideration" for indirect discrimination in practice.

- **Given the requirement for relevant health bodies (clinical commissioning groups, NHS England and local authorities) to provide funding to ensure that the health technology is available within 3 months, from the date the recommendation is published by NICE (see section 5.1), is an extension to this normal period appropriate because any of the following circumstances apply?**
  - The health technology cannot be appropriately administered until training is in place?
  - The health technology cannot be appropriately administered until certain health service infrastructure requirements including goods, materials or other facilities are in place?
  - The health technology cannot be appropriately administered until other appropriate health services resources, including staff, are in place?
  - The specific conditions in the guidance warrant a longer implementation time?
  - If so, please specify the reasons and an estimate of the time period within which the recommendation can be complied with.

No comment.

EVALUATION COMMITTEE's PRELIMINARY RECOMMENDATION

Agreed, and whilst there is considerable uncertainty, aHUSUK's expectation is that the cost can be much less. (1.1, 1.2)

THE CONDITION

No further comment. (2)

CLINICAL EVIDENCE

No further comment. (3)

EVIDENCE SUBMISSIONS

No further comment. (4)

CONSIDERATION OF EVIDENCE

Understandably, as yet, no robust evidence about the withdrawal of the drug is available. aHUSUK would not wish to see patients being taken off eculizumab in a piecemeal fashion, nor according to some arbitrary set time limit, because the risks are evident and patients need to have confidence that they will get the best possible clinical management. (5.4)

A clear distinction needs to be made between those few patients for whom eculizumab does not work, and those for whom eculizumab has worked, but for whom it may no longer be needed to do the job it has done. aHUSUK believes that Clinicians need to have advice based on robust evidence, and that patients need to be properly and fully informed before a decision is made. It is vital that they are assured of a return to eculizumab if there a recurrent episode. (5.4)

Preserving as much kidney function as possible from the acute episode of aHUS is important; this may take time as recovery continues, albeit at a slowing rate. The potential for gaining function may be influenced by the time taken between onset and diagnosis and the drug being prescribed. Whilst the Committee has focussed on the technology and protocol for starting treatment with eculizumab, the speed of diagnosis and the commencement of eculizumab are crucial, including the results of necessary lab tests. It is very clear that the faster patients access eculizumab, the less damage is done. The less damage done, the less recovery is needed and the sooner exiting the drug may be considered. (5.4)

However, underpinning the successful withdrawal of the drug is the need for patients to be assured that their complement activity has returned to a state prior to the triggering event and that the triggering event has passed. (5.4)

aHUSUK notes new evidence about the actual numbers receiving eculizumab and accepts that its baseline number in the cost estimates given in its response to ECD 1 was significantly over stated. Consequently aHUSUK's projected five year spend will be just over £30m less, and so will increase the already significant difference between its estimates and the NICE illustrative "upper range". (5.8)

aHUSUK recognises the uncertainties in constructing a budget and, indeed, was told by a representative from NICE, following its first meeting, how impossible the task might be (but that this would not be detrimental to aHUS patients). aHUSUK notes the Committee's assurance about likely budgets not being the

“sole basis” for a decision. Nevertheless it is also not clear what, in the context of NHS England, constitutes a very high budget. (5.8)

Whilst noting that the Committee has reaffirmed its acceptance of the supplier’s assertion about the considerable value of their drug, aHUSUK is disappointed that the Evaluation Committee has not, as yet, found the answers it sought so that the unit price of eculizumab is shown to be justifiable. aHUSUK would have preferred that there was no doubt about the price, particularly if the Committee had also taken into account distribution/after sales support as a key part of the business infrastructure needed for a drug to made available in a safe and sustainable way. aHUSUK, however, is of the opinion that a justification can be made from well regulated information in the public domain. Furthermore, the tolerances established within the governance arrangements of the Department of Health’s Prescription Pricing Regulatory Scheme gives aHUSUK further cause to be assured. (5.10, 5.17)

aHUS is a complex disease arising from the coming together of a variable combination of genetic and environmental risk factors, and it results in a spectrum of patient experiences. Within that spectrum some patients may need full doses at two-week intervals for life but some may not. aHUSUK supports research to understand the underlying risks so that treatment can be managed with the certainty of a safe outcome. aHUSUK is confident that putting the findings of this research into practice will make a considerable difference to overall affordability whilst fully protecting aHUS patients. (5.18)

