Response to the Questions from the Evidence Review Group

STA : Fludarabine phosphate for 1st line treatment of Chronic Lymphocytic Leukaemia

Schering Health Care Ltd

[redacted]

14th July 2006

Section A. Clarification on effectiveness data

AI. Please supply copies of the following key references:

- (10) Spriano 2000 [Available on CD supplied with submission]
- (12) Eichhorst 2005, abstract [Available on CD supplied with submission]
- (53) Jaksic 2000 [Available on CD supplied with submission]
- (81) Rai 1996, abstract [Available on CD supplied with submission]
- (83) Rai 1995, abstract [Available on CD supplied with submission]

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).

[Chlorambucil is used first line to treat 60% of patients with CLL. This is followed by FC being used in 16% of patients and fludarabine in 8%. The remainder of patients receive a range of therapies including combination treatments (reference 8). These figures are taken from the IMS Oncology Analyzer data which is an independently provided data source that collects retrospective data from patient case records from a representative panel of 121 UK treating clinicians. All drug therapies used in the treatment of patients' cancer are recorded from 1999 onwards thereby enabling the analysis of the usage of specific therapies and treatment pathways within specific oncology areas. This is the only source of independent data we are aware of to obtain such information.

Use of these treatments is consistent with the current guidelines for UK haematologists which endorse the use of chlorambucil and recommend that first line patients who are not contraindicated to fludarabine be entered into the CLL4 study for randomisation to fludarabine (+/- cyclophosphamide) or chlorambucil. Since the recruitment to CLL4 is now closed and initial findings have been reported it is expected that revised guidelines will be issued in due course. We would be happy to undertake a survey to establish first line treatment practices for UK clinicians if this is required.]

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

  [Available on CD supplied with submission]

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.

  [It is not possible to identify the exact number of patients in the CLL4 data set that are not included in the licensed indication because:
  The CLL4 case record form only recorded if patients were Binet stage A-progressive, Binet stage B, or Binet stage C: Therefore it did not distinguish between those who were Binet B (outside the licence) or those who were B with disease related symptoms or evidence of progression (within the licence). However expert clinical opinion suggests that these differences do not have a significant impact on the relevance of the data source to usual practice in the UK [redacted]]

- Please re-analyse the data without the inclusion of these patients.

  [Please see comment above that relates to Binet groups in the trial data set. An analysis considering only those patients within Binet stage A progressive and Binet stage C is presented in Tables 46 and 47 of the STA submission form to investigate the effect of removing all those with Binet stage B (with and without progressive features), however it is not possible to analyse the subgroup of stage B patients with and without progressive features separately due to the limitations of data reported on the case record forms.]

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?

[The principal source of information on the CLL4 study methods is reference 13 (CLL4 protocol). The write-up was supplemented by use of the relevant published abstracts (references 11, 15, 16, 74) and personal communication with the authors, D Catovsky, P Hillmen and M Else.]

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).

[Meta-analysis is appropriate when synthesis of data from different studies will add insight that is not obvious from inspection of the individual studies.

Seven studies were identified that met inclusion criteria for the review. Of these studies 4 are reported as abstracts only. It is our understanding that conference abstracts generally do not qualify as peer review publications for inclusion in meta-analysis.

Three studies therefore might be included in a meta-analysis of published studies. None compares all three treatments (CLB, F, FC) directly. One published study (Eichorst 2006) compares fludarabine with FC. No other published study includes this comparison. Two published studies (Rai 2000, Spriano 2000) compare fludarabine with chlorambucil (table 7). The potential meta-analysis is therefore to pool Rai and Spriano.

Both Rai and Spriano use the licensed dose of fludarabine. The dose per cycle of chlorambucil in Rai is however 40mg/m^2, compared to a dose per cycle in Spriano of 60mg/m^2 and the CLL4 dose (and UK standard) of 70mg/m^2 (table 8). Rai and colleagues treated 200 patients with chlorambucil and Spriano treated 75 patients (table 8). CLL4 treated 387 patients with chlorambucil (table 8).

