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Dear Chris

STA: Fludarabine for the treatment of lymphocytic leukaemia - Appraisal consultation document

I outline in this document our formal response to the appraisal consultation document for the recent appraisal of fludarabine. Our response is organised under the headings specified in your letter.

1. Appraisal consultation document

1.1 Consideration of relevant evidence

- Schering strongly believe that NICE should include the combination of fludarabine and cyclophosphamide within this appraisal. The SmPC for fludarabine does not mention its use in combination with cyclophosphamide however formal clarification from the MHRA has shown that this does not preclude its use in combination. According to the MHRA (see attached- MHRA.doc), "...*Malignancies very often require multiple drugs (and other therapies) and clinicians, expert groups, formulary committees etc are entitled to use/recommend drugs in combination as they see fit.*" Consideration should therefore be given to the evidence presented for combination use.
- Section 3 of the appraisal consultation document provides a summary of our submission giving key results from the UK CLL4 trial and the cost effectiveness analysis. The incremental cost effectiveness ratio for fludarabine plus cyclophosphamide (FC) compared with chlorambucil, the currently most commonly used first line treatment has been omitted from the summary. The incremental cost effectiveness ratio is £3,244 per quality adjusted life year and this should be included.
- No consideration is given to the budget impact associated with a positive recommendation for fludarabine plus cyclophosphamide (FC). Switching patients from current management would increase costs in the first year by around £3.3m, but lower costs of subsequent treatment with FC treated patients in this timeframe mean that the budget impact in year 5 would be negligible, with an annual expenditure in year 5 estimated to be £24.2 vs. £23.5 million with current treatment.

1.2 Interpretation of the clinical and cost effectiveness evidence

- The UK CLL4 trial, which compared chlorambucil with fludarabine, either as a monotherapy or in combination with cyclophosphamide is the only study to compare all three treatments relevant to the decision problem within the same population. This is the key trial upon which the submission is based. The trial is sponsored by the Leukaemia Research Fund and patient level data were kindly provided by the Principal Investigators to Schering Health Care for the purposes of this submission. Whilst we recognise this trial is currently unpublished in full it has been presented extensively in abstract form and a full manuscript is in preparation for publication in 2007. Whilst we appreciate the results cannot be verified, the speed of the STA process precludes drafting, peer review and publication of the trial results prior to the NICE submission.

- The incremental cost effectiveness ratio for fludarabine plus cyclophosphamide (FC) compared with chlorambucil, the currently most commonly used first line treatment is £3,244 per quality adjusted life year. Results of the probabilistic sensitivity analysis reported by the Evidence Review Group report that at a willingness to pay of £30,000 per QALY the probability that FC is cost effective is 0.90, thus demonstrating clearly the cost effectiveness of this treatment in the management of CLL.
- There is some criticism of the lack of efficacy data for patients receiving retreatment with fludarabine plus cyclophosphamide (FC). The CLL4 trial is ongoing and retreatment data are not yet available. A thorough search of the clinical literature was taken to identify suitable values and in the absence of clinical data extensive sensitivity analyses were conducted.
- It appears that some concerns have been raised as to whether the improvement in progression free survival with fludarabine treatment will translate into improved overall survival. The nature of oncology means that after initial treatment patients will ultimately progress and go on to receive subsequent lines of therapy over time, including a range of therapeutic regimens. For this reason it is very difficult to determine the impact of first line treatment on overall survival and therefore progression free survival has become recognised as a suitable proxy for overall survival in this field.
- Although the cost of adverse events are not included in the economic model, sensitivity analysis shows that even if the total cost of treatment for fludarabine plus cyclophosphamide (FC) was increased from £3580 to £10,350 per course of therapy the cost effectiveness would remain less than £20,000 per QALY.
- Regarding the expert comments, we believe that Professor Hamblin's perception of the side-effects of fludarabine doesn't fully reflect the scientific evidence from both our pharmacovigilance database and from what has been reported in the literature. In particular we do not believe that there is an increased risk of second malignancy with fludarabine and there is no increase of Richter's transformation associated with fludarabine. In addition, we have also reviewed the incidence of MDS/AML in patients who have received fludarabine, and we do not believe at this stage that there is an increased risk with fludarabine, above other treatments for CLL. However, our pharmacovigilance department are monitoring this closely. We are aware of a number of publications reporting on series of patients who have developed MDS/AML, but we believe that the methodology of most these studies are seriously flawed.

1.3 Provisional recommendations of the appraisal committee

- The provisional recommendations of the appraisal committee fail to consider the use of fludarabine and cyclophosphamide (FC) in combination. Clinical data clearly demonstrate that the reduced dose of fludarabine when used as part of this combination regimen demonstrates significant improvements in response rate and response duration, at a reduced cost to fludarabine monotherapy. The FC treatment option therefore dominates fludarabine monotherapy and has a cost per QALY of £3,244 when compared with chlorambucil. This cost effectiveness ratio is relatively insensitive to variation in inputs and assumptions.

2. Evaluation Report

2.1 Interpretation of the clinical and cost effectiveness evidence

- The results of the seminal study by Rai and colleagues [NEJM, 2000, 343: 1750-1757] have not been reported accurately. Within the results section (page 26 of the evidence review group report) progression free survival is stated as being 20 months for F versus 14 months for FC, but the latter treatment should have been reported as

Chlorambucil (PFS difference between F and Chlorambucil, $p < 0.001$). The same typo error is also repeated on page 19 within the table of the summary of trials. The correct data is listed on page 39.

- We would like to point out that in chapter 2 of the evidence review group report, section 2.1.4, that the description of treatment is incorrect. The reference 17 [ESMO guidelines, 2005] does not state that "patients with advanced or progressive disease should be initiated with fludarabine in combination with either chlorambucil or chlorambucil with rituximab", but recommends that the patients should receive fludarabine in combination with cyclophosphamide.

Yours sincerely

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