NICE National Institute for Health and Care Excellence

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Highly Specialised Technology Evaluation

Eculizumab for the treatment of atypical haemolytic uraemic syndrome (aHUS) [ID703]

Dear [redacted],

The Evidence Review Group, ScHARR, and the technical team at NICE have now had an opportunity to take a look at the submission received on the 11th September by Alexion. In general terms they felt that it is well presented and clear. However, the ERG and the NICE technical team would like further clarification relating to some of the data.

Both the ERG and the technical team at NICE will be addressing these issues in their reports.

Please provide a written response to this letter to the Institute by **5pm** on **Friday 18 October 2013**. Two versions of this written response should be submitted; one with academic/commercial in confidence information clearly marked and one from which this information is removed.

Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise, and all information submitted under 'academic in confidence' in yellow.

If you present data that is not already referenced in the main body of your submission and that data is seen to be academic/commercial in confidence information, please complete the attached checklist for in confidence information.

Please do not 'embed' documents (i.e. PDFs, spreadsheets) within your response as this may result in your information being displaced or unreadable. Any supporting documents should be emailed to us separately as attachments or sent on a CD.

If you have any further queries on the technical issues raised in this letter then please contact [redacted], Technical Advisor ([redacted]). Any procedural questions should be addressed to [redacted], Project Manager ([redacted]) in the first instance.

Yours sincerely

[redacted]
Associate Director – Highly Specialised Technologies
Centre for Health Technology Evaluation

Encl. checklist for in confidence information

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Section A: Clarification on effectiveness data

1. **Priority question:** The submission includes a systematic review of non-randomised evidence for eculizumab. Why does the submission not also include a systematic review of interventions used as standard care (i.e. the comparators listed in the NICE scope)? For example this might include studies such as Hovinga et al 2010, Coppo et al 2010 and Noris et al 2010.

2. **Priority question:** Please provide further details about subsequent treatments used in the clinical trials. For example, in instances whereby patients withdrew from the studies, did they continue using eculizumab? What happened to these patients?

3. **Priority question:** For the primary outcome of each study (studies C08-002, C08-003, C09-001r, C10-003 and C10-004) please provide Kaplan-Meier curves.

4. **Priority question:** Section 9.1.2 Page 60 - Why were relevant clinical data not obtained or included from unpublished studies that were not sponsored by Alexion? Were the authors of these studies contacted? If not, why?

5. **Priority question:** Which criteria were used to determine whether plasma exchange/infusion and dialysis was required for individual patients in studies C08-002, C08-003, C10-003 and C10-004? How many patients received plasma exchange/infusion in each of these studies? Also, Table C8 page 84 details the number of patients receiving PE/PI during the current aHUS event - did these patients receive plasma exchange/infusion whilst they were also receiving eculizumab?

6. **Priority question:** How were patients identified for recruitment into studies C08-002, C08-003, C10-003 and C10-004? Were consecutive patients recruited or was a convenience sample used? Please provide as much detail as possible on the selection process.

7. **Priority question**: Please provide information relating to planned dose and actual dose received (including reasons for deviation) in studies C08-002, C08-003, C09-001r, C10-003 and C10-004. Are there any data from these studies relating to a dose-response relationship? Is there any evidence to support flexible dosing?

8. **Priority question:** Please provide details of adherence rates to protocol specified doses of eculizumab in prospective studies C08-002, C08-003, C10-003 and C10-004.

9. **Priority question:** Section 9.6 Table C11. Where appropriate (e.g. CKD state) please provide baseline and final values for studies C08-002, C08-003, C09-001r, C10-003 and C10-004. For all outcomes in Table C11 please state how many patients provided data for each analysis. Were there any missing data and how were they dealt with?

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10. **Priority question:** Section 9.6. Please provide mortality data for the extension periods in studies C08-002 and C08-003 separately (the value for money section suggests 1 death in 3 years in both studies combined?).

11. **Priority question:** Page 110 - The SmPC recommends lifetime treatment, please provide the evidence to support this.

12. **Priority question:** Please provide full details as to why patients chose not to enter into the extension phases of the trials.

13. The search strategy provided in Table C1 on Page 60 of the submission does not match with the search strategy provided in Appendix 17.1.4 pages 219-220. Please clarify which search was used to identify the clinical evidence.

14. On page 218 of the submission, the date of the searches ranges from 1947 to 4 July 2013; however, the search strategy provided on page 220 suggests date and language restrictions e.g. limited to human, English Language and yr="2000-Current". Please clarify the dates of the clinical searches and justify language restrictions.

