All Wales Medicines Strategy Group

Grŵp Strategaeth Meddyginiaethau Cymru Gyfan

Final Appraisal Report

Clofarabine (Evoltra®)
BioEnvision

Advice No: 0107 – June 2007

Recommendation of AWMSG:

Clofarabine (Evoltra®) is recommended for use within NHS Wales for the treatment of acute lymphoblastic leukaemic (ALL) in paediatric patients (≤ 21 yrs) who have relapsed or are refractory after receiving at least two prior regimens and where there is no other treatment option anticipated to result in a durable response. Treatment is restricted to patients in whom there is an intention to proceed to stem cell transplantation and who are under the care of a paediatric haemato-oncologist, as it is not cost effective when used for palliation. Its use will be audited and reviewed in 2009.

This report should be cited as:

All Wales Medicines Strategy Group. Final Appraisal Report – Clofarabine (Evoltra®) June 2007

1.0 RECOMMENDATION OF AWMSG:

The advice represents the view of the All Wales Medicines Strategy Group and was arrived at after evaluation of the evidence submitted by the manufacturers up to and including 15th January 2007. Local Health Boards and Trusts are expected to follow recommendations from AWMSG within 3 months of Ministerial endorsement. AWMSG advice is interim to NICE guidance should this be subsequently published. Individual clinicians should take account of guidance issued by NICE or AWMSG when exercising their clinical judgement, unless there is evidence to justify not doing so in the light of the particular circumstances of an individual patient.

Date: 12th June 2007

Clofarabine (Evoltra®) is recommended for use within NHS Wales for the treatment of acute lymphoblastic leukaemic (ALL) in paediatric patients (≤ 21 yrs) who have relapsed or are refractory after receiving at least two prior regimens and where there is no other treatment option anticipated to result in a durable response. Treatment is restricted to patients in whom there is an intention to proceed to stem cell transplantation and who are under the care of a paediatric haemato-oncologist, as it is not cost effective when used for palliation. Its use will be audited and reviewed in 2009.

Key factors influencing recommendation:

AWMSG has considered the effect of clofarabine in enabling remission, which may then allow haematological stem cell transplantation (HSCT). This has potential for a significant impact on long-term treatment outcome. However, the estimates of the proportion of patients who subsequently receive HSCT, the life expectancy post-HSCT, and the quality of that life following clofarabine treatment, are all uncertain, which may also have a significant effect on the cost-effectiveness of the drug. Therefore, AWMSG strongly advise a review of all available data (not just within NHS Wales) in two years time. This will include a prospective collation of feedback from clinicians through a registry of patients receiving clofarabine within NHS Wales.

2.0 PRODUCT DETAILS:

2.1 Licensed indication[1]:

Treatment of acute lymphoblastic leukaemia (ALL) in paediatric patients who have relapsed or are refractory after receiving at least two prior regimens and where there is no other treatment option anticipated to result in a durable response. Safety and efficacy have been assessed in studies of patients no older than 21 years of age at initial diagnosis[1].

2.2 Dosing[1]:

The recommended dose is 52mg/m^2 of body surface area administered by intravenous infusion over two hours daily for five consecutive days. Body surface area must be calculated using the actual height and weight of the patient before the start of each cycle. Treatment cycles should be repeated every two to six weeks (from the starting day of the previous cycle) following recovery of normal haematopoiesis (i.e. an absolute neutrophil count greater or equal to 0.75 x 10^9 per litre) and return to baseline organ function. A 25% dose reduction may be warranted in patients experiencing significant toxicities. There is currently limited experience of patients receiving more than three treatment cycles. Therapy should be initiated and supervised by a physician experienced in the management of patients with acute leukaemias[1].

2.3 Market authorisation date: 29th May 2006[2]

2.4 UK Launch date: 15th August 2006[3]

3.0 DECISION CONTEXT

Acute leukaemia is the most common form of cancer in children, comprising of approximately 30 percent of all childhood malignancies. Acute lymphoblastic leukaemia (ALL) is the most common form, and accounts for approximately 85% of all cases of childhood leukaemia [4,5]. The peak incidence occurs between the ages of about two and four years, with males affected more often than females at all ages [5].

There is no current clinical standard treatment, but commonly used agents in paediatric ALL include anthracyclines, nucleoside analogues, alkylating agents and corticosteroids[6]. Survival rates for ALL have improved during the past two decades, due to the development of new combination regimens, however, approximately 20-25% of ALL in remission still relapse [4]. In general, given the intensity and number of previous chemotherapeutic regimens, patients with ALL in relapse have a broad resistance to many of the agents currently used and have concurrent conditions and accumulated organ toxicity, making it difficult to induce a second or third complete remission [4].

Based on historical data from German and Dutch cancer registries, the prognosis for patients with multiple relapsed ALL is very poor and, although such historical comparisons are notoriously difficult and prone to bias a median survival of 9-10 weeks without further intervention has been estimated [4]. In some cases, remission induction is attempted with an intensive chemotherapy and/or stem cell transplantation [4,6]. The place of haematological stem cell transplant (HSCT) is restricted to treatment of children who have experienced a relapse early in their treatment or who have suffered more than one relapse; although a small proportion of children with high-risk disease may be considered for a possible donor stem cell transplant while in first remission [5,6].

