25th August 2010

NHS
National Institute for
Health and Clinical Excellence

NICE
Midcity Place
71 High Holborn
London
WC1V 6NA

Tel: 020 7045 2248
Fax: 020 7061 9830
Email: Jeremy.Powell@nice.org.uk

www.nice.org.uk

Dear [redacted],

Re: Single Technology Appraisal – Rituximab for the first line maintenance treatment of follicular non-Hodgkin's lymphoma

The Evidence Review Group (Liverpool Reviews & Implementation Group) and the technical team at NICE have now had an opportunity to look at the submission received from Roche Products on the 10th August 2010. Although it is noted that the submission is very long, 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. The questions for clarification are listed at the end of this document. Questions considered to be a priority are labelled as priority questions in bold.

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 NICE by **17:00, Thursday 9th September 2010**. 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, please contact Panagiota Vrouchou – Technical Lead (Panagiota.Vrouchou@nice.org.uk) and Fiona Rinaldi – Technical Adviser (Fiona.Rinaldi@nice.org.uk). Any procedural questions should be addressed to Jeremy Powell – Project Manager (Jeremy. Powell@nice.org.uk) in the first instance.

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

A1. **Priority Question:** The patient population in the PRIMA trial (described in Table 15 of the manufacturer's submission) indicates that 118 (10%) patients had Stage I or Stage 2 disease. Patients with NHL at these stages are not usually considered to have advanced disease and are not usually treated with chemotherapy. Please provide clarification of the rationale for patients with Stage I and 2 disease being recruited into the PRIMA trial.

A2. **Priority Question**: Section 5.3.1.2.5 (page 67 of manufacturer's submission) is unclear and appears contradictory. Please present this information in a more coherent manner and provide clarification as to:

i) why starting a new anti-lymphocytic treatment was not counted as an event or as a reason for censoring
ii) the meaning of 'as images were not collected after the start of a new treatment, patients who started a new anti-lymphoma treatment without IRC-assessed disease progression were censored for the IRC analysis of PFS'
iii) why there appear to be differences in censoring methods between the investigator and IRC assessments

A3. Priority Question: In the PRIMA trial, some lymphomas were recorded as having transformed. Please explain i) whether patients whose disease had transformed were followed up and ii) how their data were included in the analysis

A4. Clinical data used in the economic modelling should be evidenced in the clinical effectiveness section. Therefore, please provide a description of the results for all primary and secondary clinical endpoints from the last data cut-off (June 2010), which is not available in the CSR.

A5. With reference to Section 5.4.2, please provide a complete quality assessment for the PRIMA study. It is noted that the table on page 349 of the manufacturer's submission has not been completed.

Section B: Clarification on cost-effectiveness data

B1. Priority Question: In the economic model, neither age nor response status following induction therapy have been considered as determining factors in treatment efficacy. Please provide Product-Limit Survival tables (e.g. using SAS LIFETEST procedure) from analysing the most recent follow-up PRIMA trial data for progression-free survival (PFS) and consider the following:

I. PFS by treatment arm (maintenance rituximab, and 'watch and wait')
II. PFS by 3 patient populations defined by age and by treatment arm (i.e. 3 x 2 Kaplan-Meier analyses) as follows:
    - first tertile (33% youngest patients)
    - second tertile (33% mid-age patients)
    - third tertile (33% oldest patients)
III. PFS by 3 patient populations defined by induction response and by treatment arm (i.e. 3 x 2 Kaplan-Meier analyses) as follows:
    - complete responders

- partial responders
- unconfirmed complete responders

In each case please provide a Product-Limit Survival table (e.g. using SAS LIFETEST procedure - see example below) showing for each event time:

- time of event from baseline (days)
- product-limit estimate of survival proportion
- standard error of survival proportion
- number of patients failed
- number of patients remaining at risk

In addition for each table please provide the estimated mean survival time from the relevant baseline (i.e. randomization or disease progression) up to the time of last recorded event, together with the standard error of the mean estimate.

Example of output (SAS) required from analyses

The LIFETEST Procedure

Product-Limit Survival Estimates						
SURVIVAL		**Survival**	**Failure**	**Survival Standard Error**	**Number Failed**	**Number Left**
0.000		**1.0000**	**0**	**0**	**0**	**62**
1.000		**.**	**.**	**.**	**1**	**61**
1.000		**0.9677**	**0.0323**	**0.0224**	**2**	**60**
3.000		**0.9516**	**0.0484**	**0.0273**	**3**	**59**
7.000		**0.9355**	**0.0645**	**0.0312**	**4**	**58**
8.000		**.**	**.**	**.**	**5**	**57**
8.000		**.**	**.**	**.**	**6**	**56**
8.000		**0.8871**	**0.1129**	**0.0402**	**7**	**55**
10.000		**0.8710**	**0.1290**	**0.0426**	**8**	**54**
SKIP…		**0.8548**	**0.1452**	**0.0447**	**9**	**53**
389.000		**0.1010**	**0.8990**	**0.0417**	**52**	**5**
411.000		**0.0808**	**0.9192**	**0.0379**	**53**	**4**
467.000		**0.0606**	**0.9394**	**0.0334**	**54**	**3**
587.000		**0.0404**	**0.9596**	**0.0277**	**55**	**2**
991.000		**0.0202**	**0.9798**	**0.0199**	**56**	**1**
999.000		**0**	**1.0000**	**0**	**57**	**0**

B2. Priority Question: Rituximab doses are administered based on body surface area (BSA) which is different for women and men. The costs in the manufacturer's submission appear to have not taken these gender differences into account. Please provide BSA summary data (mean, standard deviation and number of patients) for men and women separately for the following five age-related subgroups based on age at randomisation (i.e. 2 x 5 subgroups):

i) patients aged under 47 years
ii) patients aged 47-52 years
iii) patients aged 53-58 years
iv) patients aged 59-65 years
v) patients aged 66+ years

B3. In Section 6.3.6 some variables used in the economic model are listed in table 98. Please indicate if any other variables are missing from this list (including deterministic variables) and provide their values (and appropriate estimates of uncertainty), range (distribution) and source.

B4. Section 6.4.11 states that patient experience is described in section 6.4.1. This section however does not provide information for each health state. Please provide more information on the impact of NHL on a patient's quality of life for each health state included in the economic model.

B5. In Section 6.5.1 (page 280 of manufacturer's submission), year 1-2 costs in table 104 have been correctly calculated over 24 months but the caption states this is calculated over a 12 month period ("year 1-2 (12 months))". Please confirm the time period for these calculations.

B6. In Section 6.7.3, Markov traces for the intervention and comparator arms in tables 115 and 116 appear identical. Please confirm whether this information is correct.

B7. The values for mean life years appear to not be discounted in table 117 (i.e. they are the same as the undiscounted values in table 111). Please confirm the correct values for these tables and also confirm that the values in tables 112 – 119 are also correct.

B8. In table 123, the mean life years (comparator arm) is 4.579 whereas in table 118, this figure is listed as 4.597. Please confirm the correct value.

B9. Please provide sensitivity analyses that will examine how sensitive the ICERs are to alternative assumptions on subsequent lines of treatments.