Furthermore, aHUSUK supports the idea that the supplier and the NHS will explore further ways to improve cost effectiveness. With a little thought and flexibility waste can be reduced, perhaps for example, unless production processes make it impossible, an intermediate vial size could, through better tailoring to patients’ weight changes, improve treatment safety and avoid using some of the drug unnecessarily. (5.18)

IMPLEMENTATION

aHUSUK appreciates the way in which it has been engaged in both AGNSS and NICE evaluation processes, even though it was very unhappy about the nine month gap before the two were linked. Although it will not be NICE's job to do so, aHUSUK hopes that it will continue to be consulted by those implementing the recommendations, when the time comes.

PROPOSED RECOMMENDATIONS FOR FURTHER RESEARCH

aHUSUK fully supports the need for an expert centre, patient registries, clear clinical protocols and further research about treatment in practice, including examining simple and reliable self testing as well as establishing a clear, assured and sustainable care network pathway during the process of withdrawal.

GUIDANCE

No comment

PROPOSAL FOR REVIEW

Whilst understanding that the review periods may be fixed at a specific level for all NICE guidelines, aHUSUK believes that the exceptional duration of the appraisal process to which aHUS patients have been subjected, as well as the uncertainties surrounding projected patient numbers, should be taken into account and would suggest that a review should be conducted after the end of the fifth financial year of the budget estimate period so that a full comparison can be made with the estimates used in this evaluation.

CONCLUDING COMMENT

aHUSUK did not wish to be subjected to a full evaluation by NICE after having been through the AGNSS appraisal with a positive recommendation. Nevertheless, throughout the process it has found the way in which those at NICE have engaged with its trustees, to be both professional and helpful.

Our patient organisation has, because of unique circumstances, been part of the passage of highly specialised technology appraisals from one established decision making organisation to another. It has witnessed an emerging approach to this task, which is being designed and developed with a vision and commitment to produce something for those who seek equity of access to such technologies for treatment of their severe rare diseases.

aHUSUK recognises that this has not been easy to do, as it has been hard for aHUS patients to handle the uncertainties of what has been an exceptionally prolonged process. aHUSUK hopes that, from now on, the process is straight forward and that, at last, aHUS patients can have assured access to an effective treatment when they need it for as long as it is needed.

[redacted]
For aHUSUK
24 September 2014

[redacted]

National Institute for Health Care and Excellence
Level 1A, City Tower
Piccadilly Plaza
Manchester
M1 4BT

25 September 2014

[redacted]

AHUS Action response to ECD 2 HST - evaluation of Eculizumab for the treatment of aHUS

aHUS Action welcomes the advice of the NICE Highly Specialised Technologies Committee in recommending Eculizumab for the treatment of aHUS. The Committee has rightly recognised that Eculizumab marks a step change for the treatment of aHUS and this initial recommendation provides much needed hope for patients after many years of uncertainty.

aHUS Action is committed to supporting the development of a national treatment protocol, as requested by NICE, to ensure the cost effective use of Eculizumab in the NHS, and that all patients who are proven to clinically benefit from Eculizumab receive it.

Further to the recommendations, aHUS Action seeks clarification from NHS England on whether an NHS Highly-Specialised National Service is required to implement the recommendations or an Expert Centre is sufficient.

Many thanks in advance.

Yours sincerely,

[redacted]

[redacted]

[redacted]

NHS England response to:

Evaluation consultation document (ECD2): eculizumab for treating atypical haemolytic uraemic syndrome.

1. NHS England is grateful for the opportunity to comment on this document.
2. We believe that all of the relevant evidence has been taken into account.
3. We believe that the summaries of the criteria considered by the Committee and the clinical and economic considerations are reasonable interpretations of the evidence.
4. We believe that the provisional recommendations are sound and a suitable basis for guidance on the use of eculizumab for the treatment of atypical haemolytic uraemic syndrome in the context of national commissioning by NHS England.
5. We do not think that any aspects of the recommendations need particular consideration to avoid unlawful discrimination against any group of people on the grounds of race, gender, disability, religion or belief, sexual orientation, age, gender reassignment, or pregnancy and maternity.
6. We believe that we can make the health technology available within 3 months, subject to a proviso on the research programme.
7. The Committee has set the following conditions for the use of eculizumab in aHUS:

