29 July2007

Healthcare Management Director Roche

6 Falcon Way
Shire Park

Welwyn Garden City
AL 7 1TW

Dear..,

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.

80th 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 8 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 13thJuly.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 25thMay 2007.
If you have further queries please contact Dr Elangovan Gajraj.

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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

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Section A. Clarificationon effectiveness data

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A2.

A3.

A4.
A5.

A6.

Please provide full copies of any search strategies used in the review
of the clinicalliterature. On page 36 ofthe submission it is stated that a copy ofthe search strategy is appended inAppendix 2. Appendix 2
does not include a copy ofthe search strategy. Currently none of the searches is reproducible for checking by LRiG.
The submission states that databases were searched from 01/01/2000

to present, please clarify the specific end date for the search period 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.

Please provide a copy of the Eugen (2002) abstract listed in Table 4. Why were the Hainsworth and Hochster papers (referred to on page
41) not included in table 4?
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

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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).
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.

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.

Please explain why only 3 Weibull parameters were estimated instead of 4 in projections for pairs of treatment groups.
Were 'event-free' initial periods used for projection models? If so, can you clarify if these were assumed or estimated jointly with other parameters?
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?

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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

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

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Item Format Comment

1) Patient record code Alpha or Anonymised unique record identifier
numeric

2) Dateof 1SI randomisation Date -
3) Phase 1 randomised Alpha or -
treatment 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 Date -
assignment
10) Tvpe of other treatment Categorical Coded treatment (supply key to codes)
11) Withdrawal/termination from Categorical Death
trial Other treatment

Withdrawal by patienUphysician
Lost to follow-up
Not eligible for 2ndrandomisation
Other/unknown

12) Date of last observation in Date -
trial

13) Date of assessment for 2na Date -
randomisation

14) Assessed response to Categorical CR / PR / SD-NC / PD / unknown
treatment

15) 2n-oRandomisation Binary Was patient randomised again?
16) Phase 2 randomised Alpha or
treatment numeric
17) Date of 2narandomisation Date

totals in each phase. Please complete the disposition table in Excel
and not in Word.
813. 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.
814. The model assumes that all rituximab infusions occur in the outpatient setting. Can you confirm that this is what occurs in routine NHS care.

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