PUBLIC SUMMARY DOCUMENT
Product: Fludarabine phosphate, tablet 10 mg , injection 50 mg , Fludara®
Sponsor: Bayer Australia Ltd
Date of PBAC Consideration: March 2008

1. Purpose of Application

The submission sought a section 85 Authority Required listing for the treatment of B-cell chronic lymphocytic leukaemia (CLL).

2. Background

At the March 1998 meeting, the PBAC rejected an application to list fludarabine powder for injection 50 mg on the basis that the high incremental cost-effectiveness ratio was unacceptable in view of the lack of details on the quality of life (QoL) of the patient.

At the September 2002 meeting, the PBAC rejected a submission for fludarabine 10 mg tablets for an authority required listing for second-line treatment in patients with CLL. The application was rejected in view of uncertain clinical benefit and an uncertain, but high, cost-effectiveness ratio. The PBAC also considered that any restriction to list would need to specify pathology requirements for diagnosis of CLL to minimise use outside the proposed restriction in other conditions such as non-Hodgkin's lymphoma.

At the March 2004 meeting, the PBAC rejected an application for fludarabine 10 mg tablets for second-line treatment of CLL because of uncertainty in the nature and extent of clinical benefit in the proposed population and the resulting uncertain cost-effectiveness.

3. Registration Status

Fludarabine was TGA registered on 20 June 1995 for use as second-line therapy in patients with chronic lymphocytic leukaemia (CLL). Fludarabine was TGA registered on 6 April 2004 for the treatment of B-cell chronic lymphocytic leukaemia.

4. Listing Requested and PBAC's View

Authority required

Treatment of B-cell chronic lymphocytic leukaemia in combination with an alkylating agent where the patient has advanced disease (Binet stage B or C) or evidence of progressive disease.

Stage A progressive disease is defined by at least one of the following: persistent rise in lymphocyte count with doubling time less than 12 months; a downward trend in haemoglobin or platelets, or both; more than 50% increase in the size of liver, spleen, or lymph nodes, or appearance of these signs if not previously present; constitutional symptoms attributable to disease.

The diagnosis of CLL must have been established based on:

- a lymphocytosis, with $\geq 5 \times 10^9$ lymphocytes/L in the peripheral blood; and
- a clonal population of B-cells (CD5/CD19) documented by flow cytometry.

The PBAC had no objections to the requested wording of the restriction.

5. Clinical Place for the Proposed Therapy

Chronic lymphocytic leukaemia (CLL) is a slow growing cancer that affects the blood and bone marrow. The bone marrow produces too many immature lymphocytes, which crowd the marrow, interfering with normal blood cell production and the body's ability to fight infection. Over time, a shortage of red cells and platelets can also occur, causing anaemia, bleeding and/or bruising.

Fludarabine would provide a treatment alternative for patients with advanced or progressive CLL.

6. Comparator

The submission nominated chlorambucil as the main comparator. The PBAC accepted this as appropriate.

7. Clinical Trials

The re-submission presented one direct randomised comparative trial comparing fludarabine and cyclophosphamide (FC), chlorambucil monotherapy, and fludarabine monotherapy, with a median duration of follow-up of 41 months (trial CLL4); two supplementary randomised comparative trials comparing FC and fludarabine monotherapy, with a median duration of follow-up of 22 and 24 months, respectively (Eichhorst et al, 2006; Flinn et al, 2007); and one meta-analysis of the aforementioned direct randomised comparative trials comparing FC and fludarabine monotherapy in untreated patients with CLL.

Details of the published studies are presented are in the table below.