Clofarabine is a second-generation purine nucleoside anti-metabolite that was developed to overcome some of the limitations of earlier nucleoside analogues, while retaining their favourable structural and metabolic properties [7-9]. The company consider that since the benefit of a HSCT is largely restricted to patients who are in remission at the time of transplantation, responses achieved with clofarabine may allow patients to proceed to HSCT and this may influence duration of survival in paediatric patients who have exhausted all standard therapies.[10]

4.0 EXECUTIVE SUMMARY:

4.1 Review of the evidence on clinical effectiveness

Due to the rarity of the disease, clofarabine has been studied in only 61 paediatric patients with ALL and notably the number of responders to clofarabine who went on to receive HSCT was even less (18 out of 61). Consequently, data on the clinical efficacy and safety of clofarabine, including its effect on overall survival, is currently limited, and uncertainties remain due to the lack of a randomised, controlled, clinical efficacy and safety trials (with, for example, best supportive care). However, without further intervention, such patients with multiple relapse have an estimated median survival of nine to ten weeks. Hence, the effect of clofarabine in terms of remission and facilitating HSCT is considered by The European Public Assessment Report (EPAR) to be a clinically significant effect that may have a significant impact on long-term treatment outcome.

4.2 Review of the evidence on cost-effectiveness

Estimates of the proportion of patients receiving HSCT, life expectancy post HSCT, and the quality of that life, following clofarabine treatment are uncertain, and highly influential on the cost-effectiveness of clofarabine. The cost per life year gained ranged from £22,226 (base case) to over £100,000. Incremental cost per QALYs are likely to exceed these values.

Without clofarabine treatment, the alternative for this patient group is palliative care. Most patients who receive clofarabine will also not respond to treatment. However, clofarabine offers a proportion of patients the potential to receive HSCT, which may be viewed as a "definitive" therapy that may not otherwise be available.

If the company's estimates of the effectiveness and costs of clofarabine are realised in practice, then it is likely that clofarabine is within the bounds of what is considered to be cost-effective. However, the incremental cost per QALY gained indicated by the worst case scenario in the indicative cost-utility analysis exceeds what is considered to be cost-effective.

The Committee is mindful of the ultra-orphan drug status of clofarabine, and is of the opinion that clofarabine may be a cost-effective use of resources in NHS Wales, but only for treating patients with the intention of providing a potential bridge to HSCT. Clofarabine is not cost-effective when used only for palliative care.

5.0 LIMITATIONS OF DECISION CONTEXT:

Evaluation in a larger number of paediatric patients is required in order to provide further evidence of the clinical efficacy and safety of clofarabine in the treatment of such patients with relapsed/ refractory ALL. There remains limited clinical efficacy and safety data for administration of more than three treatment cycles.Further larger-scale trials are also required in order to establish the benefit of clofarabine treatment pre-HSCT on long-term outcomes.

6.0 SUMMARY OF THE EVIDENCE ON EFFICACY AND SAFETY:

6.1 Clinical efficacy:

The company submission included a Phase II trial (CLO-212), which formed the basis of registration applications in the EU and the US [4,10,11]. Further analysis of results from this study, have not been published and are available in abstract form only [12,13].

6.1.1 Phase II study of clofarabine in paediatric patients with refractory or relapsed acute lymphoblastic leukaemia [4,10,11]

This pivotal trial was a multi-centre, Phase II, open-label, non-comparative study conducted to determine the overall remission (OR) rate in heavily pretreated patients (younger than 21 years of age at initial diagnosis) with relapsed or refractory ALL. Patients must not have been eligible for therapy of higher curative potential and must have been in second or subsequent relapse and/or had failed to achieve remission after at least two prior regimens. Eligibility criteria included no prior chemotherapy within two weeks and no HSCT within the previous three months of study entry. Sixty-one paediatric patients received clofarabine administered intravenously at a dose of 52mg/m^2 over two hours daily for five consecutive days every two to six weeks following recovery of normal haematopoiesis and return to baseline organ function. Treatment was continued until disease relapse for a potential maximum of 12 cycles.

The primary endpoint was OR rate, defined as patients who achieved a complete remission (CR) or a CR without platelet recovery (CRp) divided by the total number of treated patients (Refer to Appendix 1 for further definitions). Secondary objectives included documentation of partial response (PR) rate, duration of remission, overall survival, and the safety and tolerability for the dosing regimen. Kaplan-Meier methods were used to summarise duration of remission and overall survival.

Results:
A total of 62 patients entered the study, and 61 patients received at least one dose of clofarabine. At the data cut-off point more than two years after the start of recruitment, the study population had been treated with a median of two clofarabine cycles (range: 1 to 11).

The OR rate was 20% (12/61) and for patients achieving OR, the median duration of remission was 28.6 weeks (95% CI: 9.7 to 58.6) and the median overall survival was 66.6 weeks (95%CI: 53.7 to 89.4) [10].

A total of 12% (7/61) of patients achieved a CR, 8% (5/61) achieved a CRp and 10% (6/61) achieved a PR. At the cut off date (30th September 2005), the median duration of remission in patients with a CR was 47.9 weeks (95%CI: 6.1 weeks to -), compared with 28.6 weeks (95%CI: 4.6 to 35.4 weeks) in those with a CRp and 5.2 weeks (95%CI: 2.3 weeks to -) with a PR. Median duration of remission for the 30% (18/61) responders who achieved at least a PR (CR +CRp + PR) was 11.7 weeks (95%CI: 6.1 to 47.9) [10].

The median overall survival was 66.6 weeks (95%CI: 53.7 to 89.4 weeks) for patients achieving a CR, 53.7 weeks (95%CI: 9.1 weeks to -) for those with a CRp, 33 weeks (95%CI: 18.1 weeks to -) for those with a PR, and 66.6 weeks (95%CI: 42.0 to 89.4 weeks) for patients with at least a PR. Treatment failure was reported for 54% (33/61) of patients, and a further ten patients were non-evaluable giving a non-response rate of 70% (43/61) with a median overall survival of 7.6 weeks[10].

At data cut off, there were 7/61 patients still alive, six of whom responded to treatment and one who was considered to be non-evaluable for response by the Independent Response Review Panel, but was considered a partial responder by the investigator and went on to receive a transplant. Six out of the seven patients had received a transplant and the remaining patient was expected to undergo transplantation[10].

