29th July 2009

NHS

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Dear Mr Catchpole,

Single Technology Appraisal – rituximab for treatment of relapsed chronic lymphocytic leukaemia

The Evidence Review Group (ERG), West Midlands Health Technology Assessment Collaboration 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 on some points relating to the clinical and cost effectiveness data.

Both the ERG and the technical team at NICE will address 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 address the points listed below 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 *12th August 2009.*** 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 are not already referenced in the main body of your submission and those data are seen to be academic/commercial in confidence, please complete the attached checklist for in confidence information.

If you have any further queries on the technical issues raised in this letter then please contact Sally Gallaugher, Technical Analyst (sally.gallaugher@nice.org.uk). Procedural questions should be addressed to Laura Malone, Project Manager (laura.malone@nice.org.uk) in the first instance.

Yours sincerely

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

Section A: Clarification on effectiveness data

General

A1. As there is no published data available for the REACH trial, if available, please provide the full trial report.

A2. At the cut-off date for REACH data analysis (2.1 years median follow-up), around 76% of patients were still alive or censored for overall survival and there is thus little informative data contributing to the survival curves for the Committee to consider. If available, please provide any additional data from the REACH trial for relevant outcomes after the cut-off for data analysis (23rd July 2008).

Identification of studies

A3. The submission states under 6.2.5 (p41) that there are no relevant ongoing trials from which additional evidence will be available in this time period. Please provide the search strategy for identification of ongoing and completed but unpublished trials.

A4. On p31 the submission states that the efficacy of chlorambucil with rituximab is being investigated in the UK CLL201 trial (phase II). Please confirm that this should be 'CLL208' and indicate whether this should be considered a relevant ongoing trial.

Study selection

A5. On p35 of the submission the identification of studies is described. Please provide the formal inclusion and exclusion criteria with reference to eligible/non-eligible study designs, population characteristics, intervention therapies, comparator therapies and outcomes for:

i) randomised controlled trials

ii) non-randomised studies

A6. Please clarify the flow charts (Figures 2, 3, 4 and 5, p41-44) in accordance with the formal inclusion and exclusion criteria.

A7. The list of relevant non-randomised studies (Table 5 (p37)) lists appears to include a randomised phase II trial (Hillmen 2007).

i) Please confirm whether this trial is a randomised study, and if so, please explain its exclusion from the randomised trials.

ii) If Hillmen 2007 is eligible for inclusion, please provide the trial report or any further details that are available.

Summary of methodology of relevant RCTs

A8. The submission states on p67 that patients without a PFS event were censored at their last tumour assessment date. Please provide information regarding a) the number of scheduled assessments for each arm, and b) the number of completed scheduled assessments for each arm.

A9. In table 26 (p80) at the entry against “allocation concealment” (process that prevents foreknowledge of treatment assignment) there is no information about how allocation concealment was conducted. Please elaborate on any procedures that were followed in order to achieve concealment.

A10. The submission discusses on p81 the randomisation technique. Please comment on any methodological strengths and limitations of using dynamic randomisation.

A11. In REACH the investigators were generally unable to blind for understandable reasons (p81). Please comment on the potential for bias in outcomes where blinded assessment was not possible.

A12. On p81, the submission indicates that assessors may have been aware of treatment allocation. The submission indicates that response and progression data that were assessed in a blinded manner (at interim and final analysis) are not yet available. Please confirm that this remains the case and indicate when they are likely to be available.

A13. The submission indicates that many patients were censored for progression free and overall survival (Figures 8 and 9 (p89, 91)). We are interested in numbers of patients censored because a) they reached the end of the trial without an event and b) because they were lost to follow-up before reaching the end of the trial. We are also interested in the reasons for loss to follow-up. Please provide further information on censoring and loss to follow-up, some example tables are provided in a separate attachment as a guide.

Results of the relevant comparative RCTs

A14. On p102 of the submission a sub-group analysis for del17 positive patients is presented for best overall response. Were sub-group analyses performed for progression free survival or other outcomes?

Quality of life

A15. The title of table 39 (p105) suggests that FACT-G sub-scores are available although not presented. If sub-scores are available, please provide these data.

A16. Please explain why QoL data was measured for 1 year only and not throughout the trial.

