CONFIDENTIAL

Fludarabine for the treatment of chronic lymphocytic leukaemia

Premeeting briefing

This briefing presents major issues arising from the manufacturer's submission (MS), evidence review group (ERG) report and personal statements made by nominated clinical specialists and patient experts. Please note that although condensed summary information is included for ease of reference, this briefing should be read in conjunction with the full supporting documents.

The manufacturer was asked to provide additional clarifications on the CLL4 study, clinical and cost effectiveness data, structure of the economic model and uncertainty in the economic analysis.

Abbreviations

CLL	chronic lymphocytic leukemia
ERG	evidence review group
ICER(s)	incremental cost effectiveness ratio(s)
MS	manufacturer's submission
OS	overall survival
PFS	progression-free survival
QALYs	quality adjusted life years
SA	sensitivity analysis

Licensed indication

Fludarabine (Fludara, Schering Health Care) is licensed for the treatment of B-cell chronic lymphocytic leukaemia (CLL) in patients with sufficient bone marrow reserves.

First-line treatment with fludarabine should only be initiated in patients with advanced disease, Binet stage C (Rai stages III/IV) or Binet stage A/B (Rai stages I/II) where the patient has disease-related symptoms or evidence of progressive disease.

Key issues for consideration

Clinical effectiveness

- Is the fludarabine plus cyclophosphamide combination regimen compatible with the marketing authorisation for fludarabine, as suggested by the manufacturer?
- Is there robust evidence presented on the clinical effectiveness of the fludarabine-containing regimens in comparison to chlorambucil?

Cost effectiveness

- What are the implications of the uncertainties in the manufacturer's economic model and analyses?

1 Decision problem

1.1 Decision problem approach in the MS

Population	Patients with B-cell CLL who have advanced symptomatic Binet stage B or C disease or evidence of progressive disease in Binet stage A[1], and who are chemotherapy naïve and have sufficient bone marrow reserves.
Intervention	Fludarabine monotherapy. Fludarabine in combination with cyclophosphamide.
Comparators	Chlorambucil.
Outcomes	Primary outcomes: progression-free survival (PFS), health-related quality of life. Secondary outcomes: treatment response rates, incidence of adverse events, overall survival (OS).

[1] The clinical course of CLL disease is usually reported using Binet or Rai staging (see tables 3 and 4 on page 24 of the MS).

1.2 ERG comments on the MS

1.2.1 Population

The principal source of evidence in the MS is the CLL4 trial. However, the population defined in the decision problem does not exactly match that of the CLL4 trial. Within the licensed indication, first-line treatment of CLL with fludarabine should only be initiated in patients with sufficient bone marrow reserves and who have disease-related symptoms (Binet stage B or C) or evidence of disease progression in Binet stage A. In contrast, the CLL4 trial did not specify patients with sufficient bone marrow reserves and patients with non-progressive symptom-free Binet stage B disease were included in the trial. Independent expert opinion given to the ERG indicates that inclusion of patients with non-progressive Binet stage B disease is of negligible clinical significance because very few patients in clinical practice present without progressive Binet stage B disease.

1.2.2 Intervention

The 'Summary of product characteristics' (SPC) for fludarabine does not mention its use in combination with cyclophosphamide. The MS states that various drugs have been used in combination with fludarabine but cyclophosphamide had the most promising synergistic effect in laboratory studies. Epirubicin has also been shown to have similar synergistic effects. Fludarabine plus chlorambucil was not considered because it did not improve treatment response rates and was associated with life-threatening toxic effects.

It is unclear whether fludarabine is licensed for use in combination with cyclophosphamide. The manufacturer considers the combination regimen to be licensed, and is not seeking an extension to the current license, because the SPC for cyclophosphamide states that it is indicated "in a wide range of neoplastic conditions, including leukaemias" and that "cyclophosphamide is frequently used in combination chemotherapy regimens involving other cytotoxic drugs".

1.2.3 Comparators

The alkylating agent chlorambucil is the most relevant comparator for the decision problem.

1.2.4 Outcomes

Since assessment of treatment effects on overall survival (OS) requires long trial follow-up periods, PFS was taken as a surrogate endpoint for OS. However, the relationship between PFS and OS is unclear. Health-related quality of life was measured in the CLL4 trial using a disease-specific quality of life instrument that does not provide overall quality of life measurements.

On balance, the decision problem presented in the MS is reasonable and appropriate and appears to be supported by the British Committee for Standards in Haematology (BSCH) guidelines and existing literature.

1.3 Clinical specialists' and patient experts' statements

1.3.1 It is standard practice for the treatment of CLL to be deferred until patients experience disease-related symptoms or show clear signs of progression. Although the exact point of diagnosis of CLL is arbitrary, most patients require treatment at some stage and chlorambucil has for many years been the mainstay of first-line treatment.

