

# NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

## Final Appraisal Determination

### Fludarabine monotherapy for the first-line treatment of chronic lymphocytic leukaemia

This guidance was developed using the single technology appraisal (STA) process.

#### 1 Guidance

This technology appraisal considers the clinical and cost effectiveness of fludarabine monotherapy only. No recommendations have been made with respect to fludarabine plus cyclophosphamide combination therapy because the current marketing authorisation does not specifically provide a recommendation that fludarabine should be used concurrently with other drugs for the treatment of chronic lymphocytic leukaemia.

Clarification was sought with the MHRA on the issue of the inclusion of the combination of fludarabine and cyclophosphamide in the marketing authorisation of fludarabine. In all correspondence received from the MHRA, including that shared with NICE by Schering Health Care Limited, it has been made clear that 'the MHRA does not consider that the current marketing authorisations for oral and intravenous (i/v) Fludara (PL/0053/0239 & /290) specifically provide a recommendation that fludarabine should be used concurrently with other drugs for the treatment of chronic lymphocytic leukaemia'.

The MHRA has further clarified that, in general, they would expect a manufacturer or sponsor to request a variation in the marketing authorisation when; 1. the SPC in general, and specifically in the 'therapeutic indications' section, does not contain references to the

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combination therapy and the company wish to promote the use of combination therapy, and 2. the combination use has implications for the specifications in the 'posology and method of administration' section of the SPC.

In the case of fludarabine the SPC does not contain references to the combination therapy. With reference to the second point, the dose intensity of the combination of fludarabine with cyclophosphamide (i/v 25 mg/m<sup>2</sup> for 3 days and oral 24 mg/m<sup>2</sup> for 5 days, in the combination) in the evidence base for the combination therapy that was submitted by the manufacturer (the CLL4 trial) is different from the dose intensity specified in both SPCs (i/v 25 mg/m<sup>2</sup> for 5 days and oral 40 mg/m<sup>2</sup> for 5 days).

- 1.1 Fludarabine monotherapy, within its licensed indication, is not recommended for the first-line treatment of chronic lymphocytic leukaemia.

## **2 The technology**

- 2.1 Fludarabine (Fludara, Schering Health Care Limited) is a deoxyadenosine derivative that inhibits DNA, RNA and protein synthesis, and cell replication and growth, leading to apoptosis (cell death). Fludarabine has a marketing authorisation for the first-line treatment of symptomatic B-cell chronic lymphocytic leukaemia (CLL) in patients with sufficient bone marrow reserves and either advanced disease (Binet stage C, Rai stages III/IV) or Binet stage A/B (Rai stages I/II) with disease-related symptoms or evidence of progressive disease. For further information about the drug, see the summary of product characteristics (SPC).
- 2.2 The most common adverse events associated with fludarabine treatment include anaemia, thrombocytopenia, neutropenia and infections (for

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example, pneumonia and herpes virus infections). For full details of side effects and contraindications, see the SPC.

- 2.3 The unit cost of fludarabine is £156 for a 50-mg vial, and £18.60 per 10-mg tablet, available in packs of 15 and 20 tablets (excluding VAT; 'British national formulary', edition 52). The cost per patient for a course of six cycles of treatment with fludarabine monotherapy would be approximately £4700. Costs may vary in different settings because of negotiated procurement discounts.

### **3 The manufacturer's submission**

The Appraisal Committee (appendix A) considered evidence submitted by the manufacturer of fludarabine and a review of this submission by the Evidence Review Group (appendix B).

- 3.1 The manufacturer's submission approached the decision problem by comparing fludarabine monotherapy and fludarabine plus cyclophosphamide with chlorambucil. The population under consideration was defined as people with CLL, who were chemotherapy naïve, had sufficient bone marrow reserves and had advanced symptomatic Binet stage B or C disease or evidence of progressive disease in Binet stage A. The primary outcome measures considered were progression-free survival and health-related quality of life. Secondary outcome measures included treatment response rates, incidence of adverse events and overall survival.
- 3.2 The manufacturer's submission included evidence on the clinical effectiveness of fludarabine monotherapy and fludarabine plus cyclophosphamide compared with chlorambucil. Only clinical evidence relating to fludarabine monotherapy, within its licensed indication, is presented in this section. Seven randomised controlled trials (RCTs) were identified to be relevant to the decision problem, of which two were published and five were available in abstract form. However, the CLL4 trial

