NICE National Institute for Health and Care Excellence

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Single Technology Appraisal (STA)

Obinutuzumab in combination with chlorambucil for previously untreated chronic lymphocytic leukaemia [ID650]

Dear [redacted],

The Evidence Review Group, Peninsula Technology Assessment Group, and the technical team at NICE have now had an opportunity to take a look at the submission received on the 23rd May 2014 by Roche. 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 the ERG and the technical team at NICE will be addressing these issues in their reports.

We request you to provide a written response to this letter to the Institute by **5pm** on **Monday 7th July 2014**. 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 Ella Fields, Technical Lead (ella.fields@nice.org.uk). Any procedural questions should be addressed to Nicole Fisher, Project Manager (nicole.fisher@nice.org.uk) in the first instance.

Yours sincerely

Frances Sutcliffe
Associate Director – Appraisals

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Centre for Health Technology Evaluation

Please note that there are inconsistences between the page numbering in the printed version of the submission compared with an on-screen version; the numbering used in this letter reflects an on-screen version of the submission.

Section A: Clarification on clinical effectiveness data

A1. **Priority question:** Please provide the percentage of patients in each of the World Health Organisation performance statuses (0, 1 and 2) at baseline.

A2. **Priority question:** Please clarify whether unsuitability for fludarabine therapies was an inclusion criteria in CLL11.

A3. **Priority question:** Please explain why there is a difference in the progression free survival hazard ratios reported from CLL11 in table B26 on pages 102 and 103 (obinutuzumab vs. chlorumbucil 0.183, rituximab vs. chlorumbucil 0.458, and obinutuzumab vs. rituximab 0.388) and in table B41 on page 142 ([redacted]).

A4. Please provide results from a corrected search or a corrected search strategy for Embase and MEDLINE for the update of the systematic review (page 255, section 10.3.4). Currently the following errors exist:

a. Line 28 should combine lines 24-27 but instead lines 22-25 have been combined.

b. The final line should combine lines 29 and 36 and 50, but the search actually combines 27 and 34 and 48.

A5. Please confirm that the Kaplan-Meier curves in figure B40 and B41 (pages 161 and 162) relate to the March 2014 data cut off.

Section B: Clarification on cost-effectiveness data

B1. Please explain why ‘lymphocytic’ is spelt ‘lymphocitic’ in the MEDLINE and EMBASE searches for the cost effectiveness, measurement and valuation of health effects, and resource identification. If this is an error, please re-run the search and highlight any studies that were missed.

B2. Please explain why EMBASE Alert was searched instead of MEDLINE-in-process for cost-effectiveness, measurement and valuation of health effects, and resource identification.

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Quality of life

B3. **Priority question:** Please confirm that EQ-5D data were not available for the CLL11 trial.

B4. **Priority question:** Please explain why the mapping function for mapping EORTC QLQ-C30 onto EQ-5D as reported by Kim S.H., Jo M.W., Kim H.J., and Ahn J.H. (2012) ('Mapping EORTC QLQ-C30 onto EEQ-5D for the assessment of cancer patients.' Health Qual Life Outcomes, vol 10, p151) was not used on the EORTC-QLQ-C30 data from CLL11. Alternatively, please perform this mapping on data from CLL11.

B5. Please provide the NHS EED and EconLit searches for the measurement and valuation of health effects search (section 10.11.4) and the EconLit search and the database provider for EconLit for the resource identification search (section 10.12.4).

B6. Please clarify which table is referred to in the first sentence of section 7.4.6 on page 177.

B7. Please provide the 9 vignette descriptions mentioned on page 178 and in table B50 on page 179.

Adverse events

B8. Please state whether there is any evidence of rare adverse events that might have been missed by the CLL11 trial.

Section C: Textual clarifications and additional points

C1. Please check and clarify the numbering of the figures in your submission. There is inconsistency between the figure numbering in the list of figures on page 2 and the numbering in the text (for example, figure A1 in the content list appears to be titled figure A2 in the text on page 18). The list of figures appears to be incomplete (for example, figure B11 on page 71 is not in the list of figures on page 2).