1.3.2 None of the CLL trials showing a PFS advantage with fludarabine-containing regimens have shown beneficial effects on OS over and above that achieved with chlorambucil. A recent Cochrane Collaboration meta-analysis of clinical studies involving fludarabine and chlorambucil alone or in combination showed no additional benefits in OS with fludarabine in the treatment of CLL. One of the clinical specialists stated that historical data show that survival from first-line treatments is improving in successive cohorts of patients in a way that cannot be explained by patient selection or timing of treatments. The evidence suggests that new chemotherapeutic agents may have an impact on OS and this may have been masked by

crossover effects of second-line therapy within the various CLL trials. Historical controls, on the other hand, are noted to be unreliable.

1.3.3 The International Workshop in CLL, faced with the difficulties of differentiating treatment effects on OS, formally agreed to use PFS as a surrogate endpoint for OS. However, one of the clinical specialists stated that the use of response rates and PFS as surrogate endpoints for OS may be misleading in chronic haematological malignancies as was evident from the thalidomide/double autograft trial in multiple myeloma[2].

2 Clinical effectiveness evidence

2.1 Clinical effectiveness in the MS

Summary of results from the CLL4 trial at median follow-up of 45 months (see full details in the MS, pages 41-49)

Outcome measure	n= intention to treat (ITT) number of evaluable patients		
	Fludarabine n=194	Fludarabine+ cyclophosphamide n=196	Chlorambucil n=387
Overall response (%) p value	[redacted]	[redacted]	[redacted]
Complete response (%) p value	[redacted]	[redacted]	[redacted]
Median duration of response	[redacted]	[redacted]	[redacted]
3-year progression-free survival[3] p value	31% Not reported	62% Not reported	23% Not reported
Median progression-free survival	[redacted]		
Median overall survival	[redacted]		

[2] Barlogie, B. et al (2006). Thalidomide and hematopoietic-cell transplantation for multiple myeloma. New England Journal of Medicine 354: 1021-1030

[3] 3-year progression free survival (PFS) data are early results from the CLL4 trial presented in an abstract by Catovsky, D., S. Richards, and P. Hillmen. ASH Annual Meeting Abstracts 2005. 106(11): p. 716.

2.2 ERG comments

2.2.1 Of the seven studies identified to inform the clinical effectiveness of the fludarabine-containing regimens, only two were fully published. Insufficient data meant a robust meta-analysis was not possible and pooling data from abstracts would not add further insights to the decision problem. Until the complete data are made available for evaluation, the clinical effectiveness evidence in the MS has to be interpreted with caution. Results of the CLL4 trial presented are based on unpublished data that is incomplete as trial follow-up is ongoing. In addition, patients and investigators in the CLL4 trial were not blinded to the treatments given.

2.2.2 The MS states that significant improvements in PFS and time without treatment are associated with quality of life improvements in the fludarabine-containing arms of the CLL4 trial, but no reference is made to the impact of increased hospitalisations within these groups on quality of life. Trial data show more incidents of neutropenia and thrombocytopenia with fludarabine plus cyclophosphamide than with fludarabine monotherapy or chlorambucil. Incidence of non-haematological toxicities with the fludarabine-containing regimens was also higher than with chlorambucil.

2.3 Clinical specialists' and patient experts' statements

2.3.1 Clinical experience with the fludarabine containing regimens reflects the clinical trial results, providing higher response rates and longer remissions. However, patients who are elderly or frail or those with significant co-morbidities are likely to be excluded from CLL trials involving fludarabine treatments. For less fit patients who cannot tolerate the toxicity of the fludarabine-containing regimens, chlorambucil is a useful and valid treatment option. One of the patient experts stated that some patients continue to respond to chlorambucil after relapse without a switch to fludarabine-containing regimens and

the associated treatment related side effects of the fludarabine-containing regimens.

2.3.2 Fludarabine treatments are heavily immunosuppressive and infections are the most common adverse event. In the CLL4 trial, the incidences of neutropenia and hospitalisation due to infections were approximately twice as high in the fludarabine-treated group as in the chlorambucil-treated group. Many patients have had their treatment terminated early because of low white cell count. For some patients these immunosuppressive effects may be irreversible and affected patients have to live with an immune system that has been impaired by treatment as well as a cancer of the immune system. Clinicians' decision to use fludarabine chemotherapy can have a negative impact on a patients' emotional wellbeing because some patients perceive fludarabine treatment to signal a worsening of their CLL disease.