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was considered to be the most relevant by the manufacturer because it is the largest study and the only one directly comparing fludarabine monotherapy, fludarabine plus cyclophosphamide and chlorambucil. The CLL4 trial enrolled 777 patients, of whom 194 were randomised to fludarabine monotherapy, 196 to fludarabine plus cyclophosphamide and 387 to chlorambucil. Follow-up is ongoing. Early results of the CLL4 trial published in abstract form and presented in the manufacturer's submission showed that overall treatment response rates were 77% for fludarabine monotherapy and 69% for chlorambucil (no p values or confidence intervals were reported). Early results from the CLL4 trial reported 3-year progression-free survival of 31% for fludarabine monotherapy and 23% for chlorambucil. Analysis of overall survival showed no difference between the treatment regimens.

- 3.3 The manufacturer's submission contained an economic analysis comparing fludarabine monotherapy, fludarabine plus cyclophosphamide and chlorambucil. Only the economic evidence for fludarabine monotherapy compared with chlorambucil is presented in this section. The economic analyses were based on a Markov state transition model with a 20-year time horizon. The economic model used patient-level data from the CLL4 trial to inform first-line treatment, with data for second-line and salvage treatments taken from a variety of published sources. The manufacturer submitted revised base-case economic analyses following clarifications requested by the Evidence Review Group (ERG). These showed an incremental cost-effectiveness ratio (ICER) of £26,105 per quality-adjusted life year (QALY) for fludarabine monotherapy compared with chlorambucil.
- 3.4 The ERG raised a number of issues and uncertainties relating to the clinical and cost-effectiveness evidence presented in the manufacturer's submission. The ERG stated that the clinical effectiveness evidence had to be interpreted with caution because the follow-up period for the CLL4 trial

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was not complete at the time of submission. The ERG assessed the manufacturer's economic model and noted that the main drivers of the ICERs presented were time horizon and rates of response to retreatment with the same chemotherapeutic agent as that used in first-line treatment.

- 3.5 The ICER for fludarabine monotherapy compared with chlorambucil for a 15-year time horizon was £28,178 per QALY. For 10-year and 5-year time horizons the ICERs were £42,516 per QALY and £310,663 per QALY, respectively. The ERG stated that the extrapolation of model data is likely to be central to the validity of the ICERs presented. The ERG also noted that an assumption of constant transition probabilities over time was used within the manufacturer's model. Because patient-level data from the CLL4 trial were available, the ERG stated that this assumption should have been validated using formal survival analysis. It therefore performed a survival analysis using patient-level data from the CLL4 trial, the results of which showed that the assumption of constant transition probabilities is not supported. However, incorporating the results of the ERG's survival analysis into the economic model would have required a substantial restructuring of the model. Correcting this assumption was expected to increase the ICER for fludarabine monotherapy compared with chlorambucil.
- 3.6 The ERG report noted the way in which retreatment response rates for fludarabine monotherapy and chlorambucil were modelled. For fludarabine monotherapy, the first-line treatment response rate (77%) was taken from the CLL4 study and the retreatment response rate (74%) was taken from the existing literature as presented in the manufacturer's submission. For chlorambucil, the first-line treatment response rate (69%) was taken from the CLL4 study and the retreatment response rate (35%) was taken from the existing literature as presented in the manufacturer's submission. This led to a base-case ICER of £26,105 per QALY for fludarabine monotherapy

compared with chlorambucil. Because no retreatment response rates were available from the CLL4 study, and because of the limited evidence available in existing literature, the manufacturer's submission presented a one-way sensitivity analysis in which retreatment response rates were assumed to be the same as first-line treatment response rates for all the treatment arms in the economic model. This resulted in an ICER of £86,770 per QALY for fludarabine monotherapy compared with chlorambucil.

3.7 The ERG noted that the manufacturer's submission stated that improved progression-free survival with fludarabine monotherapy was linked to improvements in quality of life in the CLL4 trial. However, the impact of the adverse effects of fludarabine, specifically the potential additional costs related to increased hospitalisations due to infections, was not explored in the manufacturer's economic model. Although the manufacturer's model included sensitivity analysis to assess potential decreases in utilities and quality of life as a result of adverse events, the ERG considered that the omission of the treatment costs of adverse events was likely to have resulted in an underestimation of the ICERs for fludarabine monotherapy compared with chlorambucil.

