Chronic lymphocytic leukaemia (CLL) is the most common type of leukaemia in the western world, with a crude incidence rate of approximately 4 per 100,000 per year in England and Wales. The clinical course of CLL is very variable; although the median survival is estimated at approximately 10 years, this will mean very little to individual patients. While some patients will have a slow, asymptomatic progression over several years, others will have an aggressive symptomatic course requiring immediate treatment. Treatment is generally initiated if the disease progresses to Rai stage III or Binet stage C, and/or when there are complications present.

In 2004, the British Committee for Standards in Haematology (BCSH) published a guideline on the diagnosis and management of CLL, which discusses the treatments available and factors to consider when starting treatment. This recommends fludarabine or chlorambucil as first-line therapy; a combination of fludarabine and cyclophosphamide (FC) is recommended if there was an initial response to fludarabine but progression within one year. In guidance issued in early 2007, NICE recommended against the use of fludarabine monotherapy in the first-line treatment of CLL; although the company supplied additional supporting data for FC, this was not considered as it falls outside of the UK license. The use of this combination is however being used in clinical practice in the UK, and this review summarises the available evidence for its use in CLL.

There have been three fully published Phase III trials evaluating FC in the first-line treatment of CLL; the main one to date (CLL4) compared it to monotherapy with chlorambucil or fludarabine (i.e. the current first-line treatments recommended by BCSH). In all three trials, FC was superior to fludarabine monotherapy (and chlorambucil in CLL4) in terms of overall response rate and duration of progression-free survival; however no overall survival benefit has been demonstrated. Further randomised data are needed to confirm whether the use of oral fludarabine is associated with a comparable efficacy to the IV formulation in the treatment of CLL.
Background

The human leukaemias arise from haemopoietic stem and progenitor cells, and are marked by distorted proliferation and development of leukocytes and their precursors in the blood and bone marrow (1). In chronic leukaemias, mature leucocytes are the predominant cells, involving either the lymphocytes (chronic lymphocytic leukaemia) or granulocytes (chronic myeloid leukaemia) (2).

Chronic lymphocytic leukaemia (CLL) is the most common type of leukaemia in the western world, accounting for 40% of all leukaemias in individuals over the age of 65 years (3). CLL is rare below the age of 30 years of age; the median age of presentation is between 65 and 70 years (3). It has a crude incidence rate of approximately 4 per 100,000 per year in England and Wales. In 2000, there were 778 deaths from CLL, which equates to a rate of 1.5 per 100,000 population (4). CLL is characterised by the clonal proliferation of highly differentiated but immuno-incompetent lymphocytes spreading in the lymphatic and haematopoietic system (5). Over 95% of CLL is of B-cell origin (B-CLL); the remaining 3% are of T-cell lineage and considered as an entity completely different from B-CLL, especially concerning therapy (5).

In about three-quarters of cases, CLL is diagnosed incidentally, with lymphocytosis (an increased number of lymphocytes in the blood) found during a blood test taken for reasons other than suspected haematological malignancy (4). Others may present with lymphadenopathy; hepatomegaly; splenomegaly or bone-marrow infiltration or both, leading to anaemia and/or thrombocytopenia (6). A definitive diagnosis of CLL is based on the combination of a lymphocytosis and characteristic lymphocyte morphology and immunophenotype (3). The underlying causes of the disease are unknown, but the tumour microenvironment is believed to play a crucial part in the pathogenesis (6).

The clinical course of CLL is very variable, with a large heterogeneity in the natural history of the disorder. For this reason, the median survival (approximately 10 years) will mean very little to individual patients (3). While some patients will have a slow, asymptomatic progression over several years, others will have an aggressive symptomatic course requiring immediate treatment (6). Two simple validated staging systems are currently used in clinical practice to predict prognosis for individual patients – Binet and Rai (see Table 1).