2.3.3 Damage to stem cells by fludarabine-containing treatments is believed to account for the development of treatment-related acute myeloid leukemia or myelodysplastic syndrome (tAML/MDS) in 5–10% of patients. This risk increases with use of combination regimens consisting of different classes of anticancer agents. Another adverse event associated with fludarabine-containing regimens is the occurrence of auto-immune haemolytic anaemia.

2.3.4 One of the clinical specialists stated that, within the international CLL community, it has been suggested that chlorambucil should be used as the first-line treatment and that fludarabine plus cyclophosphamide should be reserved for second-line treatment. The use of fludarabine plus cyclophosphamide as a first-line treatment would reduce the treatment options for second-line therapy. Long-term disease control using chlorambucil as the first-line treatment followed by fludarabine plus cyclophosphamide is likely to be similar to first-line treatment with fludarabine plus cyclophosphamide alone. Using chlorambucil followed by fludarabine plus cyclophosphamide is, however,

associated with increased toxicity, inconvenience, expense and impaired quality of life because two courses of chemotherapy are needed.

2.3.5 One of the patient experts expressed concerns that some oncologists would use fludarabine-containing regimens as the first-line treatment, instead of a better tolerated treatment that is likely to be as effective. Because fludarabine-containing regimens have serious side effects, they should not be used as a substitute for a watch and wait strategy which considers the stage of the disease and degree of progression. Fludarabine should be only used in patients who require aggressive treatment approaches.

3 Cost effectiveness evidence

3.1 Cost effectiveness in the MS

Revised base-case ICERs presented by the manufacturer following clarifications requested by the ERG (see the MS and ERG report for further details).

Treatment strategy[4]	Costs	Outcomes (QALYs)	ICER against chlorambucil	ICER against fludarabine
Chlorambucil	£11,920,074	5248	-	-
Fludarabine	£17,712,428	5469	£26,105	-
Fludarabine plus cyclophosphamide	£13,919,492[5]	5864	£3244	Dominates

[4] Costs and QALYs estimated for 1000 patients in the economic model

[5] In the course of making revisions requested by the ERG a calculation error in the fludarabine plus cyclophosphamide arm was identified and corrected. Fixing this error increased expected cost in the fludarabine plus cyclophosphamide arm by almost 2% from £13,657,485 to £13,919,492 per patient.

3.2 ERG comments

3.2.1 Economic analysis in the MS is based on a Markov decision analytic model with a 20-year time horizon. The economic model, however, differs from the decision problem because it does not specify patients with sufficient bone marrow reserves and includes patients with stage B non-progressive disease (see pages 57–58 of the ERG report for a critical appraisal checklist of the manufacturer's economic model). However, these differences are unlikely to affect the results of the economic analysis.

3.2.2 Uncertainty in the economic analysis relates to the methods used to estimate transition probabilities and the assumption that transition probabilities are constant over the lifetime horizon. One-way sensitivity analyses (SAs) presented in the MS show the time horizon and retreatment response rates with the same chemotherapeutic agent to be the key drivers of cost effectiveness ratios. The disparities between ICERs for 5-year, 10-year and 15-year time horizons (see table 5.17, page 79 of the ERG report) suggest that approaches to the extrapolation of model data over time are likely to be central to the validity of the cost effective ratios in the MS.

3.2.3 The ERG indicated that with the availability of individual patient data from the CLL4 trial, it would be more appropriate to apply formal survival analytic techniques to test the assumption of constant transition probabilities. To test this assumption, the ERG fitted a parametric Weibull regression model to the patient level data from the CLL4 trial (see section 6.4.1, pages 87–89 of ERG report). The results of the survival analysis show a non-constant, increasing risk (hazard rate) over time for disease progression for both responders and non-responders and a non-constant, increasing risk (hazard rate) of death for responders for all of the treatments. Incorporating the results of a formal survival analysis into the economic model to assess the impact on the economic results, however, requires major restructuring of the model that is beyond the remit of the ERG.

3.2.4 The manufacturer's economic model was structured on patient level data from the CLL4 trial such that censored/unobserved patients from the trial enter the economic model in the state in which they were censored, with subsequent transition probabilities derived from data on uncensored/observed patients in the trial. The MS states that a conservative approach was taken to equalising OS across the treatments in the economic model, since survival data from CLL4 trial is not complete enough to show differences in OS. The conservative approach involved offsetting the higher treatment responses, longer duration of response and PFS of the fludarabine-containing treatments with a subsequently higher mortality following disease progression. The ERG checked the external consistency of the economic model against data from the CLL4 trial by looking at 5-year mortality data for both observed and unobserved patients. The analysis showed the fludarabine-containing regimens to have higher observed mortality in the CLL4 trial than chlorambucil, although this was not statistically significant. In contrast, the fludarabine-containing regimens had a lower unobserved/censored mortality than chlorambucil in the economic model (see section 5.6.2 and figure 5.1, pages 73–74 of the ERG report).