3.8 Full details of all the evidence are in the manufacturer's submission and ERG report (see appendix B).

## **4 Consideration of the evidence**

4.1 The Appraisal Committee reviewed the data available on the clinical and cost effectiveness of fludarabine monotherapy for the treatment of chronic CLL, having considered evidence on the nature of the condition and the value placed on the benefits of fludarabine by people with CLL, those who represent them, and clinical specialists. It was also mindful of the need to take account of the effective use of NHS resources.

4.2 The Committee noted that the decision problem submitted by the manufacturer included both fludarabine monotherapy and combination therapy with cyclophosphamide. However, the Committee noted that the current marketing authorisation does not specifically provide a recommendation that fludarabine should be used concurrently with other drugs for the treatment of CLL. Therefore the Committee was unable to issue guidance on fludarabine plus cyclophosphamide.

### ***Clinical effectiveness***

4.3 The Committee considered the ERG's review of the manufacturer's submission on the clinical effectiveness of fludarabine monotherapy compared with chlorambucil, and noted that the manufacturer did not make use of evidence from all relevant RCTs to provide a more precise estimate of the clinical effectiveness of the treatments. The Committee discussed the appropriateness of basing the clinical effectiveness of fludarabine monotherapy on preliminary results from the CLL4 study (median follow-up of 45 months) while the trial follow-up period was incomplete. The Committee noted the ERG's view that using all available sources of direct and indirect clinical data comparing fludarabine monotherapy with chlorambucil would have been an appropriate approach to reducing the uncertainty over the clinical effectiveness of fludarabine. However, the Committee heard from clinical specialists that patient inclusion criteria in all the relevant RCTs (including the CLL4 study) were substantially the same and therefore they would expect treatment outcomes to be similar across the trials.

4.4 The Committee accepted, on the basis of the preliminary results of the CLL4 trial, that fludarabine monotherapy showed improved response rates (overall and complete response) and 3-year progression-free survival compared with chlorambucil. The Committee was aware that improvements in progression-free survival with fludarabine monotherapy may not translate

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directly into overall survival benefits. However, the Committee heard from the clinical specialists that an international workshop in CLL had agreed that it was appropriate to use progression-free survival as a surrogate endpoint for overall survival in CLL. This was principally because the prolonged nature of the CLL disease pathway and the use of sequential therapies at different times in the treatment pathways make estimation of differences in overall survival problematic and unreliable. The Committee was persuaded that progression-free survival is a meaningful clinical endpoint for CLL patients.

4.5 The Committee heard from clinical specialists that fludarabine monotherapy is more toxic than chlorambucil, and is associated with a higher incidence of adverse events (particularly neutropenia and infections) and potentially higher mortality rates. The clinical specialists also advised that although the incidence of autoimmune haemolytic anaemia (AIHA) was higher in the chlorambucil arm of the CLL4 trial, the severity of AIHA triggered by fludarabine monotherapy is considered to be greater. Additionally the Committee considered the issue of possible malignant transformations associated with the use of fludarabine monotherapy including the incidence of acute myeloid leukaemia. The Committee understood that there were differences in opinion about this but was persuaded that such malignant transformations were rare.

4.6 The Committee considered the evidence available on quality of life during treatment for CLL. It noted that results from the CLL4 study to date, which showed improvements in response rates and progression-free survival with fludarabine monotherapy, did not lead to improvements in overall quality of life. The clinical specialists advised that quality of life in the early stages of treatment may have been adversely affected by the toxicity of fludarabine monotherapy. However, they stated that they would expect an overall improvement in quality of life for patients who have completed and

responded to fludarabine monotherapy because it confers an extended period of progression-free survival.

- 4.7 The Committee further considered evidence from clinical specialists that the choice of treatment for CLL and the sequence in which treatments are used is made on an individual patient basis, taking into account their general health and fitness and clinical measures of disease activity, in particular the rate of disease progression. The Committee was persuaded that because of the indolent and long-term nature of CLL, watchful waiting is appropriate for some patients who are asymptomatic. Chemotherapy is reserved for those patients who are symptomatic or who are showing signs of progressive disease. The Committee heard from clinical specialists that when a decision to start chemotherapy has been made, first-line treatment and retreatment with chlorambucil may be effective and more appropriate for patients with a less aggressive form of CLL and for those with comorbidities and lower levels of general fitness. On the other hand, first-line treatment with fludarabine monotherapy may be more appropriate for patients with more aggressive forms of CLL disease and those who are considered fit enough to withstand more challenging treatments. The Committee noted statements from patient experts that said that people with CLL were cautious about fludarabine monotherapy because they were aware of its potential toxicity. The patient experts stated that fludarabine monotherapy might not, therefore, be suitable for use in all people with CLL.