Points to note from the study:

- Patients who enrolled in this study were reported to have received a median of three prior regimens of induction therapies, with over half (57%, 35/61) considered to have been refractory to their last course of therapy.
- Six out of the 12 patients achieving CR or CRp had not responded to their last regimen prior to receiving clofarabine. These regimens included etoposide, ifosfamide, and carboplatin; or combination therapy with cytarabine and either idarubicin, fludarabine or mitoxantrone [11].
- Approximately one third of patients had previously received HSCT.
- Due to the rarity of the condition, the number of evaluable patients in the pivotal study is small. Consequently, data is limited on the clinical efficacy and safety of clofarabine in the treatment of paediatric patients with relapsed/ refractory ALL.
- In this pivotal study, patients received a median of two treatment cycles with clofarabine. There remains limited clinical efficacy data for administration of more than three treatment cycles.
- Although adverse events were reported, no quality of life data was included in this study.
- The EPAR states there are still uncertainties due to the lack of a randomised, controlled, clinical efficacy trial to demonstrate the effect of clofarabine on overall survival. However, the report acknowledges it would not be reasonable to expect such comprehensive data due to the rarity of the condition[4].
- Furthermore, the report states that the effect of clofarabine in terms of remission and facilitating HSCT is considered to be a clinically significant effect that may have a significant impact on long-term treatment outcome[4].

Although not study endpoints in trial CLO-212, the submitting company included data presented in abstract form at the International Society of Paediatric Oncology in Geneva (September 2006). This includes outcome data of the participants from this study that proceeded to HSCT and those who did not after achieving a response following treatment with clofarabine (Refer to Sections 6.1.2 and 6.1.3 below) [12,13].

6.1.2 Outcome of stem cell transplant in paediatric relapsed/refractory acute lymphoblastic leukaemia (ALL) patients treated with clofarabine [12]

Ten patients (16%) went on to receive HSCT following clofarabine treatment. These included eight responders (three [CR], two [CRp], and three [PR]), one patient that was a non-responder and one non-evaluable patient mentioned previously. At the data cut off point, six patients in this group were still alive with survival ranging from 30.1+ weeks to 131.4+ weeks after initiation of clofarabine treatment. Notably this included two out of the three patients who had only a partial response to treatment with clofarabine but had proceeded to HSCT.

6.1.3 Response duration with single agent clofarabine in children with relapsed/refractory acute lymphoblastic leukaemia (ALL) [13]

Of the 18 patients who had a response to clofarabine (seven [CR], five [CRp], and six [PR]), ten did not receive HSCT. Multi-factorial reasons were proposed for responding patients not receiving HSCT including lack of donor availability, patient/parental withdrawal of consent, and institutional/physician standard practice. None were considered to have any clofarabine-related or clinically significant toxicity that would have prevented HSCT. Responses were seen in all ALL immunophenotypes, including pre-B cell and T-cell. At the time of the last data cut off, there was one patient in this group still living and expected to under go transplantation[10].

6.2 Safety:

- The toxicity profile observed with clofarabine is considered by the submitting company to be acceptable, manageable and typical of that seen with a single agent cytotoxic agent in a heavily pre-treated patient population [10].
- The incidence of Grade III and IV adverse events of neutropenia and febrile neutropenia seen in the pivotal study (CLO-212) were 15% and 49% respectively, and Grade III or higher hyperbilirubinemia was seen in 16% of children[11]. Other adverse events of Grade III and above that occurred in more than ten per cent of the patients in the pivotal study are listed in Appendix 1, along with Grade III or IV laboratory abnormalities reported.
- Clofarabine does not appear to be associated with the neurotoxicity reported with other agents in the same class[11].
- Infections reported as Grade III or more were observed in the majority (69%) of patients in trial CLO-212. Sepsis or septic shock was reported in 20%, fungal infections in 15% and viral infections in 16% of patients. Many of the infections were considered reactivations of a pre-existing infection documented before study enrolment[11].
- Of the 40 patients evaluable for cardio-toxicity, 61% (25/40) had no significant cardiac abnormalities, and 29% (12/40) had pericardial effusions, of which two were considered to be of haemodynamic significance. Increases in right ventricular pressure were reported in four patients and evidence of a decrease in left ventricular systolic function was noted in seven patients[11].
- Of the 15 deaths that occurred in trial CLO-212, two were determined to be drug-related. Further detail relating to these patients can be found in the paper published by Jeha and colleagues [11].
- Important identified risks with clofarabine are hepatic and cardiac toxicity, tumour lysis syndrome/systemic inflammatory response syndrome (SIRS)/capillary leak syndrome, and potentially renal toxicity [1,4,11].

- The summary of product characteristics states that clofarabine should be discontinued immediately should patients show early symptoms of SIRS/capillary leak syndrome, substantial organ dysfunction, or severe toxicity on a third occasion[1].
- The majority of patients respond to clofarabine after one or two treatment cycles; therefore the potential benefit and risks associated with therapy in patients who do not show haematological and/or clinical improvement after two treatment cycles should be assessed by the treating physician.
- The effects of clofarabine, like other antineoplastic agents, should be closely monitored for potentially significant haematological and non-haematological adverse events as highlighted in the Summary of Product Characteristics[1].
- Efficacy and safety have not been evaluated in children less than one year old, or in patients with renal insufficiency or hepatic impairment[1].

7.0 SUMMARY OF CLINICAL EFFECTIVENESS ISSUES:

7.1 Comparator medications:

At present there is no approved or standard therapy for the treatment of paediatric patients with ALL who have failed other currently available treatments. Therefore, an appropriate comparator in this case would be considered to be palliative care.

