September 25, 2014

[redacted]
National Institute for Health and Care Excellence (NICE)
10 Spring Gardens
London, England
SW1A 2BU

**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.