

30 June 2006



Dear [REDACTED],

Single Technology Appraisal – Fludarabine phosphate for first-line treatment of Chronic Lymphocytic Leukaemia

The Evidence Review Group (ERG) has now had an opportunity to take a first look at the industry submission document and economic model submitted by Schering Health Care Limited. In general terms they felt the document and model were well presented and clear. However there are a number of issues and queries on which we are seeking your feedback at this early stage.

The comments and queries included in this letter are divided into three sections:

- **Effectiveness data**
These points are very important to enable us to understand the selection criteria for studies which were included in the clinical evidence section and subsequently in the cost effectiveness analysis, as well as their impact on the model.
- **Economic analysis**
This section lists queries relating to the cost effectiveness modelling which will improve our understanding of the model inputs and outputs.
- **Additional discussion and rationale**
This section requests clarification in relation to the text of the submission, which may have an impact on the validity of evidence presented on clinical effectiveness and cost-effectiveness.

Both the ERG and 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 Committee Meeting you may want to do this work and provide further discussion from your perspective at this stage.

We request you to provide a written response to this letter, answering the specific queries highlighted, to the Institute by Friday 14 July 2006.

Yours sincerely

Meindert Boysen, *Pharmacist MScHPPF*
Associate Director – Single Technology Appraisals
Centre for Health Technology Evaluation

Section A. Clarification on effectiveness data

A1. Please supply copies of the following key references:

- (10) Spriano 2000
- (12) Eichhorst 2005, abstract
- (53) Jaksic 2000
- (81) Rai 1996, abstract
- (83) Rai 1995, abstract

A2. Please supply further evidence in support of the statement: “Next to chlorambucil, FC and fludarabine are the most commonly used first-line therapies in the UK” (page 14 of main submission).

- Please supply a copy of the IMS Oncology analyser data (reference 8) given in support of this statement.

A3. Please supply further information regarding the number of patients included in the CLL4 analysis who are not included in the licensed indication (pages 14 & 15 of main submission).

- Please stipulate the exact number of patients who differ from the licensed indication.
- Please re-analyse the data without the inclusion of these patients.

A4. Please clarify the exact source of the extensive report of CLL4 study methods as outlined on page 56 of main submission. Is this reference 31?

A5. Please provide further justification(s) for not performing a formal meta-analysis of the pooled response data (page 70 of main submission). We notice pooling of response data from single arms of trials and also a meta-analysis cited in the submission by Zhu et al (reference 86) used data from abstracts; the results of which were found to be robust by Richards (reference 87).

Section B. Economic Analysis

B1. Please supply copies of the following references:

- (17) Best 2000
- (95) Stephens 2005

B2. Please supply further clarification over the exact tables and data used to estimate non-CLL mortality (Question 82, pages 91 & 94 of main submission). Please clarify whether cause-elimination approaches were used to estimate these mortality estimates.

- B3. Please supply further information on the selection of sites for the resource use and cost audit CLL4 study (page 56 of main submission). In particular, please clarify:**
- The total number of UK sites in the main CLL4 trial
 - The selection procedure used to ensure “participating centres was made to reflect the UK population and clinical practice” (page 4, Appendix 9).
 - The number of patients unwilling to give informed consent
 - The number of patients with incomplete records
- B4. Please supply further clarification, in addition to that given in Appendix 9, over the number of patients whose treatment was continuing at the time of data collection for the resource use and cost audit CLL4 study (Question 104, page 113).**
- B5. Please clarify how the regression analysis (Section 5.8, pages 9 & 10, Appendix 9) is used to “make allowance for any differences that might exist between the relatively small sample included in the audit and the whole CLL4 population”.**
- B6. Please confirm the approach used for the regression analysis of cost data. In particular, was the analysis undertaken on transformed or untransformed cost data? Was a bootstrap regression used?**
- B7. Please clarify the source of the weighting used to combine the IV and oral regimens in the costing analysis (Section 2 list of tables, pages 19-24, Appendix 9).**
- B8. Please clarify whether pre-medication costs were included in the resource use and cost audit study (Sections 5.5 & 5.6, pages 8 & 9, Appendix 9).**
- B9. Please supply further information for how the unit costs were derived in Table 20 (page 37, Appendix 9)? Was part-usage of vials assumed in the costing study? We are having difficulty reconciling the unit costs in Table 20 of the resource use and cost study with the data presented on page 19 of the main submission.**
- B10. Please provide additional clarification on the calculations used to make overall survival equivalent for each strategy (Question 82, page 94 of main submission). In particular we are unclear how the survival equalisation approach takes account of the additional time in the response rate for patients retreated with F or FC. Similarly we are unclear how the approach adjusts for the differential mortality rates in ‘observed’ patients. Finally we have set utility values for all states to be 1 (i.e. an analysis based on LYG) – we would assume that outcomes would be equivalent if survival were equivalent across the strategies. However, there appear to be major differences in the LYG calculations. Please clarify why this is so.**

- B11. Please provide an explanation for the significant changes in C/E ratios for F-CLB and FC-CLB (Table 54, page 134 of main submission) in the one-way sensitivity analyses that explore the impact of 5, 10 and 15-year time horizons on cost effectiveness.**
- B12. Please provide a visual/graphical representation of the results of the one-way sensitivity analyses (Table 54, pages 133-134 of main submission), for example a tornado diagram. We would like to evaluate the relative impact of the different uncertainty parameters on cost effectiveness.**

Section C. Additional Discussion and Rationale

- C1. Please clarify the rationale behind the choice of fludarabine in combination with cyclophosphamide:**
- Is the combination of fludarabine and cyclophosphamide licensed for this indication?
 - A combination regimen is not specified in the SPC – please clarify this and the recommended doses if licensed.
- C2. Please provide evidence to support the use of fludarabine in combination with cyclophosphamide in favour of combination with other agents such as Epirubicin?**
- Please provide the clinical trial evidence to support the use of this combination, with particular respect to the dose used in the submission.