7.2 Comparative effectiveness:

- Currently there are no known ongoing or planned comparative studies [10,14].
- The company submission included an indirect comparison regarding complete response rates with three other single agent studies [15-17]. Although patients in these studies had refractory leukaemia, the study populations were not notably comparable.
- It is likely that the study population enrolled in the pivotal study adequately reflects the patient population in Wales and the licensed indication. However, it should be noted that children less than one year old have not been evaluated.
- There is an ongoing European non-randomised, open-label, phase II study of clofarabine in paediatric patients with refractory or relapsed ALL (Study BIOV-111)[18]. The patient population in study BIOV-111 is a similar population to that recruited to the pivotal CLO-212 study, however two out of 58 patients recruited so far have primary refractory ALL and as such would not have received two prior regimens of induction therapies. Enrolment will continue until 65 patients have been treated with two courses of clofarabine. The primary endpoint of study BIOV-111 is to determine the overall response (OR) rate in paediatric patients with refractory or relapsed ALL. Interim results are included with the company submission[10] and tabled in Appendix 1.

8.0 SUMMARY OF HEALTH ECONOMIC EVIDENCE:

8.1 Overview of the key economic issues for NMG to consider:

The key economic issue for the NMG to consider is:

1. Whether the additional benefits offered by clofarabine over relevant comparators justify the additional costs.
2. Whether the total budgetary impact of supporting the use of clofarabine acceptable.

8.2 Review of published evidence on cost-effectiveness:

Standard searches conducted across multiple databases and information portals have not identified any additional published economic studies of the use of clofarabine over those submitted by the company.

8.3 Review of company submission on cost-effectiveness:

8.3.1 Summary of the evidence

The company submission included an economic model, which was used to conduct a cost-effectiveness analysis of clofarabine against best supportive care (BSC) [10]. The primary outcome of this analysis was the incremental cost per life year gained. A supplemental cost utility analysis was also provided to calculate cost per QALYs gained, but rather than using utility values that had been assessed in this patient group, a range of possible utility values was applied to the cost per life year gained estimates generated by the cost-effectiveness model. This cost-utility analysis is therefore an indicative analysis only.

Estimates of the effectiveness of clofarabine used in the model were taken from the phase II study CLO-212. Survival estimates relating to BSC were taken from two European registry databases that had been used to support the clofarabine licence application to the EMEA. It is likely that these populations adequately reflect the patient population in Wales.

There are a number of assumptions that have been made in the model regarding treatment effectiveness. For clofarabine recipients who receive HSCT and survive for one year, the model assumes normal life expectancy (calculated as 67 years before discounting). No justification is provided for this assumption, which seems optimistic in this patient group. Sensitivity analysis indicates that the results are very sensitive to this assumption. In addition, the base case cost utility analysis also assumes that these patients have utility values the same as the UK norm. This would also seem to be optimistic. Patients receiving BSC are assumed not to receive HSCT; even though (by comparison) a proportion of patients not responding to clofarabine received HSCT in the model.

Health care resource utilisation and costs for patients receiving clofarabine were determined in consultation with the clofarabine clinical investigators. These were confined to the average number of vials of clofarabine used per patient in the trial (costed at the UK price per vial), estimated inpatient episodes for clofarabine administration and the resource associated with HSCT (based on costs and resources taken from 2004 NHS Schedule of Reference Costs) [19]. No consideration was given to the costs of palliation in patients unresponsive to clofarabine, or who do not subsequently receive HSCT. The costs of possible adverse effects were not considered in the base case analysis. The model did not consider personal and social service resources or costs, which could feasibly be substantial for this patient group.

Estimates of resource use associated with BSC were assumed as being the same as the costs of the most intensive resource pattern identified in a study of cancer palliative care resource use conducted in 2001 (i.e. advanced ovarian cancer in adults) [20]. There is clearly a great deal of uncertainty around this assumption, and there is no indication that it has been tested externally for validity or within the model by sensitivity analysis.

It is worth noting that, as the evaluable number of patients in the trial (n=51) and registries (n=65) are small, and the number of patients in study CLO-212 responding to clofarabine (18) and receiving HSCT (8) are even smaller, a change of even one patient regarding any particular outcome would potentially significantly affect the estimate of the probability of that outcome occurring. The company submission did not include a sensitivity analysis on the probability of patients receiving surgery following clofarabine treatment, nor did it consider the effect of confining HSCT eligibility only to specific levels of clofarabine response.

8.3.2 Summary of key findings from the company submission in cost-effectiveness:

The cost-effectiveness of clofarabine is greatly influenced by its ability to enable patients to receive HSCT, and estimates of their subsequent life expectancy.

In the base case analysis, the incremental cost-effectiveness of clofarabine relative to BSC was estimated as £22,226 per life year gained (assuming UK normal survival for patients who had survived more than one year following HSCT). This is based on clofarabine providing an average (discounted) survival benefit (over BSC) of 2.31 years at an additional cost of £51,271 per patient treated. This was sensitive to the assumed life expectancy of HSCT recipients, increasing exponentially with decreasing life expectancy in these patients to over £100,000 at a life expectancy of seven years.

In the indicative cost-utility analysis, patients who received HSCT and survived beyond one year were assumed to have UK normal life expectancy and utility values. This resulted in an incremental cost per QALY of around £25,600. Reducing the assumed utility by 0.3 points increased the incremental cost per QALY to £38,754. However, varying these assumptions to the worst-case scenario considered in the analysis (life expectancy of seven years and utility vales 0.3 less than the UK norm) raised the incremental cost per QALY to £160,580.

