5th December 2008

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Dear Dr Catchpole

Single Technology Appraisal – Rituximab for the first line treatment of chronic lymphocytic leukaemia

The Evidence Review Group, Peninsula Technology Assessment Group, and the technical team at NICE have now had an opportunity to take a look at submission by Roche Products. 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 the clinical and cost effectiveness data.

Both Peninsula Technology Assessment Group and the technical team at NICE will be addressing these points in their reports. As there will not be any consultation on the evidence report prior to the Appraisal Committee meeting you may want to do this work and provide further discussion from your perspective at this stage.

We request you to provide a written response to this letter to the Institute by **5pm** on **19th December 2008**. 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 red 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.

Yours sincerely

Dr Elisabeth George
Associate Director - Appraisals
Centre for Health Technology Evaluation

Encl. checklist for in confidence information

Section A. Clarification on effectiveness data

Executive Summary

A1. For the outcome end-of-treatment response rate (p16, table 3) the percentage of missing data for the FC arm is 12% and for the R-FC arm 5.7%. Please can you confirm how missing response data was handled for this outcome, and what if any assumptions were made about patients' health status for missing response data? Additionally, were any assumptions subject to sensitivity analysis?

Section 6

A2. The submission states the patients had an interim staging after 3 cycles and those with progressive or stable disease, did not continue treatment but were eligible for alternative treatment and followed up for survival analyses (p38). Please can you confirm whether patients were eligible for cross-over into the other treatment arm of the trial? and if so how many patients were crossed-over having experienced either progressive or stable disease between the FC and R-FC arms.

Subsequent data in the submission, presented on page 131 and table 48, infers that patients in the trial were eligible for any 2nd line CLL treatment having experienced progression or stable disease on the treatment to which they were randomised. Please can you confirm if this is correct?

A3. Please could you provide the following data:

1. Number of patients for each treatment arm (FC and R-FC) who received 4-, 5, or 6-treatment cycles.

2. The actual (as opposed to planned) mean doses administered for each treatment arm for each treatment cycle.

A4. Please could you provide the results of significance testing for the difference in proportions for the Grade 3 or 4 adverse events listed in table 31 (section 6.7.2.2).

Section 6.6: Indirect/mixed treatment comparisons

A5. Please could you supply a copy of the following:

1. The search strategy used to identify trials for inclusion in the MTC (none is provided in the appendices)

2. A MTC 'network' diagram showing the 8 included trials and their comparators and how they 'link' together to form a network. It would be helpful if this additionally highlighted the 5 trials that were included in the MTC.

3. In addition to table 22 which displays the HR for PFS for the 5 trials included in the MTC, it would be helpful if you could provide a table of the PFS rates (numbers, percentages) for each of the 8 trials by comparator for each trial arm.

4. Could you provide more details on the methods used to conduct the MTC (e.g. were any assumptions necessary in order to include multi-arm trials and if so how were these handled?). Additionally could you please supply a copy of the WinBUGS code.

5. Please provide further explanation as to why the trial by Jaksic et al. (1997) was excluded for consideration in the MTC. It appears from the submission that this was due to heterogeneity in the patient population in terms of baseline ECOG performance status (i.e., not stage 0 to 2) but can this be confirmed, as there are no inclusion/exclusion criteria for consideration in the MTC based on Binet staging as stated in the reasons for trial exclusion.

Section 6.9: Interpretation of clinical evidence

A6. The submission states that the Q-TWIST was based on 2.2 years follow-up data from CLL-8 from 408 and 409 patients in the R-FC and FC arms respectively (p101). Can you confirm these patient numbers are correct or should this read R-FC=403 and FC=407?

A7. Were any searches conducted to attempt to identify further studies that had assessed utility for patients undergoing 1st line treatment for CLL? If so, please provide a copy of the relevant identified studies.

A8. Will the ERG have access to the revised utility estimates from the study presently being conducted by Oxford outcomes due for completion Q1 2009, and if so, when will they be provided?

Section B. Clarification on cost-effectiveness data

Section 7.2: De novo economic evaluation(s)

B1. Please can you provide a copy of the clinical data from the CLL-8 trial for the analysis conducted at a median of 2.2 years on which the CUA is based? This should have the N (%) for both the outcomes of PFS and OS. Additionally, can you clarify whether this data set includes only patients who were classified as having a response at the time of final response assessment, or also those classified as having a 'late response' as per the data set reported in the ASH conference abstract by Hellek et al.

B2. In the base case analysis (R-FC vs oral FC) for cycles 2-6 for R-FC it appears that only the administration cost for R (£430) has been added, please can you clarify whether an additional cost for FC (£280) should also be added (p129)? The additional cost (£280) for oral chemotherapy in the first cycle is justified by an extra appointment. Can you please explain an extra appointment is necessary and why it is not

possible to combine the costs with the administration of rituximab (as for cycles 2-6 in R-FC arm)?

B3. The submission states that a higher oral dose of fludarabine is required to obtain equivalent bioavailability as IV administration (page103). However the oral dose used in the model are lower than the IV dose (table 36). Please can you confirm the appropriate dosing when switching from IV to oral administration, and comment on how this has been accounted for in the analysis?

B4. Can you confirm that the bioavailability of cyclophosphamide is the same regardless of administration of the dose orally or intravenously? If not, how has this been accounted for in the analysis?

B5. The submission states (pages 29 and 99) that chlorambucil would be considered in a subgroup of patients (frail/elderly patients with comorbidities) in clinical practice.

1. Please comment on the likely use of R-chlorambucil in this population?

2. Please comment on the clinical and cost effectiveness of the combination of R-chlormabucil in comparison with chlorambucil?

3. Please confirm when the results of trial UK CLL201 will be available?

4. Please provide further justification that the assumption in the model of similar adverse effect profile for chlorambucil as for FC?

<u>Section 7.3.3 Sensitivity analysis</u>

B6. Please complete a one-way sensitivity analysis to show changes in the incremental cost-effectiveness ratio based on the differential mortality rates assumed between PFS and Progressed health states?

B7. In the listed model weaknesses (page 156; item d), the assumption of aggregation in the PFS state is defended by reference to sensitivity analysis on the cost and utility differences, however, as the main impact of this assumption is caused by the differential mortality rates between PFS and progressed states, please clarify, how is this accounted for in the analysis?

<u>Subgroups</u>

B8. People with the p53 deletion/mutation were noted as a subgroup in the scope but are not analysed as a subgroup in the clinical effectiveness or economic analysis. Were such participants included in the trial and what was their outcome? Please provide a rationale for their exclusion as a subgroup in the submission.

<u>Costs</u>

B9. Does the use of rituximab entail additional costs for testing CD-20 status of malignant cells?

B10. Please can you explain why the cost for FC and chlorambucil administration in table 37 (£371 per cycle) is different from that in tables 46 & 47(£280)? The difference in the figures not seem to be explained by adjusting for cycle length of one month in model versus the 28 day cycle in trial

Textural issues

B11. Please clarify the following in the submission?

1. The labelling of curves in figures 17 and 18 (p121, 122) and the keys underneath the figures do not appear to match.
2. The text on p130 states that there were 5 and 3 bone marrow transplant events in R-FC and FC arms, while on p131, table 48, states 4 and 1 stem cell transplants in the R-FC and FC arms.