15. Please provide details of the searches used for non-RCT evidence. On Page 220, the submission states that *"Due to the difficulty in identifying a reliable search strategy, and the lack of high level evidence in the form of randomised controlled trials, the term 'trial' was extended to include case series, retrospective trials, registries, cohort and case studies";* however, no details of the search strategy are included.

16. Was Medline (R) In-Process searched? If not please provide justification for not searching Medline (R) In-Process (page 59 and 218)?

17. Given the limited evidence relating to the safety and efficacy of eculizumab, please explain and justify the decision to exclude case series from the systematic review.

18. Section 9.5 - Please explain why an RCT appraisal tool has been used to critically appraise the non-randomised studies of eculizumab.

19. Table C8 – Please clarify how “PE/PI sessions during current aHUS event, Median (min; max)” have been calculated.

20. How were patients diagnosed with confirmed aHUS within studies C08-002, C08-003, C09-001r, C10-003 and C10-004?

21. Does the age range of patients in studies C08-002, C08-003, C09-001r, C10-003 and C10-004 reflect the age range of patients in UK clinical practice? Please provide evidence to support your response.

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22. Does the baseline eGFR status of patients in prospective studies C08-002, C08-003 reflect the current mix of aHUS patients in England and Wales? Please provide evidence to support your response.

23. Are there any data available for transplant failure rates in those patients with prior kidney transplants (Section 9.4.4, page 85)?

24. Section 9.4.4. Page 85 - for the primary endpoint of reduction in TMA, what is the threshold whereby a reduction is clinically meaningful?

25. Section 9.7 - Are the adverse event data presented in Table C12 and C13- at 26 weeks or for the duration of the study (64 weeks)?

26. Were responder rules employed in prospective studies C08-002, C08-003, C10-003 and C10-004?

27. During the previous appraisal of eculizumab, study C09-001r included 15 paediatric only patients. This study now includes 30 patients in the manufacturer's submission. How were the additional 15 patients chosen for the retrospective study?

28. Page 28 states that study C08-002 includes short-duration patients and study C08-003 includes long-duration aHUS patients. However, page 70 states that study C08-002 is in patients who were newly diagnosed, had an existing diagnosis or were post-transplant. The same inclusion criterion was used in study C08-003 (see page 73). Please clarify the patient populations in these studies.

Section B: Clarification on data relating to the cost model and value for money

29. **Priority question:** The submission states that aHUS affects both adults and children and some of the clinical trial evidence includes paediatric patients. However, the economic analysis relates to a single cohort aged 28 years and does not include younger patients. Please explain why no analysis has been undertaken for children.

30. **Priority question:** Please explain why the model only uses data from studies C08-002 and C08-003. Specifically, given the paucity of evidence relating to eculizumab, why were interim data from studies C10-003 and C10-004 not also used to inform the economic analysis?

31. **Priority question:** The ERG has concerns about the calculation of transition matrices for eculizumab. Specifically, please explain how it is mathematically appropriate to observe time-dependent matrices and then weight these by sample size to derive time-independent matrices?

32. **Priority question:** The standard care transition probabilities are based on the results of the LOWESS regression of the pre-treatment phase in the C08-002 and C08-003 studies. This regression uses the rate of change in eGFR per day to derive 6-monthly transition probabilities. The estimated rate of change was -0.03 points/day which

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according to the submission, given a 15-point interval in each CKD band, leads to a transition probability of 0.367 (calculated as [0.03 x 182.5]/15). The ERG believes that this is mathematically incorrect – if the rate had been -0.10 or higher this would lead to a probability which is greater than 1.0. Please consider which approach is most appropriate and provide justification for your choice, or updated analyses (if a different approach is adopted).

33. **Priority question:** Please explain why the probability of receiving a transplant for patients receiving eculizumab is zero - this was non-zero in versions of the model considered in the previous appraisal.

34. **Priority question:** Please explain why the cost of eculizumab in the model includes dose reductions (and hence lower costs for eculizumab) for paediatric patients when the model cohort enters the model at age 28 years.

35. **Priority question:** Please explain why HRQoL for each state is valued 0.208 lower for standard care compared to eculizumab. What is this utility loss intended to represent? Please clarify the evidence available to support this.

36. **Priority question:** Why were the adverse events associated with eculizumab (Section 9.7 of the submission) excluded from the model?