8.4 Review of evidence on budget impact:

8.4.1 Summary of the evidence

The budget impact analysis assumes there will be 23 children diagnosed with ALL in Wales each year[10]. Of these 23 children, 80% are estimated to be cured with first-line treatment. Half of the remaining children are estimated to be cured with second line treatment, leaving two children who would meet the licensed indication for clofarabine. The company estimated 10 patients would be eligible for clofarabine over a five-year period.

The budget impact model considered only the drug costs of clofarabine, and the costs of BSC as used in the cost-effectiveness analysis. No consideration has been given to the wider costs of clofarabine, such as costs of administration, HSCT in responders, possible adverse events, or the costs of palliative care in non-responders to clofarabine or those who do not subsequently receive HSCT. The cost of clofarabine has been assumed as £43,200 per patient treated, based on the average costs of the drug volumes used in study CLO-212 (based on 1.8 cycles of treatment, a patient body surface area of $1.2m^2$ and the licensed dose of $52mg/m^2$/five-day treatment cycle). The cost of three months of BSC is taken as £5,501 per patient. This is subject to great uncertainty, as this estimate has been assumed from a review of palliative care costs in adult patients.

There are no direct savings considered in the analysis, such as possible savings in palliative care costs for patients who respond to clofarabine. No consideration is given to any differential rates of adoption of clofarabine, or subgroups of patients. Uptake is assumed as 100% in all patients meeting the licensed indication for clofarabine.

8.4.2 Summary of key findings from the company submission on budget impact:

The budget impact analysis presented expects that two patients or less per year would be prescribed this treatment by paediatric haematology consultants at a total annual cost for NHS Wales of £86,400 (based on two patients being treated). This excludes the administration costs of clofarabine (which would be £9,200 for two patients according to the costs assumed in the cost-effectiveness model) and may be a conservative estimate due to uncertainty around the actual dose that will be required by those two patients.

9.0 ADDITIONAL INFORMATION:

9.1 Guidance and audit requirements:

- At present there is no nationally accepted standard therapy for this patient population.
- To minimise risk and monitor safety of clofarabine AWMSG could consider encouraging prescribers to participate in a voluntary adverse reporting system to collect information from all registered patients on any serious treatment-emergent possibly drug-related events, including CTC Grade III or higher renal, hepatic or cardiac events, suspected drug interaction adverse events and all possibly drug-related deaths.
- Details of the special warnings and precautions for treatment with clofarabine, as well as interaction with other medicinal products, can be found in the Summary of Product Characteristics[1].
- It is the view of AWMSG that clofarabine is not suitable for shared care.

9.2 Related advice:

NICE has issued cancer service guidance on improving outcomes for haemato-oncology cancer[21]and also on improving outcomes with children and young people with cancer[22].

9.3 Previous AWMSG/NICE advice:

There has been no previous guidance from AWMSG or NICE relating specifically to clofarabine therapy or to acute lymphoblastic leukaemia in paediatric patients.

9.4 Medical Expert

Medical expert opinion was sought and provided prior to the meeting.

9.5 Patient Interest Group

A patient interest group submission by Leukaemia Care was provided to AWMSG members.

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APPENDIX 1 Additional clinical information

DEFINITION OF RESPONSE RATES[1]

To enable systematic evaluation of the responses seen in patients, an unblinded Independent Response Review Panel (IRRP) determined the following response rates based on definitions produced by the Children's Oncology Group:

Complete Remission (CR)

Patients who met each of the following criteria:

- No evidence of circulating blasts or extramedullary disease
- An M1 bone marrow (≤ 5% blasts)
- Recovery of peripheral counts (platelets ≥ 100 x 10^9/l and ANC ≥ 1.0 x 10^9/l)

Complete Remission in the Absence of Total Platelet Recovery (CRp)

- Patients who met all of the criteria for a CR except for recovery of platelet counts to > 100 x 10^9/l

Partial Remission (PR)

Patients who met each of the following criteria:

- Complete disappearance of circulating blasts
- An M2 bone marrow (≥ 5% and ≤ 25% blasts) and appearance of normal progenitor cells
- An M1 marrow that did not qualify for CR or CRp

Overall Remission Rate (OR)

Overall remission rate = (Number of patients with a CR + Number of patients with a CRp) ÷ Number of eligible patients who received clofarabine

Treatment Failure (TF)

All other responses were considered to be treatment failures

ADVERSE EVENTS (Grade III or IV) AND LABORATORY ABNORMALITIES FROM THE PIVOTAL PHASE II STUDY[11]

Table 4. Grade 3, 4, and 5 Adverse Events Regardless of Causality That Occurred in ≥ 10% of Patients (N = 61)

	Patients With Grade ≥ 3 Adverse Events in All Cycles*		No. of Total Grade ≥ 3 Adverse Events in All Cycles	Grade ≥ 3 Adverse Events in Cycles 1 and 2*		Grade ≥ 3 Adverse Events in Cycles 3+*	
Adverse Event	No.	%		No.	%	No.	%†
Febrile neutropenia	30	49	53	38	71.7	15	28.3
Anorexia	12	20	13	12	92.3	1	7.7
Hypotension	11	18	11	11	100	—	—
Nausea	10	16	10	10	100	—	—
Pyrexia	9	15	10	10	100	—	—
Neutropenia	9	15	10	8	80	2	20
Epistaxis	8	13	8	6	75	2	25
Diarrhea	8	13	8	8	100	—	—
Sepsis	8	13	8	8	100	—	—
Hallucination	8	13	9	9	100	—	—
Bacteremia	8	13	8	7	87.5	1	12.5
Respiratory distress	7	12	7	7	100	—	—
Hepatomegaly	7	12	7	6	85.7	1	14.3
Dermatitis	7	12	7	7	100	—	—
Petechiae	7	12	7	7	100	—	—
Staphylococcal infection	6	10	6	3	50	3	50
Pneumonia	6	10	6	5	83.3	1	16.7
Hypertension	6	10	7	7	100	—	—
Pleural effusion	6	10	6	6	100	—	—

*The number of cycles administered was as follows: total, 122 cycles; cycles 1 and 2, 79 cycles; and cycles 3+, 43 cycles.
†Nine patients received three or more cycles of clofarabine.