<table>
<thead>
<tr>
<th>Stage</th>
<th>Features</th>
<th>% of patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>BINET stage</td>
<td></td>
<td></td>
</tr>
<tr>
<td>A</td>
<td>No anaemia or thrombocytopenia; &lt;3 areas of lymphoid involvement*</td>
<td>60</td>
</tr>
<tr>
<td>B</td>
<td>No anaemia or thrombocytopenia; ≥3 areas of lymphoid involvement</td>
<td>30</td>
</tr>
<tr>
<td>C</td>
<td>Anaemia and/or thrombocytopenia; any number of areas with lymphoid enlargement</td>
<td>10</td>
</tr>
<tr>
<td>RAI stage</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>Lymphocytosis only (&gt;15,000/mm³)</td>
<td>30</td>
</tr>
<tr>
<td>I</td>
<td>Lymphocytosis with lymphadenopathy</td>
<td>25</td>
</tr>
<tr>
<td>II</td>
<td>Lymphocytosis, hepatomegaly, ± splenomegaly</td>
<td>25</td>
</tr>
<tr>
<td>III</td>
<td>Lymphocytosis and anaemia (Hb&lt;11 g/dL) ± lymphadenopathy, hepatomegaly, or splenomegaly</td>
<td>10</td>
</tr>
<tr>
<td>IV</td>
<td>Lymphocytosis and thrombocytopenia (&lt;100,000/mm³) with or without lymphadenopathy, hepatomegaly, splenomegaly, or anaemia</td>
<td>10</td>
</tr>
</tbody>
</table>

* The five lymphoid areas assessed for involvement are the cervical, axillary, and inguinal lymph nodes, hepatomegaly and splenomegaly.

Infectious complications, particularly of the upper respiratory tract, are the main cause of morbidity in CLL; in part due to the hypogammaglobulinaemia and the inability to mount a humoral defence against bacterial or viral agents (1). Other complications of CLL include autoimmune phenomena such as haemolytic anaemia, and the development of other malignancies (5).

Current treatment options

Treatment is not necessary for all patients when CLL is first diagnosed, but over half will require treatment at some stage. A meta-analysis of studies of chemotherapy for CLL found no advantage in treating the condition before symptoms develop; thus it is generally recommended not to treat patients with early stage disease unless there are clear signs of progression (4, 5). A Working Group of the National Cancer Institute has recommended that treatment be initiated if (5):

- The disease progresses to Rai stage III or Binet stage C
- There are infectious or autoimmune complications
- Lymphocyte doubling time is less than 12 months or
Fludarabine and cyclophosphamide in chronic lymphocytic leukaemia (CLL)

- The patient becomes symptomatic in terms of night sweats, weight loss (>10% in previous 6 months), extreme fatigue or fever ("B-symptoms")

The British Committee for Standards in Haematology (BCSH) published a guideline on the diagnosis and management of CLL in 2004. This recommends that before treatment is initiated, consideration should be given to a number of factors, including patient age, performance status, co-morbidities, symptom severity, presence of adverse prognostic factors, past response to any previous therapies, and the presence of any contra-indications. There is currently no curative treatment for CLL, and most patients will receive a number of different treatment modalities during the course of the disease (3).

The alkylating agent chlorambucil (as monotherapy or in combination with steroids) has been considered the mainstay of treatment and the standard first-line therapy of B-CLL over the years. Nowadays, combination therapies including cyclophosphamide, vincristine, anthracyclines and prednisolone (COP, CHOP, CAP regimens) are widely used, but there is no evidence for any survival benefit over chlorambucil monotherapy (5). A Cochrane systematic review concluded that purine antagonists (e.g. fludarabine) were associated with increased overall response and complete remission rates versus alkylating agents in previously untreated B-CLL; however, there was no evidence of an improvement in overall survival, and these agents appear to increase the risk for grade III/IV infections and haematolytic anaemia.

In summary, the treatment options recommended in the BCSH guideline are as follows:

**a) Initial treatment:**
- Fludarabine
- Low-dose chlorambucil (no survival advantage for including an anthracycline)

The use of alemtuzumab or rituximab monotherapy is not recommended in untreated CLL; fludarabine in combination with rituximab (±cyclophosphamide) and high-dose chlorambucil require further evaluation before they can be recommended.