Trials and associated reports presented in the re-submission

Trial ID	Publication title	Publication citation
Direct randomised trial		
Catovsky 2007 (CLL4)	Catovsky D, Richards S, Matutes E, Oscier D, Dyer MJS, Bezares RF et al Assessment of fludarabine plus cyclophosphamide for patients with chronic lymphocytic leukaemia (the LRF CLL4 Trial): a randomised controlled trial	*Lancet* 2007; 370:230-9
Supplementary randomised trials		
Eichhorst 2006	Eichhorst BF, Busch R, Hopfinger G, Pasold R, Hensel M, Steinbrecher C et al Fludarabine plus cyclophosphamide versus fludarabine alone in first-line therapy of younger patients with chronic lymphocytic leukaemia	*Blood* 2006; 107:885-91
	Eichhorst BF, Busch R, Obwandner T, Kuhn-Hallek I, Herscbach P, Hallek M Health-related quality of life in younger patients with chronic lymphocytic leukaemia treated with fludarabine plus cyclophosphamide or fludarabine alone for first-line therapy: a study by the German CLL Study Group	*Journal of Clinical Oncology* 2007; 25(13):1722-31
	Eichhorst BF, Busch R, Schweighofer C, Wendtner CM, Emmerich B, Hallek M and the German CLL Study Group (GCLLSG) Due to low infection rates no routine anti-infective prophylaxis is required in younger patients with chronic lymphocytic leukaemia during fludarabine-based first line therapy	*British Journal of Haematology* 2007; 136(1):63-72
	Hallek M, Schmitt B, Wilhelm M	*British Journal*

	Fludarabine plus cyclophosphamide is an efficient treatment for advanced chronic lymphocytic leukaemia (CLL): results of a phase II study of the German CLL Study Group	*of Haematology* 2001; 114(2):342-8
Flinn 2007	Flinn IW, Neuberg DS, Grever MR, Dewald GW, Bennett JM, Paietta EM et al Phase III trial of fludarabine plus cyclophosphamide compared with fludarabine for patients with previously untreated chronic lymphocytic Leukaemia: US Intergroup Trial E2997	*Journal of Clinical Oncology* 2007; 25:793-8
	Grever MR, Lucas DM, Dewald GW, Neuberg DS, Reed JC, Kitada S et al Comprehensive assessment of genetic and molecular features predicting outcome in patients with chronic lymphocytic leukemia: results from the US Intergroup Phase III Trial E2997	*Journal of Clinical Oncology* 2007; 25(7):799-804

8. Results of Trials

Overall survival

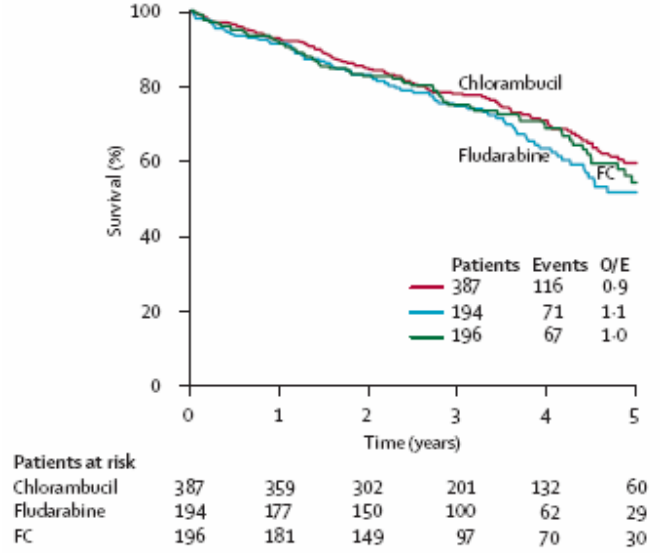
Results for overall survival (OS) from trial CLL4 are presented below.

Trial CLL4 - overall survival

Treatment	Number of events, n/N (%)	5-year OS, % (95% CI)
FC	67/196 (34)	54 (44, 64)
CHL	116/387 (30)	59 (53, 66)
Relative risk reduction		15%, p=0.4

Abbreviations: CHL = chlorambucil; FC = fludarabine + cyclophosphamide; OS = overall survival.

Trial CLL4 – overall survival by treatment group[a]



chlorambucil

fludarabine

FC

[a] follow-up to July, 2006. p-value for heterogeneity for survival = 0·4; FC = fludarabine + cyclophosphamide; O = observed; E = expected

There was no statistically significant difference in the primary outcome, overall survival (OS), between patients randomised to FC or chlorambucil. The PBAC considered that this result was difficult to interpret given:

(i) the use of subsequent therapies, which are determined somewhat by first-line therapy;

(ii) the absence of complete data regarding second-line treatments; and

(iii) the duration of the trial, which may not be long enough to show a difference in OS.