Commonly reported Grade III or IV laboratory abnormalities[11]:
Hypokalaemia (46%), increases in ALT (43%) and AST (38%), hyperbilirubinemia (16%), and hypophosphatemia (15%).

Trial BIOV-111[18]

Summary of Baseline Characteristics

Number of Patients	60
Age in Years: Median (Range)	10 (0.5-21)
Sex (Male: Female)	37:23
Prior Regimens: Median (Range)	2 (1-5)
ALL subtype B-lineage T-lineage Unverified	 27 9 24
Prior Transplants:	21 (35%)
Refractory : Relapsed	29: 31

Efficacy

Response	Responses after 1 course n=57	Reponses after 2 courses n=32
CR+CRp	13 (23%)	10 (31%)
CR	6 (11%)	3 (9%)
CRp	7 (12%)	7 (22%)
PR	3 (5%)	0 (0%)
CR+CRp+PR	16 (28%)	10 (31%)

Characteristics of Responding Patients

Responding patients	n=16
Previous transplant	10 (63%)
Proceeding to transplant after clofarabine Of these patients, 1 had prior transplant	4 (19%)
Duration of remission (range)	1.1 – 99.1+weeks
Survival (range)	8.0 - 108+weeks

APPENDIX 2 Health economic review

1. Description of company submission
The company submission included a Microsoft Excel decision model, which was used to conduct a cost-effectiveness analysis of clofarabine against best supportive care (BSC) [10]. The primary outcome of this analysis was the incremental cost per life year gained. A supplemental cost-utility analysis was also conducted to provide an indication of possible incremental costs per QALY.

2. Population
The decision model compares the population of study CLO-212 against a sample of 71 patients (65 evaluable patients) identified from two European registry databases as meeting the entry criteria for that study. These patients from the registry databases provide the BSC outcomes data. It is not possible to determine whether or not these patients represent all patients within the registry databases who would be classed as meeting the entry criteria for study CLO-212, or are a sub-sample.

As these populations reflect the licensed indication for clofarabine they are appropriate for providing outcomes data for the model. It is likely that these populations adequately reflect the patient population in Wales.

3. Perspective and time horizon
The model considers only direct costs from the perspective of the NHS Wales. No consideration is given to any personal and social service costs/resources, which is a limitation of the model as these could feasibly be substantial for this patient group.

The time horizon for analysis has been chosen to represent the assumed expected life time of the included patients. In the base case analysis it has been assumed that patients who are successfully treated with clofarabine and go on to receive HSCT and survive at least one year will subsequently achieve normal life expectancy. Based on the average age of patients at entry into study CLO-212, the base case analysis assumes this survival to be 67 years (before discounting).

4. Comparator
BSC has been chosen as the comparator for the analyses. This is appropriate given the licensed indication for clofarabine. Outcomes data (survival) for BSC are derived from two registry databases. Patients entered in the registries are reported to have received the current best treatment practice from the institution where they were treated, which included additional active therapy and/or BSC. No further details are provided with respect to the treatment actually received by these patients.

5. Clinical inputs
5.1 Efficacy & Health Outcomes
Response rates, probability of receiving HSCT and survival for patients treated with clofarabine were derived from study CLO-212. Duration of survival with BSC was derived from the two registry databases. It is worth noting that, as the patient numbers in these trials and registries are small, even a change of one patient regarding any particular outcome can significantly affect the probability of that outcome occurring. A probabilistic analysis, that would have captured the parameter uncertainty, was not employed.

For patients who receive HSCT and survive for one year, the model assumes normal life expectancy. No justification is provided for this assumption and it seems optimistic to assume normal life expectancy in these patients who, by their nature, have been exposed to intensive treatment with cytotoxic agents that may potentially have significant

long-term adverse effects. This assumption has been tested in a sensitivity analysis, which considered life expectancies following HSCT ranging from 7–87 years. No justification for this range of years is provided and the company submission acknowledges that more research is required regarding survival post HSCT.

In the cost-utility analysis, the utility values used to convert life years gained into QALYs were not informed by research or published literature relating to ALL in paediatric patients. Instead, a range of utility values has been assumed and tested via sensitivity analyses (see section 8.2 below). The base case cost utility analysis not only assumes that those who survive longer than a year following HSCT have normal life expectancy, but also that they have utility values the same as the UK norm. This may also be an optimistic assumption. Sensitivity analysis was conducted by reducing the utility values in one-year survivors of HSCT by 0.1–0.3 points (see section 8.2).

5.2 Adverse events

Adverse events associated with clofarabine treatment have not been incorporated into the model. A *post hoc* analysis on the total *cost* of clofarabine treatment has been reported in the company submission. In a worst case scenario of 4 additional inpatient episodes as a result of clofarabine adverse events, the incremental cost per life year gained was not significantly changed, which the company infers to mean the model is not very sensitive to this parameter. Adverse events in study CLO-212 commonly included infections, and significant cardiac abnormalities developed in 39% of the 40 patients for who echocardiograms or multiple-gated acquisition (MUGA) scans were available.

6. Healthcare resource utilisation and cost

The model considers only direct resources and costs. No consideration is given to any personal and social service resources or costs, which is a limitation of the model as these could feasibly be substantial for this patient group (especially given the uncertainty regarding the assumed utility values and life expectancy of patients who survive over one year post HSCT). Resource use and costs of adverse events with clofarabine have not been specifically incorporated in the model.