The current BCSH guidelines recommend enrolment in the UK CLL4 trial, which is comparing three treatment arms: fludarabine, chlorambucil, and fludarabine plus cyclophosphamide (see later discussion). Enrollment for this trial is now closed, and new guidelines are currently being developed.

**b) Second-line treatment:**
- Initial response to chlorambucil but relapsed - repeat course
- Refractory to low-dose chlorambucil – fludarabine (or CHOP [cyclophosphamide, vincristine, doxorubicin, prednisolone] if fludarabine unsuitable)
- Initial response to fludarabine but progression more than one year later – repeat course
- Initial response to fludarabine but progression within one year – combination of fludarabine and cyclophosphamide

**c) Subsequent treatment:**
- Refractory to/resistance to fludarabine (poor prognosis) - high-dose methylprednisolone
- Patients without bulky lymphadenopathy, previously treated with alkylating agents and refractory to fludarabine - alemtuzumab

The use of rituximab monotherapy is not recommended and its use in combination with fludarabine (±cyclophosphamide) requires further evaluation.

**Evidence for fludarabine in combination with cyclophosphamide**

Fludarabine (Fludara®, Bayer Schering Pharma) is licensed in the UK for the treatment of B-CLL in patients with sufficient bone marrow reserves. The Summary of Product Characteristics (SPC) for Fludara® states that ‘first line treatment with fludarabine should only be initiated in patients with advanced disease, Rai stages III/IV (Binet stage C), or Rai stages I/II (Binet stage A/B) where the patient has disease related symptoms or evidence of progressive disease’. The use of fludarabine as part of combination treatment (e.g. with cyclophosphamide) is outside of the current licensed indication for this product (7, personal communication).

The National Institute for Health and Clinical Excellence (NICE) recently published guidance on fludarabine, recommending against its use as monotherapy for the first-line treatment of CLL (8). Although the company supplied data also supporting its use in combination with cyclophosphamide, the Committee did not consider this as it falls outside of the current license. This review therefore focuses on the data for the use of fludarabine in combination with cyclophosphamide (FC) in the treatment of CLL.

The Scottish Medicines Consortium (SMC) has accepted fludarabine for use within NHS Scotland for the treatment of B-cell chronic CLL in patients with sufficient bone marrow reserves (9). First line treatment should only be initiated in patients with advanced disease, Rai stages III/IV (Binet stage C), or Rai stages I/II (Binet stage A/B) where the patient has disease related symptoms or evidence of progressive disease. It is restricted to use by specialists in haematology.
US Intergroup Trial E2997

The Phase III US Intergroup Trial E2997 was initiated in 1999 to evaluate the FC combination, following positive results from Phase II studies (10). This multicentre study enrolled patients aged 18 years or above with a diagnosis of progressive B-CLL (according to National Cancer Institute [NCI] criteria), who had not received any previous chemotherapy for their condition. Patients were excluded if they had a performance status (PS) of more than 2, a creatinine clearance below 40mL/min, total bilirubin >2mg/dL (34 micromol/L), active infection, autoimmune haemolytic anaemia or thrombocytopenia, or a second malignancy (other than basal cell carcinoma).

A total of 278 patients were randomised to FC combination therapy (n=141) or to single-agent fludarabine (F arm; n=137), administered in 28-day cycles (maximum 6 cycles in total), as follows:

- **FC arm** – 600mg/m² IV cyclophosphamide on day 1 and 20mg/m² IV fludarabine on days 1-5
- **F arm** – 25mg/m² IV fludarabine on days 1-5

Treatment was continued until maximal response, or the absence of residual disease; those with progressive disease after receiving at least two cycles of chemotherapy discontinued treatment. All patients received *Pneumocystis carinii* (PCP) prophylaxis and allopurinol; additionally those in the FC arm received filgrastim (G-CSF) and prophylaxis against herpes zoster. The use of corticosteroids for any indication was prohibited.