The PBAC noted that the event rate was 50% and the number of patients still at risk at the end of the trial was very low, so that the trial duration was probably sufficient to detect a difference in survival if one was present. The absence of difference in survival was consistent with the findings the two supportive trials. It was suggested that the large number of censored subjects may be confounding the results (100 in the fludarabine and FC arms and 200 in the chlorambucil arm), although this appears to be non-differential and is consistent with the other trials presented.

The PBAC accepted that this result was highly confounded, as most of the patients in the chlorambucil alone arm went on to receive combination FC therapy within a year of commencing on the study.

Progression-free survival

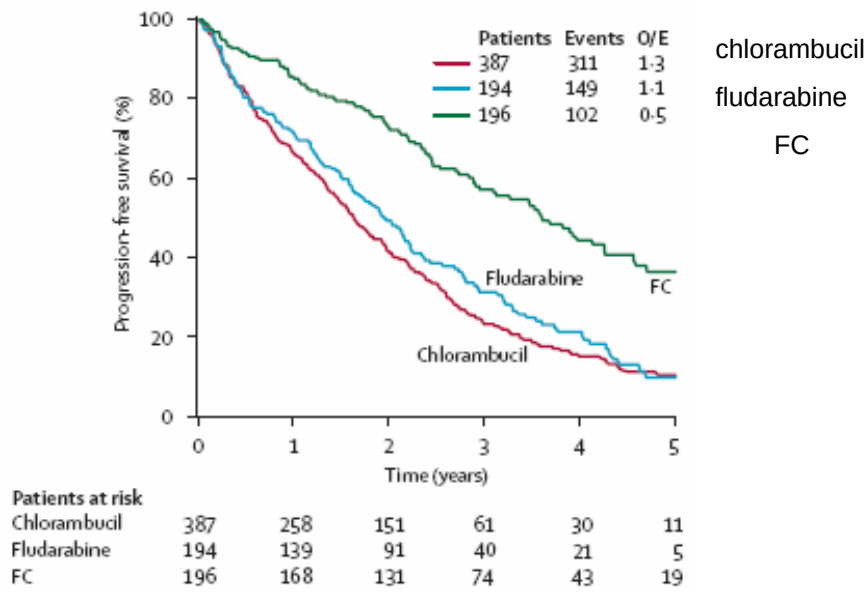
Results for progression-free survival (PFS) from trial CLL4 are presented below.

Trial CLL4 – progression-free survival

Treatment	Number of events, n/N (%)	5-year PFS, % (95% CI)	Median PFS, years, months (range)
FC	102/196 (52)	36 (28, 46)	3.6 (2.9 – 4.3)
CHL	311/387 (80)	10 (6, 15)	1.7 (1.5 – 1.8)
HR (95%CI), p-value	0.45 (0.37, 0.54), p<0·00005		

Abbreviations: CHL = chlorambucil; FC = fludarabine + cyclophosphamide; HR = hazard ratio; PFS = progression-free survival.

Trial CLL4 – progression-free survival by treatment group[a]



[a] follow-up to July, 2006. p value for heterogeneity for survival = 0.4. Log rank for progression-free survival: FC chlorambucil p<0.00005; FC = fludarabine + cyclophosphamide; O = observed; E = expected

The PBAC noted that FC resulted in a statistically significant increase in PFS compared with either chlorambucil or fludarabine monotherapy. The median PFS increased by almost 2