37. **Priority question:** Reasons for patient discontinuation within studies C08-002 and C08-003 are given on Page 86 of the submission. Please provide the patient number for each of these patients so that they can be identified in the ”Ecu_trials_data” worksheet in the submitted model. E.g. patient number 2-029-001. Please provide the patient number for the following patient discontinuations:

    a. CO8-002 - Protocol violation: patient diagnosed with SLE approximately one week after the first dose of eculizumab

    b. CO8-002 - Discontinued due to an adverse event deemed not related to study drug

    c. CO8-002 - Completed treatment period, and the investigator elected not to enrol patient in extension period

    d. CO8-002 - Completed treatment period, and investigator elected not to enrol patient in extension period. Data were not collected during follow-up period as patient refused to continue participation

    e. CO8-002 - Adverse event (“decrease in renal function” per investigator) deemed not related to study drug (during extension study)

    f. CO8-002 - Adverse event (worsening or renal function) deemed not related to study drug (during extension study)

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g. C08-003 – Patient who completed the 26 week study period who did not continue to the extension study period due to personal reasons

h. C08-003 – Discontinued during the extension study period due to an AE deemed not related to the study drug

38. **Priority question:** Page 18 includes estimates of losses in productivity, government benefits and tax revenues. Please provide the underlying calculations, evidence sources and assumptions used to produce these estimates.

39. Table D2 page 135 - In the economic analysis, costs and outcomes are discounted at a rate of 1.5%. Please explain why the discount rate of 3.5%, as stipulated in the NICE Reference Case was not used.

40. Section 9.8.1 states the following:

    "Studies C08-003 and C08-002, described in detail within this submission, enrolled patients with different clinical characteristics. Study C08-003 included patients with long duration of aHUS, prolonged PE/PI exposure and substantial kidney damage, whereas C08-002 included patients with progressing TMA and shorter disease duration. These trials demonstrated the efficacy of eculizumab in a broad range of aHUS patients, reflective of the addressable population. However, this does not lend itself to meta-analysis and would not provide results which are more informative than those included within the submission document. Due to the lack of RCTs and the heterogeneity of patients included in the non-randomised prospective and observational trials included in this submission, evidence synthesis or meta-analysis were not performed."

    Please comment on validity of pooling patient-level data from studies C08-002 and C08-003 in the model to estimate CKD transition probabilities.

    a) Please explain why the rate of eGFR change was used rather than calculating the CKD state at the beginning and end of the pre-treatment period and adjusting for observation time.

    b) Please explain why data from the pre-treatment period were used rather than published studies e.g. Noris et al 2010 or Hovinga et al 2010.

    c) Please suggest more plausible values for these quantities.

41. Please explain how the model deals with competing risks of events (e.g. mortality and disease progression).

42. Please explain why patients CKD0-2 in the model have a utility score of 1.0 (perfect health).

43. Please justify why 3.6% of the modelled population is still alive at age 100 years. Why does the model use 5-year banded mortality rates?

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44. Table D4 includes a column which appears to describe standard deviations rather than standard errors. The same appears to be the case in the model. For all parameters in which standard deviations have been used, please provide either standard errors or sample sizes.

45. The model uses bootstrapping within the uncertainty analysis. Bootstrapping tells us about variability in the sample rather than uncertainty in the population parameters. Please explain why standard methods were not used e.g. sampling multinomial data from Dirichlet distributions with non-informative priors.

46. Please explain why several of the cost parameters (e.g. plasmapheresis, eculizumab administration costs) are held fixed at their point estimates?

47. For the excess death rate for SOC please clarify why "solver solution for death at 1.5 years" (value = 0.177) was used, when the submission states that the model used a mortality rate of 0.13 from Coppo *et al* (2010) for death at 1.5 years.

48. Please provide the timings of the 25 transplants in the 16 patients used to calculate the SOC transplant rate i.e. how many days from diagnosis did they take place? Please clarify how the SOC transplant rate was calculated.

49. Please provide the supplementary data tables from Fremeaux-Bacchi et al (2013).

50. Page 17 of the submission states *"eculizumab for the treatment of aHUS represents good value for money"* yet the subsequent mention only clinical criteria and do not discuss cost. Please clarify the criteria used to make this judgement.

Section C: Textual clarifications, additional points and additional data requests

51. **Priority question:** Please state expected dates for the final analyses of ongoing studies mentioned in Table A4.

52. **Priority question:** The submission mentions Clinical Study Reports (CSRs) for the eculizumab studies. In particular, Section 9.7 states that *"Complete AE listings are available in the respective clinical study report"* and *"Additional details regarding AEs are available in the clinical study report."* These reports have not been submitted to the ERG but appear to contain AE data not reported in the submission. Please provide the CSRs.

53. **Priority question:** For each patient in studies C08-002 and C08-003, please provide patient-level EQ-5D utilities at baseline and at each possible timepoint.

54. Please clarify why it has not been possible to undertake a randomised controlled trial of eculizumab versus standard care.

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55. The submission makes several references to the proposed Homecare service (pages 17, 46, 57 and elsewhere in the submission). Please provide more details on this scheme.