### ***Cost effectiveness***

- 4.8 The Committee discussed the differences between the ICERs for the 5-year, 10-year, 15-year and 20-year time horizons in the manufacturer's economic analysis. It considered that the assumptions underlying the extrapolation of data beyond the current CLL4 trial evidence were overly optimistic given the ageing of the population cohort over the lifetime of the

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model. The Committee noted the assumption in the manufacturer's economic model of a constant risk of disease progression and death over time and considered that this was not a true reflection of the course of the disease. The Committee considered the results of the ERG's survival analysis using patient-level data from the CLL4 trial, which showed that an increasing risk of disease progression and death over time was more appropriate for both responders and non-responders to fludarabine monotherapy and chlorambucil. The Committee noted that the ERG's survival analysis indicated that extrapolation of the model data as presented in the manufacturer's submission was likely to give an overly optimistic estimate of the ICER for fludarabine monotherapy compared with chlorambucil.

- 4.9 The Committee discussed the manufacturer's assumption that overall survival is the same for fludarabine monotherapy and chlorambucil. The Committee noted that the way in which the manufacturer's economic model equalised overall survival meant that people in the fludarabine arms spent less time in the salvage treatment state, which is associated with lower utilities and additional costs. The Committee further considered that the manufacturer's survival equalisation approach may be inconsistent with the higher mortality rates observed with fludarabine monotherapy compared with chlorambucil in the CLL4 trial (although this was not statistically significant). The Committee concluded that the manufacturer's assumption of equal overall survival in the economic model may have resulted in an underestimation of the ICERs for fludarabine monotherapy compared with chlorambucil.
- 4.10 The Committee considered the clinical and economic significance of the adverse events associated with fludarabine and noted that these adverse events were important for the cost-effectiveness modelling. The Committee noted however that the manufacturer's model did not incorporate these

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costs, specifically those related to increased infections, (for example, hospitalisations and prophylaxis for *Pneumocystis carinii* pneumonia and herpes virus infections) or for treatment of AIHA associated with fludarabine monotherapy. The Committee agreed that omitting the number, type, severity and treatment costs of adverse events from the manufacturer's economic model would have contributed to an underestimate of the ICERs for fludarabine monotherapy compared with chlorambucil.

- 4.11 The Committee considered the manufacturer's one-way sensitivity analysis on retreatment response rates for fludarabine monotherapy and chlorambucil. It noted that the ICER increased from £26,105 to £86,770 per QALY when the base-case assumptions for the retreatment response rates were changed (see section 3.6). The Committee heard evidence from the clinical specialists that there is limited evidence on retreatment response rates, and complete follow-up of the CLL4 trial may provide more evidence. The Committee concluded that even a small improvement in the retreatment response rates over the ones used in the base-case, particularly for chlorambucil, is likely to increase the ICER for fludarabine monotherapy compared with chlorambucil.

### ***Summary of the considerations***

- 4.12 In summary, the Committee noted that the ICERs for fludarabine monotherapy in comparison with chlorambucil were associated with substantial uncertainties related to the extrapolation of the model data, the exclusion of costs of adverse events and consideration of retreatment response rates; all of which would have resulted in an underestimation of the ICERs for fludarabine monotherapy compared with chlorambucil. The Committee noted that although additional evidence could help to clarify these uncertainties, it was unlikely that such evidence would result in ICERs for fludarabine monotherapy within the range of cost effectiveness that is usually considered to be appropriate for the NHS. The Committee

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was therefore unable to recommend fludarabine monotherapy for the first-line treatment of CLL as a cost-effective use of NHS resources.