Adverse events

A17. Adverse events (AE) may relate to treatment, with more cycles potentially generating more treatment related AEs. On p108 of the submission it states that 67.5% patients in the R-FC arm received 6 cycles of therapy, and 61.4% of patients in the FC arm received 6 cycles of therapy. Please provide information on:

i) the number of patients receiving 0, 1, 2, 3, 4 and 5 cycles of therapy in both arms at the time of the safety analysis

ii) whether patients who restart treatment with rituximab at any time in the follow-up phase are included in the safety analysis

iii) total and average amount of rituximab exposure in the rituximab arm (and those who crossed over to the R arm) in the safety analysis

iv) how late (e.g. months, years) after treatment has been completed AEs related to treatment can occur

Interpretation of clinical evidence

A18. Please provide a reference for the methodology of the Q-Twist analysis described on p161.

A19. Please confirm that the median follow-up time for Q-Twist is 30.75 months, and for the other clinical effectiveness outcomes it is 2.1 years.

A20. It states in the submission that a utility of 1 represents a state as good as TWIST (time without symptoms of disease or toxicity of treatment). Does this imply that CLL patients who are in remission and not experiencing side effects are equivalent to people in perfect health?

Section B: Clarification on cost-effectiveness data

De novo economic evaluations

B1. To aid the ERG and the committee in the understanding of the economic model (the committee do not see the model-only the submission), please provide a table which expands on table 59 and includes the following information:

- the names of **all** parameters as used in the model
- the values for all parameters
- the range of values they can take
- their function in the model
- the evidence base behind them

B2. Please clarify in a single table the information given in tables 58, 67 and 68 and on page 47 about dosages and costs for R, F and C. Please highlight any differences between (a) REACH, (b) the economic model inputs and (c) planned licensed dose specifically for the following parameters:

i) single doses in mg/m2

ii) number of doses of each drug in one cycle and total number of doses

iii) mode of administration (iv/oral)

iv) conversion from iv to oral dose

v) costs per dose/cycle of F, C, R

vi) total cost per patient

The following points relate to question B2. Please ensure these points are addressed in the table provided in response to the above question or that further explanation is provided.

i) The submission states on p164 that a higher oral dose of FC is required to obtain the equivalent iv dose.

The **iv** doses in REACH (p47 of the submission) are:

F: 25 mg/m2 on 3 days (stated given on days 1,2,3) = 75 mg/m2
C: 250 mg/m2 on 3 days (stated given on days 1,2,3) = 750 mg/m2

The **oral** doses in the economic model are:

F: 24 mg/m2 on 5 days (stated given days 1-5) = 120 mg/m2
C: 150 mg/m2 on 5 days (stated given days1-5) = 750 mg/m2

Please confirm if these calculations are correct and if so why the oral dose of F is higher (as expected) but the oral dose of C is not.

ii) The oral doses of FC were taken from the CLL-4 trial, where patients are previously untreated, as opposed to the population in the decision problem where patients have previously been treated. Please clarify how this difference in patient populations might impact on the dosages used.

iii) Table 67 (p189) states that the actual doses from REACH were 700 mg/m^2 (cycle 1) and 900 mg/m^2 (cycle 2-6) and that this includes rounding up to the nearest vial. Our calculations for the recommended dose of rituximab suggest the dose is 697.5 mg/m^2 (cycle 1) and 930 mg/m^2 (cycle 2-6). Please clarify the actual dose in REACH with no rounding, and the number and size of vials required to provide the actual dose provided in REACH and the dose recommended in the SPC.

iv) Please complete sensitivity analyses if there are any changes in vial numbers or size

v) Please clarify the calculation of cost of rituximab for cycle 1 and cycles 2-6;

500ml@ £873.15 + 2* 100ml @ 174.63=£1222.41 (not £1328.81)
500ml@ £873.15 + 4* 100ml @ 174.63=£1571.67 (not £1708.47)

vi) Please confirm whether the unit cost for a 500mg vial of rituximab is £874.15 or £873.15 (both figures appear in table 67).

vii) Table 67 (p189) describes the costs per infusion/cycle. Please confirm that 500ml should be 500mg.

viii) Please confirm the unit cost in table 68 (p190) for 1mg oral F is £1.86 (same as body surface area figure).

ix) Table 68 (p190) provides the daily dose of cyclophosphamide. Our calculations suggest 150 mg/m^2 equates to 279 mg for a body surface area of 1.86 m^2 which multiplied by an adjustment factor of 150/250, results in 167.4 mg on 5 days (not 265 as stated). Please clarify how the average daily dose for cyclophosphamide is calculated.

x) Table 68 (p190) provides the daily dose for fludarabine. Our calculations suggest 25mg * 1.86 * (24/25), equates to 44.64 (not 42 as stated). Please clarify how the average daily dose for fludarabine is calculated.

xi) In table 68 (p190; column headed 'Description'), C is stated to be chlorambucil. Please confirm this should be cyclophosphamide.

xii) On p199 of the submission it states that "the utilisation of actual doses of R-FC and FC from the trial were considered in the base case analysis. The sensitivity analysis explores the planned licensed dose." However, the submission states on p166 that "the main study used in support of this submission (REACH) used a regime that will become the licensed dosing schedule for rituximab in CLL and as such will be documented in the SmPC."