In order to receive the scheduled therapy, the haemoglobin (Hb) had to be at least 10g/dL (max 13g/dL) and platelets had to be at least 75,000/microL, or within 10% of the pre-treatment baseline level. The following dose reductions for fludarabine were made if the creatinine clearance was 70mL/min or below at the first cycle:

<table>
<thead>
<tr>
<th>Creatinine clearance (mL/min)</th>
<th>Fludarabine dose (mg/m²)</th>
</tr>
</thead>
<tbody>
<tr>
<td>FC arm</td>
<td>F arm</td>
</tr>
<tr>
<td>71 and above</td>
<td>20</td>
</tr>
<tr>
<td>61-70</td>
<td>14</td>
</tr>
<tr>
<td>51-60</td>
<td>12</td>
</tr>
<tr>
<td>40-50</td>
<td>10</td>
</tr>
<tr>
<td>0-39</td>
<td>Not eligible for inclusion</td>
</tr>
</tbody>
</table>

Dose reductions for both agents at cycles 2 and beyond were specified in the protocol according to blood counts (nadir platelet or Hb levels) and the development of toxicities. Treatment was discontinued for any patient developing grade 3 or above fludarabine-related pneumonitis, grade 4 cardiac toxicity, or any autoimmune disorder (including haemolytic anaemia, thrombocytopenia).

The two treatment groups were well balanced at baseline, with no significant differences reported in any of the characteristics listed. The median age of the study population was 61 years (range 33-86), 70% were male, and the median time since diagnosis was 13.2 months (0-240). The Eastern Cooperative Oncology Group (ECOG) PS scores were 0 (47%), 1 (37%) or 2 (14%), and Rai stages varied between 0 (3%), 1 (25%), 2 (27%), 3 (22%) and 4 (22%). The majority of patients presented with lymphadenopathy (86%) and/or splenomegaly (62%) at baseline.

Clinical response was defined according to the NCI workshop criteria. The primary efficacy endpoint was the complete response (CR) rate for each arm; secondary endpoints included overall survival (OS) and progression-free survival (PFS). The study had a 90% power to detect an increase in CR from 25% in the F arm to 45% in the FC arm. More patients in the FC arm withdrew early from treatment due to excessive toxicity (23 patients versus 15 in the F arm); however more patients in the F arm withdrew early due to progressive disease (11 versus 4, respectively). A total of 169 patients received the full six cycles of chemotherapy (83 in the FC arm and 86 in the F arm). The main results are summarised in Table 3.

**German CLL Study Group**

This Phase III trial compared FC and fludarabine monotherapy in the first-line treatment of CLL, specifically in patients aged 65 years or younger (11). Patients were eligible for inclusion if they had:

- Binet stage C disease, or
- Binet Stage B with rapid disease progression or symptoms of enlarged lymph nodes and organs, or severe B symptoms, or
- Binet Stage A if B symptoms present

Other inclusion criteria specified were no previous treatment for CLL, a life expectancy of over 6 months, and an ECOG PS of 0-2. Subjects were excluded if they had severe organ dysfunction (no specific details given), concomitant or previous neoplasms, or autoimmune haemolytic anaemia or thrombocytopenia.

A total of 362 patients were randomised to receive either F alone (25mg/m² IV for 5 days; n=182) or FC (30mg/m² fludarabine IV and cyclophosphamide 250mg/m² IV daily for 3 days; n=180) in 28-day cycles (maximum of six courses in total). Doses were reduced in cases of grade 3 infection, neutrophil count <1x10⁹/L, and/or thrombocytopenia with concurrent bleeding complications. No infection pro-
Fludarabine and cyclophosphamide in chronic lymphocytic leukaemia (CLL)

Phylaxis or G-CSF was administered routinely. Treatment was discontinued if the disease was stable or progressive after 3 courses of treatment, or if life-threatening adverse events occurred. Clinical response was evaluated for all patients who received at least one cycle of chemotherapy, and was defined according to the NCI workshop criteria. The study’s primary endpoint was not stated in this publication.