## 5 Implementation

- 5.1 The Healthcare Commission assesses the performance of NHS organisations in meeting core and developmental standards set by the Department of Health in 'Standards for better health' issued in July 2004. The Secretary of State has directed that the NHS provides funding and resources for medicines and treatments that have been recommended by NICE technology appraisals normally within 3 months from the date that NICE publishes the guidance. Core standard C5 states that healthcare organisations should ensure they conform to NICE technology appraisals.
- 5.2 'Healthcare Standards for Wales' was issued by the Welsh Assembly Government in May 2005 and provides a framework both for self-assessment by healthcare organisations and for external review and investigation by Healthcare Inspectorate Wales. Standard 12a requires healthcare organisations to ensure that patients and service users are provided with effective treatment and care that conforms to NICE technology appraisal guidance. The Assembly Minister for Health and Social Services issued a Direction in October 2003 which requires Local Health Boards and NHS Trusts to make funding available to enable the implementation of NICE technology appraisal guidance, normally within 3 months.
- 5.3 NICE has developed tools to help organisations implement this guidance (listed below). These are available on our website ([www.nice.org.uk/TAXXX](http://www.nice.org.uk/TAXXX)). [Note: tools will be available when the final guidance is issued]

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## 6 Recommendations for further research

- 6.1 The Committee recommended using data from all clinical trials comparing fludarabine monotherapy, fludarabine plus cyclophosphamide and chlorambucil to provide definitive information on treatment effects including retreatment response rates, overall survival outcomes, incidence and severity of adverse events.
- 6.2 The Committee recommended further research to identify prognostic markers that would allow better characterisation of subgroups of patients who would benefit the most from fludarabine-containing regimens.

## 7 Related NICE guidance

- Improving outcomes in haematological cancers. *NICE cancer service guidance* (2003). Available from: [www.nice.org.uk/csgho](http://www.nice.org.uk/csgho)
- Guidance on the use of fludarabine for B-cell chronic lymphocytic leukaemia. *NICE technology appraisal guidance* no. 29 (2001). Available from: [www.nice.org.uk/TA029](http://www.nice.org.uk/TA029)

## 8 Review of guidance

- 8.1 The review date for a technology appraisal refers to the month and year in which the Guidance Executive will consider whether the technology should be reviewed. This decision will be taken in the light of information gathered by the Institute, and in consultation with consultees and commentators.
- 8.2 The guidance on this technology will be considered for review in October 2009.

David Barnett  
Chair, Appraisal Committee  
December 2006

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## **Appendix A. Appraisal Committee members and NICE project team**

### **A. Appraisal Committee members**

The Appraisal Committee is a standing advisory committee of the Institute. Its members are appointed for a 3-year term. A list of the Committee members who took part in the discussions for this appraisal appears below. The Appraisal Committee meets three times a month except in December, when there are no meetings. The Committee membership is split into three branches, each with a chair and vice-chair. Each branch considers its own list of technologies and ongoing topics are not moved between the branches.

Committee members are asked to declare any interests in the technology to be appraised. If it is considered there is a conflict of interest, the member is excluded from participating further in that appraisal.

The minutes of each Appraisal Committee meeting, which include the names of the members who attended and their declarations of interests, are posted on the NICE website.

#### **Dr Jane Adam**

Radiologist, St George's Hospital, London

#### **Professor A E Ades**

MRC Senior Scientist, MRC Health Services Research Collaboration, Department of Social Medicine, University of Bristol

#### **Dr Amanda Adler**

Consultant Physician, Addenbrooke's Hospital, Cambridge

#### **Dr Tom Aslan**

General Practitioner, Stockwell, London

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**Professor David Barnett (Chair)**

Professor of Clinical Pharmacology, University of Leicester

**Mrs Elizabeth Brain**

Lay Member

**Dr Karl Claxton**

Health Economist, University of York

**Dr Richard Cookson**

Senior Lecturer in Health Economics, School of Medicine Health Policy and Practice,  
University of East Anglia

**Mrs Fiona Duncan**

Clinical Nurse Specialist, Anaesthetic Department, Blackpool Victoria Hospital,  
Blackpool

**Dr Paul Ewings**

Statistician, Taunton & Somerset NHS Trust, Taunton

**Professor John Geddes**

Professor of Epidemiological Psychiatry, University of Oxford

**Mr John Goulston**

Director of Finance, Barts and the London NHS Trust

**Ms Linda Hands**

Consultant Surgeon, John Radcliffe Hospital

**Dr Rowan Hillson**

Consultant Physician, Diabeticare, The Hillingdon Hospital

**Professor Philip Home (Vice-Chair)**

Professor of Diabetes Medicine, University of Newcastle upon Tyne

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**Dr Terry John**

General Practitioner, The Firs, London

**Professor Richard Lilford**

Professor of Clinical Epidemiology, Department of Public Health and Epidemiology,  
University of Birmingham