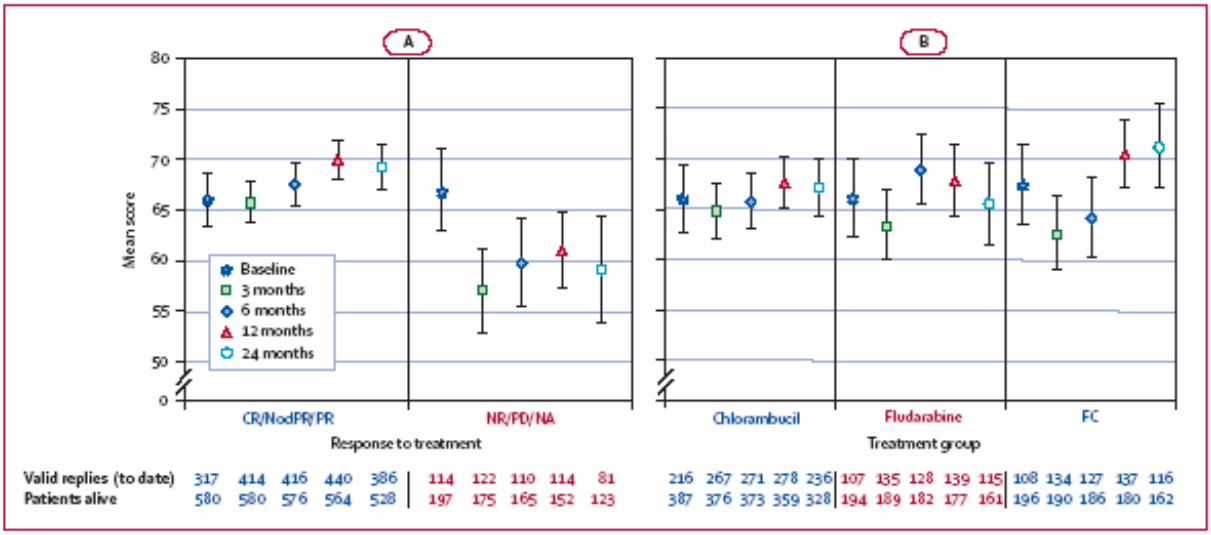
years with FC compared with chlorambucil and at 5 years 36% of FC patients remained progression free versus 10% of chlorambucil patients.

Quality of life (QoL)

Results for quality of life (QoL) from trial CLL4 are presented below.

There was no statistically significant or clinically important difference in the mean QoL score between the treatment arms, despite the statistically significant differences in PFS in the FC versus the chlorambucil treatment arm. Trial CLL4 was open-label in design, therefore important biases may not have been minimised when assessing comparative QoL.

Mean QoL scores by response to treatment and treatment group



Abbreviations: A = mean QoL by response to treatment; B = mean QoL by treatment group; CR = complete remission; FC = fludarabine + cyclophosphamide; NA = not assessable; NodPR = nodular partial remission; NR = no response; PD = progressive disease; PR = partial remission.

Oral versus I.V. Fludarabine

A retrospective analysis of oral versus IV FC from trial CLLL4 reported higher response rates for IV versus oral administration (see table below). However, these results should be interpreted in the context of a post hoc sub-group analysis.

Response rates for fludarabine and FC by route of administration, post hoc analysis

Treatment	**FC**			**Fludarabine**		
Route of administration	**IV**	**Oral**	**p-value**	**IV**	**Oral**	**p-value**
Number received treatment	55	116		51	107	
Number not assessable	15			6		
CR/NPR, %	73	59	NR	54	41	NR
No response, %	2	10	0.04	8	26	0.02

Abbreviations: FC = fludarabine + cyclophosphamide; IV = intravenous; CR = complete remission; NPR = nodular partial remission; NR = not reported.

The re-submission presented new toxicity data. In trial CLL4, there was a clinically important increase in the incidence of the following in the FC treatment arm versus the chlorambucil treatment arm:

- serious adverse events (11%, 22/196 versus 4%, 14/380 respectively);
- neutropenia (56% versus 28% respectively);

- febrile episodes (35% versus 25% respectively);
- hospital admissions (38% versus 22% respectively);
- nausea and vomiting (53% versus 33% respectively);
- alopecia (27% versus 6% respectively); and
- 'other' grade 3 or 4 toxic effects (9% versus 3% respectively).

There was a trend towards more deaths in the FC treatment arm than the chlorambucil arm (2% versus 0.3% respectively). There was a greater incidence of haemolytic anaemia in the chlorambucil treatment arm versus the FC treatment arm (12% versus 5% respectively). One patient developed myelodysplasia 3 years after receiving five courses of FC.

It was reported that there were no significant differences in the main toxicities between oral and IV FC in trial CLL4. However, no data were provided to validate this conclusion.

From the new toxicity data from trial CLL4 presented in the re-submission, the PBAC agreed that FC appears to be more toxic than chlorambucil.

9. Clinical Claim

The re-submission describes fludarabine with cyclophosphamide as superior in terms of comparative effectiveness and inferior in terms of comparative safety, over chlorambucil.

See Recommendation and Reasons for PBAC's view.

10. Economic Analysis

The economic evaluation utilised a Markov model, which had a 15-year timeframe, and a 3-month cycle length. The model compared two treatment regimens for CLL, simulating the course of the disease using three health states: unprogressed; progressed; and death.