Meta-analysis of published studies would therefore pool findings from 200 patients treated with a low dose of chlorambucil (Rai) with 75 patients treated with a more commonly used dose. We did not consider that this would add insight to what we can derive by observing the design and findings of the individual studies.

The UK CLL4 study is considered the most relevant study to the decision problem because it is the largest and most applicable to UK clinical practice. The study is the only study to compare all three treatments within the same study population and therefore overcomes the bias introduced through an indirect comparison between heterogeneous studies.]

Section B. Economic Analysis

B1. Please supply copies of the following references:

- (17) Best 2000 [Reference 17 which is Best 1995 is available on the CD supplied with the submission.]
- (95) Stephens 2005 [available on CD supplied with submission]

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.

[Non-CLL mortality is estimated as the unweighted average of male and female all cause mortality from UK life tables. No cause-elimination was conducted to modify these data.]

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

  [76 of the 86 centres (88%) in the CLL4 trial were UK centres.] (http://www.clinicaltrials.gov/ct/gui/show/NCT00004218;jsessionid=19440867F8556ED6E7624EA65FD1E683?order=1)

- The selection procedure used to ensure "participating centres was made to reflect the UK population and clinical practice" (page 4, Appendix 9).

  [Participating centres were selected at a meeting of the study managers so as to give a reasonable geographic spread and variety of hospital types whilst ensuring data collection was possible within budget and time constraints.
  [redacted]]

- The number of patients unwilling to give informed consent

  [The total possible patient pool was 126. The sample obtained was 113/126 = 90% of potential patients at these centres.
  [redacted]]

- The number of patients with incomplete records

  [One of the exclusion criteria was incomplete notes, so these patients were not included in the analysis.]

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).

[[redacted] patients [redacted] had not completed treatment at the time of the audit. In order to make maximum use of the data available these patients were included in the analysis. Patients with incomplete treatment had a lower number of cycles for which data were available than those who had completed treatment (Table below). We used regression analysis to determine cost per cycle of treatment received. This corrects for the smaller number of cycles received by these patients.]

	CLB	FC	F
All			
N	[redacted]	[redacted]	[redacted]
Mean number of cycles	[redacted]	[redacted]	[redacted]
Treatment complete			
N	[redacted]	[redacted]	[redacted]
Mean number of cycles	[redacted]	[redacted]	[redacted]
Treatment not complete			
N	[redacted]	[redacted]	[redacted]
Mean number of cycles	[redacted]	[redacted]	[redacted]

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".

[In the audit population the mean number of cycles per patient was [redacted] for chlorambucil, [redacted] for fludarabine + cyclophosphamide and [redacted] for fludarabine (audit report Table 3). In the CLL4 database at the time the audit was undertaken the mean number of cycles received across the whole population was higher: [redacted] for chlorambucil, [redacted] for fludarabine + cyclophosphamide and [redacted] for fludarabine (audit report Table 25). Chemotherapy and associated activities account for a good deal of the total cost and might be expected to increase with the number of cycles given. It is therefore likely that the costs in the audit understate the average cost in the whole population. We speculate that this may be related to a number of patients who had not completed therapy at the time of the audit.

We estimated patient cost **per cycle** for each arm as (plus a constant term to allow for pre-treatment costs) using a simple regression. Per patient cost for the full population is then estimated as a function of the number of cycles received. This is intended to correct for any difference between the audit dataset and the full CLL4 population in the mean number of cycles received.]

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?

[The regression used ordinary least squares using untransformed data.]

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).

[These sections report average resource use for patients according to treatment received, not according to route of administration. They therefore reflect the balance of iv vs oral administration recorded in the dataset.]

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).

[Prophylactic medication was included. Costs incurred before chemotherapy was initiated (such as initial diagnosis and associated visits) were not collected as these are common across all arms considered.]

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.