    - coordination of the use of eculizumab through an expert centre;
    - monitoring systems to record the number of people with a diagnosis of atypical haemolytic uraemic syndrome, the number of people who receive eculizumab, and the dose and duration of treatment for these people
    - 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 first three requirements are straightforward to implement. A research programme will take longer to establish. Ideally this should be multi centre and international so as to recruit large numbers of patients: we understand that the UK clinical experts are applying for European funding. If that proposal fails, we will work with the National Institute for Health Research to set up an England-only trial. Agreeing the protocol, securing ethical consent and clearing research governance procedures is likely to take 12 – 18 months.

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[redacted]

[redacted]

25 September 2014

[redacted]

Re: Eculizumab for treating atypical haemolytic uraemic syndrome (aHUS) [ID703] - ECD2

The Royal College of Physicians (RCP) plays a leading role in the delivery of high quality patient care by setting standards of medical practice and promoting clinical excellence. We provide physicians in the United Kingdom and overseas with education, training and support throughout their careers. As an independent body representing over 30,000 Fellows and Members worldwide, we advise and work with government, the public, patients and other professions to improve health and healthcare.

I write on behalf of the RCP and the Renal Association with regard to the above ECD2 consultation. We are grateful for the opportunity to respond and would like to make the following joint submission.

We welcome the recommendation of the committee that eculizumab should be available for use in aHUS subject to certain conditions (addressed below). We believe this to be the right decision for patients with aHUS and those yet undiagnosed who will experience significant health benefit from eculizumab. We are pleased that the culmination of years of successful medical research has been translated into an effective treatment, and that patients will now benefit from this.

We believe that all relevant evidence has been taken into account and that the summaries of the criteria considered by the Committee and the clinical and economic considerations are reasonable interpretations of the evidence.

Our experts note the robust defence of costs by the manufacturer and feel that the main areas of contention now appear to rest within the remit of health economics. We do, however, wish to respond with regard to two outstanding clinical issues, as below:

- The main clinical issue is that of dosage and interval, and whether the drug can be withdrawn. We note that the manufacturer firmly rejects the proposal that the drug can ever be withdrawn, and our experts are uncomfortable with this stance. The manufacturer quotes previous EMA recommendation for lifelong treatment. However, this ignores the fact that the evidence base will inevitably improve as studies are carried out and that there is no scientific or ethical imperative to continue lifelong treatment in all patients. The manufacturer also states that lifelong complement inhibition is necessary in those with a complement gene abnormality. This is theoretical and we do not currently understand

either the nature of second hits required for disease relapses or the adverse consequences of long-term complement inhibition.

- Our experts believe that the cost analysis provided by the manufacturer, compared to other ultra-rare disease therapies, is a compelling set of calculations to justify its use. Our only comment here is that this would only hold true if a similar number of patients were being treated with each of the drugs being compared, across the UK. If Eculizumab is being used (or will be used) in a significantly higher number of patients (particularly as it is or has been evaluated for several other conditions) then the cost to the NHS will be far higher, and the comparison with other ultra-rare disease therapies is less relevant.

The recommendation of eculizumab by the committee is subject to a number of conditions, considered below:

- We agree that use of eculizumab should be co-ordinated through an expert centre. We strongly propose that eculizumab should be delivered locally with local expertise but recognise the value of the resource provided by an expert centre or specialised service, including diagnostic and management support.

- We agree with the recommendation that the number of people with aHUS and the number receiving eculizumab should be monitored and information collected about dosing and duration. There is great value in collecting this independently of the manufacturer-sponsored registry and would be best achieved by having an expert centre or specialised service.

- We propose that a national protocol for starting and stopping eculizumab should be developed, but that this should be informed by well-conducted clinical trials.

We do not think that any aspects of the recommendations pose a risk of unlawful discrimination.
The provisional recommendations are sound and provide clear guidance on the use of eculizumab in aHUS and are a suitable basis for guidance on the use of eculizumab for the treatment of aHUS in the context of national commissioning by NHS England.

Since an interim national aHUS service is already in place we believe that the health technology will be available within three months of the publication of the recommendation.

Yours sincerely

[redacted]