All costs are presented in 2005 UK£. Health care resource utilisation and costs for clofarabine patients were determined in consultation with the clofarabine clinical investigators. These were confined to the average number of vials of clofarabine used per patient in the trial (costed at the UK price per vial), estimated inpatient episodes for clofarabine administration and the resource associated with HSCT (based on costs and resources taken from 2004 NHS Schedule of Reference Costs).

Estimates of resource use associated with BSC were not readily available for this patient group. Average costs for BSC have been assumed as being the same as the costs of the most intensive resource pattern identified in a study of cancer palliative care resource use conducted in 2001 (i.e. advanced ovarian cancer in adults) [19]. There is clearly a great deal of uncertainty around these costs. There is no indication that these assumed costs of BSC have been tested externally for validity or that they have been tested in the model by sensitivity analysis.

The model assumes that patients who do not respond to clofarabine, or who respond and receive HSCT but do not survive beyond one year, do not consume any further healthcare resources (i.e. no consideration is given to resources and costs of palliative care in these patients). Given that 70% of patients did not respond to clofarabine, and 30% of those who responded and received HSCT did not survive beyond one year, this assumption can be said to underestimate the total costs associated with clofarabine treatment. The effect of this assumption appears not to have been explored in the company submission.

7. Discounting

Outcomes and costs in the model were discounted at 3.5%. No sensitivity analyses were conducted to explore the effect of different discount rates on the model outputs.

8. Results

8.1 Base-case analysis of the cost-effectiveness model

The incremental cost-effectiveness of clofarabine relative to BSC was estimated as £22,226 per life year gained (assuming UK normal survival for patients who had survived more than one year following HSCT). This is based on clofarabine providing a survival benefit of 2.31 years at an additional cost of £51,271 per patient treated.

8.2 Indicative cost-utility analysis

In the base case indicative cost-utility analysis, life expectancy and utility were assumed to be the same as UK norms for patients who had received HSCT and survived beyond one year. The utility values attached to the life years gained for patients who did not respond to clofarabine or who died within a year of HSCT were varied between 0.2 and 1.0. This produced costs per QALY gained ranging from £25,600 to £26,100 (i.e. the model was not sensitive to utility values in children with limited life expectancy).

8.3 Sub-group analysis

No subgroup analysis has been presented in the company submission.

9. Sensitivity analysis

The company submission describes three one-way sensitivity analyses that have been conducted on the cost-effectiveness model. No attempt was made at a probabilistic sensitivity analysis. Details of additional analyses performed on the indicative cost-utility model, and performed by the assessment team are provided in sections 9.4 and 9.5, respectively.

9.1 Life expectancy in patients surviving more than one-year post HSCT

The model was very sensitive to this assumption. Varying the assumed life expectancy from 67 years down to 7 years generated incremental costs per life year gained of £22,226 to £100,960. No justification is given for not testing life expectancies lower than 7 years. The increase in incremental costs per life year gained is exponential - at a life expectancy of 3 years it is £251,500.

9.2 Life expectancy in patients receiving BSC

The model was sensitive to this assumption. The base case analysis uses a life expectancy of 0.37 years for BSC based on registry data. Increasing this estimated life expectancy up to 1.4 years increased the incremental cost per life year gained to £40,156. No justification is provided for the upper limit of 1.4 years.

9.3 Number of clofarabine vials used per treatment

As would be expected, the model was sensitive to the number of clofarabine vials used per treatment, as this would affect the direct costs of clofarabine treatment. The base case analysis assumes 36 vials per treatment, based on an average of 1.8 treatment cycles, a patient body surface area of 1.2m^2 (based on a median patient age of around 12 years), and the licensed dose of clofarabine (52mg/m^2/day for five days per treatment cycle). No consideration was given in the base-case analysis to the variance in dose, which would be expected given the potential age range of eligible patients. In addition, the total number of vials used would also be influenced by the number of treatment cycles, which may exceed the average of those seen in study CLO-212. Increasing the number of vials per treatment from 36 to 56 in the sensitivity analysis increased the incremental cost per life year gained to £32,600. No sensitivity analyses have been

conducted around the costs of BSC, which have been assumed from a completely different patient group.

9.4 Health state utility (indicative cost utility analysis)

Reducing the utility values attached to life years gained in those surviving over one year by up to 0.3 points (but keeping life expectancy the same as UK norm and assuming a utility value of 0.4 for the other patient groups) increased the cost per QALY gained to £38,800, indicating that the model was more sensitive to utility values amongst these patients.

A two-way sensitivity analysis of life expectancy and utility values in patients surviving more than one year following HSCT found that the most optimistic scenario tested (67 year survival with utility values equal to the UK norm) produced an estimated cost per QALY of £25,700. The worst-case scenario tested (seven-year survival at utility values 0.3 points lower than the UK norm) produced an estimated cost per QALY of £160,580 No justification has been provided for using 0.3 as the worst reduction in utility values or seven years as the minimum life expectancy tested in these analyses.

9.5 Eligibility for HSCT

In study CLO-212 only eight of 18 clofarabine responders received HSCT. This was thought to be due to a number of factors, such as a lack of donor availability, or physician standard practices, but the probability of receiving HSCT for each level of response (except 'No Response') was similar. The impact of different practices of offering HSCT on the basis of response to clofarabine has been explored by the Committee, by setting the relevant probabilities of receiving HSCT for specific levels of clofarabine response to zero within the model (all else being equal):

Clofarabine response levels eligible for HSCT:	**Description of policy in relation to clofarabine response**	**Incremental cost per life year gained**
CR+CRp+PR+NoR	As in base case analysis	£22,226
CR+CRp+PR	HSCT only available to those with a response	£27,676
CR+CRp	HSCT only available to those with a complete remission	£37,434
CR	HSCT only available to those with complete remission and complete platelet recovery	£60,172
None	No-one eligible for HSCT – clofarabine used only for palliation	£2.36 million
CR = complete remission, CRp = complete remission without platelet recovery, PR= partial remission, NoR = No evaluable response		

This analysis highlights that the incremental cost per life year gained estimated in the base case analysis is heavily dependent upon a proportion of clofarabine recipients receiving HSCT.