[The costing study was conducted in 2003-4 and used unit costs available from the BNF at that time (BNF 47: March 2004). The findings have been inflated to a consistent 2006 price base using the health service inflation index and the consumer price index. The full submission was conducted in 2006 and reports the most up to date prices available. Part usage of vials in the costing study was addressed by assuming that a full vial was used for each day of iv administration.]

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.

[As agreed we are rerunning the analysis in the light of this query and we will be providing revised analyses and updated documentation.]

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.

[Fludarabine and in particular FC are associated with an extended duration of response when compared to chlorambucil. In the model, patients managed with CLB return for second and subsequent treatments at an earlier stage than patients managed with fludarabine or FC due their shorter duration of response.

On the cost side, longer time horizons reduce the incremental cost of fludarabine and FC, as increasing numbers of chlorambucil patients return for expensive second line therapy.

On the outcomes side, patients initially managed with chlorambucil are able to maintain good quality of life by “using up” their second and subsequent therapy options more quickly than fludarabine and FC patients. As the time horizon becomes more extended increasing numbers of chlorambucil patients have experienced and relapsed after all three lines of available chemotherapy and experience poorer quality of life. Patients

managed with fludarabine and FC are more likely to still be experiencing response, or to have additional effective therapies available to them.]

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.

[Please see response to question B10. These will be provided to present the results of the amended base case as discussed.]

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?

  [Cyclophosphamide is licensed for combination chemotherapy as shown in the UK SmPC: "Cyclophosphamide is frequently used in combination chemotherapy regimens involving other cytotoxic drugs" . Fludarabine is a cytotoxic drug and therefore within this context the use of fludarabine and cyclophosphamide together is licensed.

  The efficacy of the combination has been documented extensively in both treated and untreated patients with CLL. There are now 3 studies which have been reported in 3 different countries showing superiority of FC compared to F: one in the USA [Flinn et al, 2004, reference 13] , one in Germany [Eichhorst al, 2006, reference 1], and now CLL4 in the UK [Catovsky et al, 2005, reference 11].

  Most of the clinical trials which are being conducted in, or designed for, patients in first line CLL are based on this combination. This is because FC is now considered the combination therapy to build upon (e.g. by adding other chemotherapeutic agents or antibodies such as rituximab or alemtuzumab), and it would be extremely difficult to design a new study, which would get ethical approval, with single agent fludarabine (unless for specific subgroup of patients).]

- A combination regimen is not specified in the SPC - please clarify this and the recommended doses if licensed.

  [The dose for the combination was the dose used in the CLL4 study, which was agreed among the clinicians running the MRC/LRF UK-CLL group. The dose for the IV administered regimen is Fludarabine 25 mg/m^2/day for 3 days and cyclophosphamide is 250 mg/m^2/day for 3 days. The doses were decided by the MRC/LRF group after consulting their colleagues from the MD Anderson (M Keating and colleagues), with extensive experience on the FC combination. The recommendation was to use slightly lower doses of fludarabine (25 mg/m^2/day instead of 30 mg/m^2/day), because this dose was thought to be safer, but effective, for a multicenter trial [redacted]. The dose of FC used in the CLL4 is now the dose used by the MD Anderson, and other groups, using the next generation FCR regimen (FC with rituximab) [Keating M et al, 2005[1]].

  In relation to the oral administered FC regimen, the bioavailability of oral fludarabine is 50-60% [Fludara oral SmPC] and of cyclophosphamide is > 75% [Struck R et al, 1996[2]]. The dose for oral FC was therefore calculated and used by the CLL4 group on the basis of the oral formulation bioavailability and on the ground that the total dose for one cycle should be spread over 5 days (instead of 3 days for the IV regimen) in order to minimise potential gastro-intestinal side effects.]

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.

[The unique mode of action of fludarabine, which affects DNA and RNA synthesis, including DNA repair, suggested that this agent could be used in combination to potentiate the effect of other drugs.

The mode of action of fludarabine and cyclophosphamide suggest that the 2 classes of drugs may be synergistic as the repair of the DNA damage created by the alkylating agents (such as cyclophosphamide) may be interfered with by purine analogues (such as fludarabine). This synergy was confirmed by demonstrating that the DNA repair that occurs after exposure to cyclophosphamide is blocked by fludarabine by its inhibition of DNA polymerase which is required for DNA repair [Kohl et al. 1997[3]].

