29 July 2007

[redacted]
Healthcare Management Director
Roche
6 Falcon Way
Shire Park
Welwyn Garden City
AL7 1TW

Dear [redacted],

Single Technology Appraisal – Rituximab for follicular lymphoma

The Evidence Review Group, LRiG, and the technical team at NICE have now had an opportunity to take a look at submission 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 LRiG 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.

The data provided in the submission, although extensive, are not sufficient to allow exploration of the survival analysis. In particular, the Assessment Group having explored the de novo economic evaluations described in detail, make an urgent request for the information presented in Section B of this letter. Without this level of detail, they feel unable to provide definitive comment on the cost effectiveness of rituximab for the treatment of relapsed follicular lymphoma.

We request you to provide a written response to this letter to the Institute by 13th July.2007. 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.

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.

This clarification letter does not explore the interpretation of the marketing authorisation. We are still considering your letter of 25th May 2007.
If you have further queries please contact Dr Elangovan Gajraj.

Yours sincerely

Meindert Boysen, Pharmacist MScHPPF
Associate Director - STA
Centre for Health Technology Evaluation

Encl. 1: checklist for in confidence information

Encl. 2: EORTC20981 disposition table

Section A. Clarification on effectiveness data

A1. Please provide full copies of any search strategies used in the review of the clinical literature. On page 36 of the submission it is stated that a copy of the search strategy is appended in Appendix 2. Appendix 2 does not include a copy of the search strategy. Currently none of the searches is reproducible for checking by LRiG.

A2. The submission states that databases were searched from 01/01/2000 to present, please clarify the specific end date for the search period

A3. The scope for this appraisal requires a review of the evidence base for the current guidance on remission induction with rituximab monotherapy that was given in TA37. Very few details of the methods used to review this specific evidence base are presented. Please provide more detail on this particular aspect of the review of clinical literature.

A4. Please provide a copy of the Eugen (2002) abstract listed in Table 4.

A5. Why were the Hainsworth and Hochster papers (referred to on page 41) not included in table 4?

A6. Table 7 on page 49 of the submission appears to be incorrect. The assessment group were particularly interested in the numbers for bone marrow involvement that do not sum up across the row. In addition many of the totals in individual rows do not sum up to the number at the top of the column? Is there a reason for this? Please provide us with the correct figures.

Section B. Clarification on cost-effectiveness data

B1. Please provide the estimated means and standard errors for Kaplan-Meier analyses of OS and PFS for each treatment group in both models (full data set, without truncation).

B2. Please provide details of the number of patients who were still in the trial beyond 1500 days by randomised treatments, and by response to initial treatment.

B3. Please clarify the case for using Weibull survival models for all models (OS & PFS, all treatment groups) when the 'goodness of fit' statistics appear to favour other options (exponential and log normal) in several cases.

B4. Please explain why only 3 Weibull parameters were estimated instead of 4 in projections for pairs of treatment groups.

B5. Were 'event-free' initial periods used for projection models? If so, can you clarify if these were assumed or estimated jointly with other parameters?

B6. Please confirm that survival analyses for 2-arm model use only data from time of second randomisation. Was the same truncation point (1500 days from first randomisation) used for these analyses as for the 4-arm model?

B7. Was any consideration given to the differing proportions of patients receiving rituximab initiation treatment, when modelling OS and PFS for the 2-arm model?

B8. The following links shown in the 2ARM model appear not to be functional:
- 2ARM Weibull parameters .xls
- 2ARM LogLog parameters .xls

B9. Please provide the protocol document for EORTC20981

B10. Please provide the CSR for EORTC20981 including results and supplementary tables and appendices relating to analyses of outcome variables.

B11. Please provide an anonymised extract IPD file of EORTC20981 data, as specified in the attached specification file below

Item	Format	Comment
1) Patient record code	Alpha or numeric	Anonymised unique record identifier
2) Date of 1st randomisation	Date	-
3) Phase 1 randomised treatment	Alpha or numeric	-
4) Death indicator	Binary	Did death occur?
5) Date of death	Date	-
6) Progression indicator	Binary	Did disease progression occur?
7) Date of disease progression	Date	-
8) Other Treatment indicator	Binary	Was patient assigned to non-trial disease treatment?
9) Date of other treatment assignment	Date	-
10) Type of other treatment	Categorical	Coded treatment (supply key to codes)
11) Withdrawal/termination from trial	Categorical	Death Other treatment Withdrawal by patient/physician Lost to follow-up Not eligible for 2nd randomisation Other/unknown
12) Date of last observation in trial	Date	-
13) Date of assessment for 2nd randomisation	Date	-
14) Assessed response to treatment	Categorical	CR / PR / SD-NC / PD / unknown
15) 2nd Randomisation	Binary	Was patient randomised again?
16) Phase 2 randomised treatment	Alpha or numeric	
17) Date of 2nd randomisation	Date	

B12. Please provide the information required to complete the disposition table attached to this letter for EORTC20981 in order to ensure that a comprehensive summary of all randomised trial patients is available. All categories are mutually exclusive, and should sum to the correct

totals in each phase. Please complete the disposition table in Excel and not in Word.

B13. The methods and results of the economic searches are unclear. Please can you provide further details on the economic searches undertaken (e.g summary table of number of identified studies by database; summary of the inclusion and exclusion terms used). Please can you confirm that all of the papers identified (n=73) could have been identified by searching NHS EED and HEED only.

B14. The model assumes that all rituximab infusions occur in the outpatient setting. Can you confirm that this is what occurs in routine NHS care.