Company submission - budget impact analysis

The perspective adopted by the budget impact analysis is that of NHS Wales. However, it is based on cost data derived from the decision model provided by the company and extrapolated incidence data from the US, which has been taken from an article that reviews the treatment of ALL. Although this review article was published in 2006, the reference cited for the incidence data it contains is dated 1998 [23]. Data on the rates of

cure after initial diagnosis are taken from this same review article and cure rates after first relapse are taken from a recently published UK study (data collected between 1995 and 2002) [24]. In the absence of other incidence data, this would seem a reasonable approach.

Based on a US incidence of childhood ALL of eight per million population, and taking the population of Wales as 2.9 million, the budget impact analysis assumes there will be 23 children diagnosed with ALL in Wales each year. Of these 23 children, 80% are estimated to be cured with first-line treatment. Half of the remaining children are estimated to be cured with second line treatment, leaving 2.5 children who would meet the licensed indication for clofarabine. The company has rounded this down to two children per year, who are currently treated with palliative care. This should have been rounded up to three children.

No consideration is given to any differential rates of adoption or subgroups of patients. Uptake is assumed as 100% in all patients meeting the licensed indication for clofarabine.

The budget impact analysis estimates the net number of patients over a five-year period as 10 patients on the assumption of two children per year. If we assume that the annual incidence of two cases per year is correct, this net number of patients would represent the maximum net number of patients over a five-year period.

The direct costs of treatment used in the budget impact analysis consider only the drug costs of clofarabine and the costs of BSC as used in the cost-effectiveness analysis. No consideration has been given to the wider costs of clofarabine, such as costs of administration, HSCT in responders, possible adverse events, or the costs of palliative care in non-responders to clofarabine or those who do not subsequently receive HSCT. Indirect costs associated with clofarabine use are not incorporated. No sensitivity analyses have been conducted on the direct costs.

The cost of three months of BSC is taken as £5,501 per patient. This is subject to great uncertainty, as this estimate has been assumed from a review of palliative care costs in adult patients (see discussion in section 6).

The cost of clofarabine has been assumed as £43,200 per patient treated, based on the average costs of the drug volumes used in study CLO-212 (based on 1.8 cycles of treatment, a patient body surface area of 1.2m^2 and the licensed dose of 52mg/m^2/five-day treatment cycle. As it is not possible to predict the body surface area of the 2 patients estimated to become eligible for treatment with clofarabine each year in Wales, or the number of treatment cycles they will receive, this cost is uncertain and could be conservative. It is worth noting that the SPC states the majority of patients who respond to clofarabine achieve a response after one or two treatment cycles. Therefore, the potential benefit and risks associated with continued therapy in patients who do not show haematological and/or clinical improvement after two treatment cycles should be assessed by the treating physician.

There are no direct savings considered in the analysis, such as possible savings in palliative care costs for patients who respond to clofarabine. The analysis considers that net resource implications will be the same each year (no attempt has been made to discount these over the five-year period).

The budget impact analysis presented expects that $\leq$ two patients or less per year would be prescribed this treatment by paediatric haematology consultants at a total annual cost for NHS Wales of £86,400 (based on two patients being treated).

If administration costs are included, based on those assumed in the cost-effectiveness model, this would add £9,200 to this estimate (based on two cycles of treatment at an inpatient cost of £2,308 per cycle per patient).

All Wales Medicines Strategy Group Data Collection Form
Clofarabine (Evoltra®)

To be completed by the prescribing physician for paediatric patients receiving clofarabine in the treatment of acute lymphoblastic leukaemia (ALL) in accordance with the licensed indication, where the intention is to proceed to stem cell transplant.

TO BE RETAINED UNTIL REQUESTED BY AWMSG SECRETARIAT (August 2009)

PATIENT INITIALS:	**PRESCRIBING PHYSICIAN:** **GP:**
D.O.B.	Patient Hospital No.
Male/Female	Patient NHS No.
Height: Weight:	Year of Diagnosis:
HISTORY OF DISEASE: **Date of diagnosis:** **Date of first remission:** **Date of first relapse:** **Date of second remission:** **Date of second relapse:** **Date of current relapse:**	**PREVIOUS TREATMENT:** **Name of protocol used for first induction:** **Treatment used for second induction:** **Has patient had SCT? Yes No** **Type Date**
START DATE AND DOSE OF CLOFARABINE: **CONCURRENT MEDICATIONS:** **POSSIBLE SERIOUS TREATMENT-EMERGENT ADVERSE EVENTS:**	**PLANNED Treatment after CLOFARABINE** **A potential BM Donor available?** **Yes No** **If Yes, is donor:** **Full HLA Match** **Matched at……Loci**
Common toxicity criteria grade III or higher Renal events: Hepatic events: Cardiac events:	**Laboratory abnormalities**:
No. WEEKS DURATION OF TREATMENT (may be ongoing)	
No. WEEKS DURATION OF REMISSION (may be ongoing)	
DISCONTINUATION DATE:	
Please indicate reason for discontinuation:	
Successful bridge to HSCT	
Withdrawal of patient consent	
Adverse event(s)	
Disease progression	
Deceased	

Please return on request to:

Secretariat: The Welsh Medicines Partnership
Department of Pharmacology, Therapeutics & Toxicology
Wales College of Medicine
Heath Park
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CF14 4XN

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