Following on this, the MD Anderson Cancer Center have tested various drugs in combination with fludarabine and found cyclophosphamide to be the most promising, with high level of responses in both untreated and previously treated patients [Keating et al. 1996[4]][O'Brien S et al. 1996[5]]. This synergy was again confirmed *in vivo* in many different trials [Flinn et al, 2000[6], O'Brien et al 2001, reference 21]. There are now 3 studies which have been reported in 3 different countries showing superiority of FC compared to F: one in the USA [Flinn et al, 2004, reference 13] , one in Germany [Eichhorst et al, 2006, reference 1], and now CLL4 in the UK [Catovsky et al, 2005, reference 11].

It has also been demonstrated that fludarabine single agent confers higher response rate and longer progression free survival than CAP [Johnson et al, 1996, reference 71], or chlorambucil [Rai K et al, 2000, reference 9]. Fludarabine in combination with chlorambucil induced a degree of myelosuppression and led to discontinuation in a large US trial [Rai et al, 2000, reference 9].

In relation to the combination of fludarabine with other anthracyclines, further studies may be needed to evaluate the combinations of fludarabine plus doxorubicin and fludarabine plus epirubicin (E). Studies have been limited and there is no head-to head comparison between FC and FE. Following the result of a small phase II trial [Rummel M et al, 1999[7]] testing the combination of fludarabine IV 25 mg/m^2 per day over 5 days and epirubicin 25 mg/m^2 on day 4 and 5 to a maximum of 6 cycles, an overall response rate of 92 % (CR 40%) was demonstrated in 32 patients in first line or first relapse treatment. The preliminary results of the phase III have been presented at ASH 2005 [Rummel M et al, 2005, reference 23] and showed in 150 patients with CLL receiving first line therapy that the ORR was 88% (CR= 29%) for FE (n = 73) and was 73% (CR = 9%) for fludarabine single agent (n = 77). By comparison, in the CLL-4 study, the ORR was 91% (CR = 38%) for FC (n = 196) and 77 % (CR= 15%) for fludarabine single agent (n = 194).

Treatment with fludarabine (+/- cyclophosphamide) within the CLL4 trial is currently recommended for 1st line treatment of CLL as an alternative to chlorambucil in the BCSH guidelines on the management of CLL. Although enrolment in this trial is now closed new guidelines are expected following the outcomes of this study. Further to this the original review of the second line appraisal of fludarabine was delayed by NICE pending the outcomes of the UK CLL4 trial (communication with NICE – Jan 2005)]

References

[1] Keating M et al. Early results of a chemoimmunotherapy regimen of fludarabine, cyclophosphamide and rituximab as initial therapy for chronic lymphocytic leukaemia. Journal of Clinical Oncology. 2005; 23: 4079-4088.

[2] Struck R et al. Plasma pharmacokinetics of cyclophosphamide and its cytotoxic metabolites after intravenous versus oral administration in a randomised crossover trial. Cancer Research 1987: 47: 2723-2726.

[3] Kohl et al. Synergistic cytotoxicity using cyclophosphamide and nucleoside analogues (abstract). Annal of Hematology; 1997; 74: 75

[4] Keating et al. Clinical Experience with fludarabine in haemato-oncology. Hematology and cell therapy; 1996: 38:S83-91

[5] O'Brien S et al. Fludarabine and cyclophosphamide therapy in chronic lymphocytic leukaemia. Blood 1996; 88: 480a

[6] Flinn IW et al. Fludarabine plus cyclophosphamide with fligastrim supports in patients with previously untreated indolent lymphoid malignancies. Blood 2000; 96: 71-75.

[7] Rummel M et al. Fludarabine and epirubicin in the treatment of chronic lymphocytic leukaemia: a German multicenter phase II study. Annals of Oncology 1999; 10: 183-188.