The two treatment groups had similar characteristics at baseline, and no significant differences were identified. The median age of the study population was 58 years (range 42-65) and over 70% were male. The ECOG PS scores were 0 (53%), 1 (44%) or 2 (3%), and almost equal proportions had Rai stage I-II (57%) or III-IV (40%) disease. The main findings after a median follow-up of 22 months are summarised in Table 3.

The researchers also analysed the response rates according to Binet disease stage, and found that the overall response (complete or partial response) rate for FC was highest in stage C (96.2% versus 76.8% in the F arm), but the highest CR rate was seen in stage A patients (46.2% versus 21.1%, respectively). The median observation time was probably too short to enable the detection of any significant between-treatment differences in OS.

A total of 70.7% of the F arm and 64% of the FC arm completed all six cycles of chemotherapy. More patients in the FC arm withdrew early from treatment due to excessive toxicity (30% versus 14% in the F arm); however more patients in the F arm withdrew due to non-response (33% versus 9%, respectively).

Table 3: Main results for two Phase III trials assessing the first-line use of FC versus F in patients with CLL

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>E2997 trial (n=278)</th>
<th>GCLLSG trial (n=362)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient characteristics</td>
<td>Median age 61 (33-86) years 44% Rai stage III/IV</td>
<td>Median age 58 (42-65) years 40% Rai stage III/IV</td>
</tr>
<tr>
<td>Endpoint</td>
<td>FC arm (n=137)</td>
<td>F arm (n=132)</td>
</tr>
<tr>
<td>Complete response, N (%)</td>
<td>32 (23.4)</td>
<td>6 (4.6)</td>
</tr>
<tr>
<td>Partial response, N (%)</td>
<td>69 (50.4)</td>
<td>72 (54.6)</td>
</tr>
<tr>
<td>Overall response, N (%)</td>
<td>74 (3.3)</td>
<td>69 (54.6)</td>
</tr>
<tr>
<td>Stable disease, N (%)</td>
<td>20 (14.6)</td>
<td>31 (23.5)</td>
</tr>
<tr>
<td>Median PFS* (months)</td>
<td>31.6</td>
<td>19.2</td>
</tr>
<tr>
<td>Estimated 2-year survival+</td>
<td>79%</td>
<td>80%</td>
</tr>
<tr>
<td>Estimated 3-year survival</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

* p=0.0001 for E2997 trial and 0.001 for GCLLSG; median PFS estimated using the Kaplan-Meier method
+ No survival benefit seen at this time, but limited follow-up (55 deaths)
The majority of patients were male (74%), with a median age of 65 (range 35-86) years. All patients had progressive CLL, of Binet stage A (25%), B (45%) or C (30%). The main results after a median follow-up of 3 years and 5 months are summarised in Table 4 (12). There were no statistically significant differences between the groups in terms of 5-year OS; FC was however superior to both FDR (HR 0.45; 95% CI 0.35-0.59, p<0.00005) and chlorambucil (HR 0.45; 95% CI 0.37-0.54, p<0.00005) in 5-year PFS (no significant difference between chlorambucil and FDR monotherapy). FC was associated with statistically significantly higher rates of CR (p<0.0001), CR or nodular partial remission (p=0.0004) and overall response (p<0.0001) than FDR monotherapy. There were no significant differences in treatment effects between subgroups in terms of age (<60, 60-69, 70+), stage (Binet A, B or C) or sex (12).

Table 4 – Results from the CLL4 trial (12)

<table>
<thead>
<tr>
<th></th>
<th>CMB I (n=309)</th>
<th>FDR (n=176)</th>
<th>FC (n=176)</th>
</tr>
</thead>
<tbody>
<tr>
<td>5-year survival; % (95% CI)</td>
<td>59 (53-66)</td>
<td>52 (42-61)</td>
<td>54 (44-64)</td>
</tr>
<tr>
<td>5-year PFS; %</td>
<td>10 (6-15)</td>
<td>10 (3-16)</td>
<td>36 (28-46)</td>
</tr>
<tr>
<td>Median PFS (months)</td>
<td>20 (18-22)</td>
<td>23 (18-27)</td>
<td>43 (35-51)</td>
</tr>
<tr>
<td>Complete response (CR); %</td>
<td>7</td>
<td>15</td>
<td>38</td>
</tr>
<tr>
<td>Partial response (PR); %</td>
<td>46</td>
<td>38</td>
<td>34</td>
</tr>
<tr>
<td>Nodular PR (NPR); %</td>
<td>19</td>
<td>27</td>
<td>23</td>
</tr>
</tbody>
</table>

