Scottish Medicines Consortium

clofarabine, 1mg/ml concentrate for solution for infusion (Evoltra®) (No. 327/06)

Bioenvision Limited

8 December 2006

The Scottish Medicines Consortium (SMC) has completed its assessment of the above product and advises Area Drug and Therapeutic Committees (ADTCs) on its use in NHS Scotland. The advice is summarised as follows:

ADVICE: following a full submission

clofarabine (Evoltra®) is accepted for restricted use within NHS Scotland for the treatment of acute lymphoblastic leukaemia (ALL) in paediatric patients (≤ 21 years) 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.

It is restricted to patients in whom clofarabine is being used as a treatment to bridge to HSCT and restricted to use by specialists in paediatric haemato-oncology. It is not cost-effective when used for palliation.

Overleaf is the detailed advice on this product.

Chairman,
Scottish Medicines Consortium

Indication

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 ≤ 21 years old at initial diagnosis.

Dosing information

The recommended dose is 52mg/m^2 of body surface area administered by intravenous infusion over 2 hours daily for 5 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 2 to 6 weeks (from the starting day of the previous cycle) following recovery of normal haematopoiesis (i.e. absolute neutrophil count ≥ 0.75 x 10^9/l) 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 3 treatment cycles.

Product availability date

July 2006. Designated orphan status for this indication in February 2002.

Summary of evidence on comparative efficacy

Clofarabine is a purine nucleoside anti-metabolite. It is an inhibitor of both ribonucleotide reductase and DNA polymerase α.

A multi-centre, phase II, open label, non-comparative study was conducted to determine the overall remission (OR) rate in heavily pretreated patients (≤ 21 years old 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 refractory i.e. failed to achieve remission after at least two prior regimens. Other eligibility criteria included no prior chemotherapy within two weeks and no haematopoietic stem cell transplant (HSCT) within the previous 3 months. Clofarabine was administered intravenously at a dose of 52mg/m^2/day over 2 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 number of treated patients. Secondary objectives included documentation of CR, CRp, and of partial response (PR) rates, as well as duration of remission and overall survival and the safety profile and tolerability of clofarabine for this dosing regimen in this population. Kaplan-Meier methods were used to summarise duration of remission and overall survival. Toxicity was graded according to the National Cancer Institute - Common Toxicity Criteria (NCI-CTC).

In the intention-to-treat analyses at a data cut-off point more than three years after the start of recruitment, 61 patients had been treated with a median of two clofarabine cycles. The OR rate was 20% (12/61) and for patients achieving OR, the median duration of remission was 29 weeks (95% CI: 9.7 to 59) and the median overall survival was 67 weeks (95%CI: 54 to 89).

12% (7/61) of patients achieved CR, 8% (5/61) achieved CRp and 10% (6/61) achieved a PR. The median duration of remission in patients with CR was 48 weeks (95%CI: 6.1 to -),

compared with 29 weeks (95%CI 4.6-35 weeks) in those with CRp and 5.2 weeks (95%CI: 2.3 to -) with PR. Median duration of remission for the 30% (18/61) responders who achieved at least a PR (CR +CRp + PR) was 12 weeks. The median overall survival was 67 weeks with CR, 54 weeks with CRp, 33 weeks with PR and 67 weeks with at least PR.

Treatment failure was reported for 33 patients, and 10 further patients were non-evaluable giving a non-response rate of 43/61 (70%) with a median overall survival of 7.6 weeks.

At data cut off, there were 7/61 patients surviving. Although transplantation rate was not a study endpoint, 16% (10/61) received HSCT, of whom six survived - five responding patients (2CR, 1CRp and 2PR) and one non-evaluable patient. In this group, survival ranged from 30.1+ weeks to 131.4+ weeks after initiation of clofarabine treatment. The remaining survivor had achieved CRp and was planned for HSCT.

Summary of evidence on comparative safety

The European Public Assessment Report (EPAR) from the European Medicines Agency states that 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. The summary of product characteristics states that clofarabine should be discontinued immediately should patients show early symptoms of tumour lysis syndrome and cytokine release that could develop into SIRS / capillary leak syndrome or organ dysfunction.

To minimise risk and monitor safety of clofarabine prescribers are encouraged 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 3 or higher renal, hepatic or cardiac events, suspected drug interaction adverse events and all possibly drug-related deaths.

As patients usually show a haematological and/or clinical improvement after one or two treatment cycles the potential benefit and risks associated with continued therapy in patients who do not show haematological and/or clinical improvement after two clofarabine cycles should also be assessed.

Summary of clinical effectiveness issues

The EPAR states that patients with multiple relapsed ALL have an estimated median survival of 9-10 weeks without further intervention. In the pivotal trial, there was an overall remission rate of 20% and this was associated with a median overall survival of 67 weeks (compared with 7.6 weeks for non-responders) and a median duration of remission of 29 weeks. At a data cut-off more than three years after the start of recruitment 7/61 patients survived, of whom six had achieved a response to clofarabine.

Responses achieved with clofarabine may allow patients to proceed to HSCT and this may influence duration of survival. In the pivotal study, 10/61patients (16%) had received HSCT and a further patient is planned for HSCT. At data cut off, five of these transplanted patients were alive for more than one year and one alive more than two years after starting treatment. Ten responders did not receive HSCT. One of those was alive for more than one year after starting treatment and at data cut off was planned for transplant. Multifactorial 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.