C2. Please check and clarify the numbering of the tables in your submission. Some table numbering is duplicated in the list of tables in pages 3 to 5 (for example, there are 2 tables referred to as B42 and 2 tables referred to as B47). There are tables in the main text of the submission that do not appear in the list of tables on pages 3 to 5 (for example, tables B43 and B46).

C3. Please check and clarify the formatting of your submission since there are inconsistencies in the page numbers between an onscreen version and a printed version of the submission.

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C4. Please clarify the wording in the sentence that starts 'The fact that in the Clb and Benda arms the predicted….' (on line 3 of page 163) since there is a typographical error which makes the content of the sentence unclear.

C5. Please clarify which reference 'Hillmen, 2008' on page 149 refers to and add this to the reference list if it is not included already.

C6. Please lift some of the confidentiality marking in your submission. Following the NICE team review of your submission, we have identified several issues with the confidential marking.

The NICE STA process guide states that confidential information should be kept to an absolute minimum to ensure transparency in the appraisal process (please see the link at the end of the email) and the relevant section of the STA process guide page 23-24 section 3.2.23 states

'NICE expects consultees to keep confidential material within a submission to an absolute minimum. When consultees believe that part of a submission should be treated as confidential, they must clearly state the reason for this according to the following principles:
• Information that has been put into the public domain, in written form, anywhere in the world may not be marked as confidential.
• The list price of a technology (after launch) and incremental cost-effectiveness ratio (ICER) estimates cannot be marked as 'commercial in confidence'.

The NICE team have noted that some of the confidentiality requires lifting to enable the Committee to show the evidential basis of their decision and to keep the amount of confidential data to an absolute minimum.

In addition, the confidentiality marking is inconsistent throughout your documentation for this appraisal topic.

The following issues with the confidential marking within your manufacturer submission were identified:

Inconsistent marking in the submission
NICE takes the protection of your CiC seriously and discrepancies can present a risk of accidental disclosure. Please be consistent and clear in your marking, and limit marking only to items that are confidential. NICE has identified the following areas where the marking is inconsistent or unclear:

- There is information marked in one section of the submission but not another.
  - Page 9 [date of the new data cut marked as CiC] is inconsistent with pages 11, 69, 114 and 142.

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- Table B22 on page 79 [the number of participants in the 2 groups is marked as CiC] is inconsistent with other parts of the document, such as table B18 on page 52 and table B20 on page 76.
- Page 160 [percentage of patients alive at 20 years is marked as CiC] is inconsistent with table B40 on page 140.

Inappropriate marking in the submission

- The title of several tables and figures is marked as CiC. Titles of tables and figures should not be marked as confidential, only the content.
- Some information that has been marked as CiC is in the public domain.
  - Description of the CLL208 trial on page 149
  - Description of the Knauf trial on pages 150, 162 and 163
  - Figure B34 from the Knauf trial on page 151
  - Description of the CLL8 trial on page 155
  - Description of the CLL5 trial on page 155 and 162

AiC rather than CiC

The information on pages 9, 10, 71, 72, 74, 79, 142-152, 154, 155, 160-163, and 198 is marked as commercial in confidence; however the reason given for the marking appears to suggest that it should be marked as academic in confidence. Please would you review the status of this information. Please note that, unlike commercial-in-confidence material, evidence designated as academic in confidence can be presented at Appraisal Committee meetings with members of the public and press present. This should be highlighted to any third party providers of academic in confidence information.

Blocks of text highlighted as confidential

We note that several sections of the submission contain blocks of text which have been highlighted as confidential. Please reconsider the information highlighted and reduce it to the absolute minimum.

Please resubmit two versions of your submission by **5pm** on **Monday 7th July 2014** and include a revised and fully completed Checklist of Confidential Information stating, for each piece of information, the rationale for treating it as confidential and the expiry date of that confidentiality.

One version of your submission should contain the remaining confidential information clearly marked. Please therefore 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. The second version of your submission should have that information replaced with the following text: 'academic / commercial in confidence information removed'. The revised

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documents should be consistent with the principles described in section 3.2.36 of the Guide to the Single Technology Appraisal Process.