Certain genetic abnormalities have been associated with a poor outcome and response to treatment in CLL; these include 17p deletion (5% CR/NPR) and 11q deletion (28% CR/NPR). The CLL4 investigators note that the group of patients with >20% of 17p deleted cells had low responses even to FC, and that this suggests treatments which use the p53 pathway for their activity are not very effective. They suggest that future work focuses on new treatments that are independent of p53 (12).

Route of administration: The proportion of patients receiving oral fludarabine was 65% in the FDR group and 67% in the FC group. A preliminary analysis of the differences in response rates between the IV and oral formulations of fludarabine has been presented at conference and is available in abstract form (13). Responses were found to be better with IV fludarabine (FDR: CR/NPR of 54% versus 41%, p=0.02); FC: CR/NPR of 73% versus 59%, p=0.04). The investigators note however that these differences were probably not due to the different routes of administration and were likely to reflect the fact that those receiving oral fludarabine were older and had a poorer prognosis (13). A prospective, randomised comparison would need to be carried out to answer this question and confirm this hypothesis.

Adverse events/Safety issues

In the E2997 trial, the combination arm was associated with higher rates of haematological toxicity, including (10):

- Leukopenia - 42% grade 3 and 29% grade 4 in the FC arm, compared with 36% and 6% in the F arm (p=0.00001)
- Anaemia – 17% G3 and 13% G4 in the FC arm, versus 14% and 6%, respectively, in the F arm (p=0.032)
- Thrombocytopenia – 24% grade 3 and 4% grade 4 in the FC arm; 15% and 1% respectively in the F arm (p=0.046)

The occurrence of non-haematological toxicity (grade 3 or above) was 50% overall in the FC arm and 33% in the F arm (p=0.007). There was no statistically significant difference between the two treatment groups in the rates of infection (with or without neutropenia).

In the German CLL Study Group trial, more patients receiving FC experienced grade 3 or 4 toxicities (72.6% versus 54% overall); specific toxicities identified as occurring more frequently in the FC arm included (11):

- Myelotoxicity – 64.2% versus 39.3% (p=0.001)
- Leukopenia – 55.5% versus 26.0% (p<0.001)
- Gastro-intestinal – 5.8% versus 1.7% (p=0.05)
- Thrombocytopenia – 34.9% versus 23.3% (p=0.02)

There was no difference between the two treatment groups in the incidence of grade 3 or 4 infections (8.7% in both groups).

The incidence of the main adverse effects observed in the CLL4 trial are summarised in Table 5 (taken from reference 12).
In the CLL4 trial, health-related quality of life was assessed using the European Organisation for Research and Treatment of Cancer Quality of Life (EORTC QLQ-C30) questionnaire; with measurements made at baseline, 3, 6, 12 and 24 months and yearly thereafter (12). Those who responded to treatment had higher quality of life scores (9.1 points higher at 3 months \[p=0.0001\] and 10.5 higher at two years \[p=0.0004\]); however there were no statistically significant differences between treatments. Further, more detailed analyses are due to be reported in the future (12).

The manufacturer submitted a cost utility analysis to the SMC, comparing fludarabine monotherapy, FC combination and chlorambucil as first-line treatment for CLL (9). This model used patient-level data from the CLL4 trial to estimate survival and duration of response; fludarabine and FC were not assumed to have a survival advantage but the duration of response and the relative percentage of patients showing a response to treatment were assumed to vary between treatments. The results of the analysis indicated an incremental cost of FC compared to chlorambucil of £2600-£3200 per QALY, depending on the assumptions made in the calculations of life years (9).