There are limited safety and efficacy data for administration of more than three treatment cycles and an enhanced adverse event reporting system is being established, aimed at risk minimisation and includes monitoring adverse events occurring after three or more cycles.

The EPAR states that there are still uncertainties due to the limited size of the safety database and the lack of a randomised, controlled, efficacy trial to demonstrate the effect of clofarabine on overall survival, but concludes 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.

Summary of comparative health economic evidence

The incremental cost-effectiveness of clofarabine compared to best supportive care (BSC) was estimated by the manufacturer to be £23,514 per life year gained. The main data source for clofarabine survival outcomes was the phase II single arm clinical trial in 61 patients with ALL aged ≤21 years. Long term survival in the 6 patients remaining alive more than 1 year post HSCT was estimated to be an additional 67.3 years (i.e. normal life expectancy), or 26.6 years when discounted at 3.5% per annum. Overall, for all patients receiving clofarabine average survival was estimated at 2.68 years (discounted). The survival estimates for best supportive care (including best active palliative treatment) were derived from two observational European registries in ALL containing 71 patients who matched the entry criteria for the phase II trial. Survival was estimated to be an average of 19 weeks in these patients. Best supportive care (including some active therapy) is an appropriate comparator as patients eligible for clofarabine should be relapsed or refractory after at least 2 prior therapies and not be expected to be able to achieve a durable response to any other treatment option.

The economic analysis was constrained by the limited clinical data available. However, acceptable cost-effectiveness was very much dependent on the success of clofarabine in enabling patients to receive HSCT and the duration of survival benefit beyond this. The assumption of normal life expectancy in survivors 1 year post HSCT appears optimistic and when this assumption was relaxed in sensitivity analysis, the cost-effectiveness of clofarabine was significantly reduced. In addition, the economic analysis may have underestimated the costs per patient of clofarabine treatment. The manufacturer provided additional analysis to show the potential cost-effectiveness of clofarabine after taking into account the quality of life of patients who have HSCT. If quality of life in HSCT survivors was equivalent to the UK age-matched general population norms, the incremental cost per QALY of clofarabine over BSC was £25606. If quality of life values were 0.2 points lower in HSCT survivors than the general population, this figure rose to £33162 per QALY. These estimates assume normal life expectancy in survivors. If, for example, survival was only seven years post-HSCT and quality of life was equivalent to UK norms during this time the cost per QALY would to rise to over £100000.

When assessing medicines with orphan drug status, in addition to the usual assessment of clinical and cost-effectiveness, SMC may consider other factors, such as whether the drug may bridge a gap to a “definitive” therapy. Within this context the overall budget impact of the therapy may also be considered.

Summary of patient and public involvement

A Patient Interest Group Submission was not made.

Additional information: guidelines and protocols

Clofarabine was designated an orphan medicinal product in February 2002.

Additional information: comparators

There are no single agent comparators for clofarabine.

Additional information: costs

Drug	Body Surface Area (m^2)	Regimen	Cost per cycle (5days) (£)
Clofarabine	1.25	52mg/m^2/day by intra-venous infusion (52x1.25 =65mg/day)	24,000 (4 vials daily for 5 days)

Cost calculated using the mean age of 12 years from the baseline characteristics for the pivotal trial. The body surface area of 1.25m^2 is a mean value for a 12year old child from BNF for Children 2006. The cost of four 20ml (20mg) vials is £4800 (Monthly Index of Medical Specialities, August 2006). The SPC advises that children with a body surface area of ≤ 1.44 m^2 should have a total infusion volume of 100ml. Additional administration costs including the sodium chloride 100ml infusion bag have not been added.

Additional information: budget impact

The manufacturer has estimated a budget impact of £216k over a 5 year period based on 5 new eligible patients being treated per annum and a cost for clofarabine per year of £43,200. Given the number of vials the manufacturer assumed would be used in treatment, this may be a conservative estimate of the cost per patient.

Advice context:

No part of this advice may be used without the whole of the advice being quoted in full.

This advice represents the view of the Scottish Medicines Consortium and was arrived at after careful consideration and evaluation of the available evidence. It is provided to inform the considerations of Area Drug & Therapeutics Committees and NHS Boards in Scotland in determining medicines for local use or local formulary inclusion. This advice does not override the individual responsibility of health professionals to make decisions in the exercise of their clinical judgement in the circumstances of the individual patient, in consultation with the patient and/or guardian or carer.

This assessment is based on data submitted by the applicant company up to and including 23 November 2006

Drug prices are those available at the time the papers were issued to SMC for consideration. These have been confirmed from the eVadis drug database.

The undernoted references were supplied with the submission.

Jeha, S., Gaynon, P., Razzouk, B., Franklin, J., Kadota, R., Shen, V., Luchtman-Jones, L., Rytting, M., Bomgaars, L., Rheingold, S., Ritchey, K., Albano, E., Arceci, R., Goldman, S. C., Griffin, T., Altman, A., Gordon, B., Steinherz, L., Weitman, S., & Steinherz, P. 2006, "Phase II study of clofarabine in pediatric patients with refractory or relapsed Acute Lymphoblastic Leukemia", J Clin Oncol., vol. 24, no. 12, pp. 1917-1923.

Campbell J, Wallace WHB, Bhatti LA, Stockton DL, Rapson T, Brewster DH (2004). Childhood Cancer in Scotland: trends in incidence, mortality and survival 1975-1999. Edinburgh: Information and Statistics Division.