3.2.5 The manner in which survival equalisation was implemented in the economic model means that people in the fludarabine and fludarabine plus cyclophosphamide arms spend less time in salvage treatment states that are associated with lower utilities and additional costs. It appears the higher observed mortality data in the CLL4 trial has not been correctly used and the extrapolation of a lower unobserved/censored mortality for the fludarabine-containing regimens over a longer time horizon in the economic model potentially could have a large effect of biasing cost effectiveness ratios in favour of the fludarabine-containing regimens. However, it is unclear whether the inclusion of observed mortality data from the CLL4 trial in the economic model in an appropriate way would change the economic results. The current higher observed mortality in the CLL4 trial may be

due to chance and until more complete survival data is reported from the CLL4 trial it cannot be confirmed whether the manufacturer's approach to equalising OS is conservative or not (see sections 5.5.4, pages 66–67 of the ERG report).

3.2.6 The ERG noted that retreatment response rates for the fludarabine plus cyclophosphamide regimen was assumed (in the absence of supporting data) to be the same as first-line treatment response. This assumption effectively double counts first-line treatment response rates for fludarabine plus cyclophosphamide. In contrast, retreatment response rates for fludarabine monotherapy and chlorambucil are lower than that applied for first-line treatment. Since first-line treatment response rates and hence retreatment response rates for fludarabine plus cyclophosphamide are higher than that of the other treatments, the model potentially biases cost effectiveness ratios in favour of fludarabine plus cyclophosphamide (see section 6.2, pages 83–85 of the ERG report).

3.2.7 Because retreatment response rates were estimated from very limited data, the MS presents a one-way SA in which retreatment response rates were assumed for all the treatments to be equal to first-line treatment response. The SA shows for fludarabine monotherapy against chlorambucil, an increase from the base-case of £26,105 to £86,770 per QALY. For fludarabine plus cyclophosphamide against chlorambucil, the ICERs appear robust to retreatment response rates with the base-case increasing from £3,244 to £4,185 per QALY. The ERG however does not consider the SA for fludarabine plus cyclophosphamide to be sufficiently robust as the range of values used were based on the 95% confidence interval for the bootstrap of first-line treatment response rates from the CLL4 trial. The range of values used does not correct the potential bias introduced by assuming that retreatment response with fludarabine plus cyclophosphamide is the same as first-line treatment response.

3.2.8 Results of additional analyses carried out by the ERG in which retreatment response rates for fludarabine plus cyclophosphamide varied between 10% and 90% show that if retreatment response rates are less than 30%, fludarabine plus cyclophosphamide no longer appears cost effective. The ERG report stated that further evidence on the retreatment response rates of fludarabine plus cyclophosphamide is needed to clarify uncertainties in cost effectiveness ratios.

3.2.9 In addition, the ERG noted that the response rates for fludarabine-containing regimens as second-line treatments have been estimated from pooled data from single arms of different trials in a way that ignores the randomised structure of clinical trials. Differences in estimates of response rates of second-line treatments used in the economic model may be due to different population characteristics of the studies from which data were pooled. Despite the lack of head-to-head trials comparing fludarabine, fludarabine plus cyclophosphamide and chlorambucil simultaneously, evidence syntheses using mixed treatment comparisons could have been used to inform and increase the precision of data used in the economic model.

3.2.10 The ERG expressed concerns about the failure to incorporate the impact of adverse events on treatment costs in the economic model, the appropriateness of using utility values that were not measured with a preference-based instrument and the costing of treatments based on a small section of the CLL4 trial population with a high proportion of non-progressive Binet stage B disease who may have low resource utilisation rates. Further, the ERG report stated that the limited sequence of treatments considered in the economic model excludes alternative treatment sequences which may be more efficient. The choice of retreatment and second-line strategies could influence the cost effectiveness ratios of the first-line treatments.

3.2.11 Although the ICERs presented in the MS tended to be biased in favour the fludarabine containing regimens, the current structure of the

economic model and the absence of adequate supporting data makes it is difficult to determine the magnitude of any bias that may be introduced by the uncertainties and issues identified (see section 5.8, page 82 of the ERG report for a summary). For an accurate assessment of cost effectiveness, additional evidence is needed to clarify uncertainties in the economic analysis of the fludarabine-containing regimens and chlorambucil in the first-line treatment of CLL.

4 Authors

4.1.1 Ebenezer Tetteh and Eleanor Donegan, on behalf of the Committee Chair (David Barnett) and the Lead Team (Kate Thomas and Richard Lilford).