Table 5 – Drug costs of the different CLL regimens

<table>
<thead>
<tr>
<th>Regimen</th>
<th>Drug</th>
<th>Dose</th>
<th>Cost per cycle</th>
<th>**Total cost per treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>FDR IV</td>
<td>fludarabine</td>
<td>25mg/m² IV 5 days</td>
<td>£780</td>
<td>£4,880</td>
</tr>
<tr>
<td>FDR oral</td>
<td>Fludarabine</td>
<td>40mg/m² oral for 5 days</td>
<td>£651</td>
<td>£3,906</td>
</tr>
<tr>
<td>FC (IV)</td>
<td>fludarabine</td>
<td>25mg/m² IV for 3 days</td>
<td>£479</td>
<td>£2,872</td>
</tr>
<tr>
<td></td>
<td>cyclophosphamide</td>
<td>250mg/m² IV for 3 days</td>
<td></td>
<td></td>
</tr>
<tr>
<td>FC (oral)</td>
<td>fludarabine</td>
<td>24mg/m² oral for 5 days</td>
<td>£375</td>
<td>£2,250</td>
</tr>
<tr>
<td></td>
<td>cyclophosphamide</td>
<td>150mg/m² oral for 5 days</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chlorambucil</td>
<td>Oral chlorambucil</td>
<td>10mg/m² for seven days</td>
<td>£21</td>
<td>£252</td>
</tr>
</tbody>
</table>

*Costs based on an average surface area of 1.8m² and taken from BNF 53 (March 2007)

**Duration of treatment: In CLL4, chlorambucil – until max response is achieved, up to one year. Fludarabine schedules – minimum of three and maximum of six cycles in order to achieve maximum response. Above, the totals represent six months of fludarabine-containing schedules and 12 months for chlorambucil, although the lengths of treatment will differ for each patient.
The manufacturer also estimated the net budget impact for Scotland of moving to the current treatment plan to a treatment pattern that would see 80% of eligible patients treated with off-label FC - £279k, £205k, £135k, £83k and £60k in years 2007-2011 (these include non-drug costs) (9).

### Ongoing research

A number of studies looking at fludarabine either alone or in combination in the treatment of CLL are underway. Examples include (14):

- Fludarabine, cyclophosphamide, and rituximab versus pentostatin, cyclophosphamide and rituximab in previously untreated or treated B-Cell CLL (Phase III)
- Fludarabine with or without alemtuzumab in the second-Line treatment of B-cell CLL (Phase III)
- Fludarabine versus fludarabine plus cyclophosphamide in first-line therapy of younger patients (up to 65 years) with advanced CLL (Phase III)
- Fludarabine, cyclophosphamide, rituximab and bevacizumab in the treatment of relapsed CLL (Phase II)

### Issues for consideration

- The use of fludarabine in combination with cyclophosphamide for the treatment of CLL falls outside of the UK license for Fludara®; in addition the doses used in the Phase III trials differ from that recommended in the SPC
- The cost of treatment with FC is lower than that associated with FDR due to a reduced dose of fludarabine (cost of cyclophosphamide is minimal in comparison)
- Although three Phase III trials have found that the combination of fludarabine and cyclophosphamide (FC) is associated with improved overall response rates and progression-free survival compared to fludarabine monotherapy (FDR) (and chlorambucil in one trial), there has been no demonstration of any survival benefit associated with the first-line use of this combination. However, as trials have allowed patients who progress to cross over or to receive salvage therapy, it can be argued that response to second-line therapy confounds interpretation of overall survival (12).
- NICE recommends against the use of fludarabine as monotherapy for the first-line treatment of CLL. Although the company additionally supplied supporting data for the use of fludarabine in combination with cyclophosphamide, this was not considered by the Committee as it falls outside of the UK license.
- Further prospective randomised data are required to confirm that the activity of oral fludarabine in CLL is at least equivalent to that of the IV preparation
References

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The document reflects the views of LCNDG and may not reflect those of the reviewers

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