Please clarify the differences between the dosages used in the REACH trial, the dosages used in the model (and any sensitivity analyses) and the planned licensed doses.

xiii) Please also clarify whether in the base case analysis the "utilisation of actual doses" (p199) means actual iv dose or adjusted oral dose.

B3. The submission describes on p170 the time horizon of the economic model. Please explain why the lifetime time horizon is 25 years, when the previous submission for rituximab as first line treatment assumed 15 years. For relapsed CLL, a shorter rather than longer timeframe might be expected.

B4. The submission states on p175 that treatment cycles were given every 28 days but the model uses monthly cycles. Please explain how treatment costs were assigned to the correct month in the model.

B5. The submission describes on p180 (figure 23) post progression survival. The log rank was non-significant and data considered to be from a single population with assumed exponential distribution. Please provide a Kaplan-Meier (for all patients) with an exponential fit (and scale parameter).

Survival curves

B6. Survival curves are described on page p198 of the submission. It would be helpful for the ERG if a single table were constructed defining:

i) the S(t) function for each of the parametric fits shown on page 198

ii) the parameter values corresponding to each fit that was used for the economic model (base case and sensitivity analyses)

iii) please also define the time unit to which the parameters apply

B7. The interpretation of figure 26 on p204 of the submission may be confusing. Please plot this figure extended to the life-time of the model (25 years rather than 15 years), and so that the vertical axis starts at 0 and the x axis ticks are only every 8 months.

B8. Please provide, if available, a standard survival curve (based on cohort or registry data) for no or standard UK treatment.

Adverse events

B9. The number of grade 3 and 4 side effects is higher in the R-FC arm (see Table 64, p183). However, the cost of AEs is higher in the FC arm (£554.68) than in the R-FC arm (£504.19). Please clarify these data.

- Number of grade 4 events in R-FC: 222
- Number of grade 4 events in FC: 142
- Number of grade 3 events in R-FC: 511
- Number of grade 3 events in FC: 421

B10. Please comment on why, in the sensitivity analysis on p205 of the submission, the adverse events costs are varied by 50%, but the health effects of AEs are not varied.

B11. Please provide sensitivity analyses that include both the costs and health effects of adverse events.

Economic model

B12. On the sheet "Mortality Table UK", the entry in cell J5, named "male2female" is set at 1.6 representing the ratio of males to females. However, it is used in the formulae in cells E6 to E56 as if it were the proportion of males in the population, thus giving an overall death rate that is actually higher than the separate male and female death rates. It would seem that the correct value to use in the formulae in column E is 1.6/2.6. Since background mortality is in practice only used in the later stages of the model, the effect of this error is negligible, as shown in the following table:

Extract from Table 79 (p205) with extra column added

Sensitivity analyses	ICER as claimed	Corrected
Base case (Weibull)	£14,240	£14,236
Gamma function	£13,461	£13,448
Exponential function	£12,007	£11,992
Log logistic function	£13,394	£13,345
Log normal function	£12,122	£12,072
Gompertz function	£15,817	£15,817
Planned dosing including wastage	£15,598	£15,593
Utilities: PFS=0.9; Progressed = 0.5	£11,886	£11,884
Utilities: PFS=0.75; Progressed = 0.65	£15,804	£15,799
Adverse event costs increased by 50%	£14,196	£14,192
Adverse event costs decreased by 50%	£14,283	£14,279

Please confirm that this interpretation is correct.

B13. This model appears to be similar to the model used for the appraisal of rituximab for the first line treatment of chronic lymphoid leukaemia. The ERG for that appraisal highlighted the importance of assumptions about overall survival in the model. There does not appear to be any deterministic sensitivity analysis testing the equivalent assumption in the current submission. Please provide an analysis assuming no overall survival benefit as was done for the previous appraisal.

Section C: Additional questions

C1. Please provide a list of abbreviations and definitions used in the submission.

C2. Please give a breakdown of how the figure of £10,923 was calculated for the budget impact (p213).

C3. Please provide PDFs (where available) or hardcopies of all the references listed in the report (please also indicate where, if any, copyright legalities apply).