Movement between health states was determined by transition probabilities derived from hazard rates calculated from individual patient data reported in trial CLL4. The model was driven by: (i) the hazard rates used to extrapolate PFS beyond the trial duration; (ii) the disutility associated with progression; and (iii) the incremental treatment costs for FC.

A stepped economic evaluation was presented which produced an incremental discounted cost per extra discounted quality-adjusted life-year (QALY) gained of between $15,000 and $45,000.

See Recommendation and Reasons for PBAC's view.

11. Estimated PBS Usage and Financial Implications

The submission estimated a likely number of patients per year of less than 10,000 in Year 5 and a financial cost per year to the PBS (excluding co-payments and minus savings in the use of other drugs) of less than $10 million in Year 5 (assuming 4.6 cycles per patient). A sensitivity analysis assuming 6 cycles of FC estimated a financial cost per year to the PBS of between $10 - $30 million in Year 5.

12. Recommendation and Reasons

The PBAC recommended the listing on fludarabine on the PBS for the treatment of B-cell chronic lymphocytic leukaemia in combination with an alkylating agent where the patient has

advanced disease (Binet Stage B or C) or evidence of progressive disease on a cost-effectiveness basis against the main comparator, chlorambucil, at the price proposed.

In making this recommendation, the PBAC noted that treatment with fludarabine in combination with cyclophosphamide (FC) resulted in a statistically significant increase in progression-free survival in the key trial, CLL4, compared to treatment with either fludarabine or chlorambucil monotherapy. The Committee further noted that the new submission presents new toxicity data from trial CLL4, and members agreed that FC appears more toxic than chlorambucil.

Although the trial CCL4 did not demonstrate an improvement in overall survival in the FC treated group, the Committee accepted that this result is highly confounded, as most of the patients in the chlorambucil alone arm went on to receive combination FC therapy within a year of commencing on the study. Furthermore, the economic model does not include any improvement in survival in the FC arm, so the cost-effectiveness of fludarabine does not rest upon such a claim.

Progression free survival is used as a surrogate for QoL in the modelled evaluation, in that the model attributes a higher QoL score to patients who have not progressed as opposed to patients who have progressed. This distinction is based on numerical differences observed in trial CLL4 (patients in the FC group had lower QoL score at 3 and 6 months, but higher scores later), although the overall QoL score in FC arm was not statistically significantly different from the comparator arm. The QoL results from trial CLL4 are linked to utility values via the QoL results reported in Doorduijn et al (2005), which were derived from a population with Non-Hodgkin Lymphoma and a low international prognostic index.

The PBAC considered the model's approach to estimating disutility was acceptable. In reaching this view the Committee noted that trial CLL4 was underpowered to detect a difference in overall QoL within the period of trial follow-up (partially because patients who progressed on chlorambucil switched to FC) and that the data from the chlorambucil arm in this study will have been compromised by a healthy cohort effect which would have tended to overestimate QoL in this group.

Recommendation

FLUDARABINE PHOSPHATE, tablet 10 mg, injection 50 mg

Restriction: <u>Section 85 Authority required</u>

B-cell chronic lymphocytic leukaemia in combination with cyclophosphamide where the patient has advanced disease (Binet Stage B or C) or evidence of progressive Stage A disease.

Stage A progressive disease is defined by at least one of the following: persistent rise in lymphocyte count with doubling time less than 12 months; a downward trend in haemoglobin or platelets, or both; more than 50% increase in the size of liver, spleen, or lymph nodes, or appearance of these signs if not previously present; constitutional symptoms attributable to disease.

The diagnosis of CLL must have been established based on:

(a) a lymphocytosis, with ≥ 5 x 10^9 lymphocytes/L in the peripheral blood; and
(b) a clonal population of B-cells (CD5/CD19) documented by flow cytometry.

Maximum quantity: 20 (tablet), 5 (injection)
Repeats: 5 (tablet), 3 (injection)

13. Context for Decision

The PBAC helps decide whether and, if so, how medicines should be subsidised in Australia. It considers submissions in this context. A PBAC decision not to recommend listing or not to recommend changing a listing does not represent a final PBAC view about the merits of the medicine. A company can resubmit to the PBAC or seek independent review of the PBAC decision.

14. Sponsor's Comment

The sponsor chose not to make a comment.