**Dr Simon Maxwell**

Senior Lecturer in Clinical Pharmacology and Honorary Consultant Physician, Queens  
Medical Research Institute

**Dr Simon Mitchell**

Consultant Neonatal Paediatrician, St Mary's Hospital, Manchester

**Dr Alec Miners**

Lecturer in Health Economics, London School of Hygiene and Tropical Medicine

**Ms Judith Paget**

Chief Executive, Caerphilly Local Health Board, Wales

**Dr Ann Richardson**

Lay Member

**Dr Stephen Saltissi**

Consultant Cardiologist, Royal Liverpool University Hospital

**Mr Mike Spencer**

General Manager, Clinical Support Services, Cardiff and Vale NHS Trust

**Dr Debbie Stephenson**

Head of HTA Strategy, Eli Lilly and Company

**Professor Andrew Stevens**

Professor of Public Health, University of Birmingham

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**Dr Cathryn Thomas**

General Practitioner & Associate Professor, Department of Primary Care & General Practice, University of Birmingham

**Simon Thomas**

Consultant Physician, General Medicine and Clinical Pharmacology, Newcastle Hospitals NHS Trust

**Mr David Thomson**

Lay Member

**Dr Norman Vetter**

Reader, Department of Epidemiology, Statistics and Public Health, College of Medicine, University of Wales, Cardiff

**Professor Mary Watkins**

Professor of Nursing, University of Plymouth

**Dr Paul Watson**

Director of Commissioning, East England Strategic Health Authority

**B. NICE Project Team**

Each technology appraisal is assigned to a team consisting of one or more health technology analysts (who act as technical leads for the appraisal), a technical adviser and a project manager.

**Ebenezer Tetteh and Emma Pugh**

Technical Leads

**Elisabeth George**

Technical Adviser

**Alana Miller**

Project Manager

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## Appendix B. Sources of evidence considered by the Committee

A The following manufacturer provided a submission for this appraisal:

- Schering Health Care Limited.

B The Evidence Review Group report for this appraisal was prepared by the Centre for Health Economics, University of York (Walker S, Palmer S) and the NHS Northern and Yorkshire Regional Drug and Therapeutics Centre (Erhorn S, Brent S, Dyker A et al.), August 2006. *Fludarabine phosphate for the first-line treatment of chronic lymphocytic leukaemia*.

C The following individuals were selected from clinical specialist and patient advocate nominations from the professional/specialist and patient/carer groups. They gave their expert personal view on fludarabine by providing written and oral evidence to the Committee. They were also invited to comment on the appraisal consultation document (ACD).

- Professor Terry Hamblin, Professor of Immunohaematology, nominated by the Leukaemia Research Fund as a clinical specialist
- Dr Andrew Pettitt, Reader and Consultant Haematologist, nominated by the British Committee for Standards in Haematology as a clinical specialist
- Jane Barnard, patient member, nominated by the Chronic Lymphocytic Leukemia Support Association as a patient expert
- Dr Howard Pearce, chairman of and nominated by the Chronic Lymphocytic Leukemia Support Association as a patient expert.

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## Appendix C. List of organisations involved in this appraisal

The following organisations are consultees/commentators in this appraisal. They were invited to comment on the ACD and supporting evidence. Consultees are also invited to appeal against the final appraisal determination.

### I Professional/specialist and patient/carer groups:

- British Committee for standards in Haematology
- Cancer Networks Pharmacists Forum
- Cancer Research UK
- Royal College of Nursing
- Royal College of Pathologists
- Royal College of Radiologists
- Cancerbackup
- Children with Leukaemia
- Chronic Lymphocytic Leukemia Support Association
- Leukaemia Care

### II Other consultee organisations:

- Department of Health
- Welsh Assembly Government

### III Commentator organisations (without the right of appeal):

- British National Formulary
- NHS Quality Improvement Scotland
- Janssen-Cilag Ltd
- Roche Products Ltd
- Liverpool Review and Implementation Group, University of Liverpool
- National Coordinating Centre for Health Technology Assessment
- National Collaborating Centre for Cancer

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