Scottish Medicines Consortium

nelarabine, 5mg/ml solution for infusion (Atriance®) No. (454/08)
GlaxoSmithKline UK

07 March 2008

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

ADVICE: following a full submission

nelarabine (Atriance®) is accepted for restricted use within NHS Scotland for the treatment of patients with T-cell acute lymphoblastic leukaemia (T-ALL) and T-cell lymphoblastic lymphoma (T-LBL) whose disease has not responded to, or has relapsed following, treatment with at least two chemotherapy regimens. It is restricted to patients in whom nelarabine is being used as a treatment to bridge to allogeneic stem cell transplant and restricted to use by specialists in haemato-oncology. It is not cost-effective when used for palliation.

Overleaf is the detailed advice on this product.

Chairman,
Scottish Medicines Consortium

Indication

The treatment of patients with T-cell acute lymphoblastic leukaemia (T-ALL) and T-cell lymphoblastic lymphoma (T-LBL) whose disease has not responded to, or has relapsed following, treatment with at least two chemotherapy regimens.

Due to the small patient populations in these disease settings, the information to support these indications is based on limited data.

Dosing information

The recommended dose of nelarabine for adults and adolescents (aged 16 years and older) is 1,500mg/m^2 administered intravenously over two hours on days 1, 3 and 5 and repeated every 21 days. The recommended dose of nelarabine for children and adolescents (aged 21 years and younger) is 650mg/m^2 administered intravenously over one hour daily for 5 consecutive days, repeated every 21 days.

In clinical studies, the 650mg/m^2 and 1,500mg/m^2 have both been used in patients in the age range 16 to 21 years. Efficacy and safety were similar for both regimens. The prescribing physician should consider which regimen is appropriate when treating patients in this age range.

Product availability date

17th September 2007.

In June 2005 nelarabine was granted orphan drug status in Europe for the treatment of acute lymphoblastic leukaemia.

Summary of evidence on comparative efficacy

The T-cell phenotype of acute lymphoblastic (lymphocytic) leukaemia (T-ALL) and lymphoblastic lymphoma (T-LBL) are rare, aggressive, life-threatening and difficult-to-treat conditions. Around 25-30% of children experience relapse or are refractory to initial induction therapy with a resultant poor prognosis.

Nelarabine is a nucleoside analogue prodrug that is rapidly converted to its active form 9-β-D-arabinofuranosylguanine 5'-triphosphate (ara-GTP) following intravenous administration. Accumulation of ara-GTP in cancer cells inhibits DNA synthesis, resulting in cell death.

The clinical efficacy of nelarabine has been evaluated in two phase II, single-arm, two-stage, open-label, multicentre pivotal studies, one in adult and one in paediatric patients, who had experienced recurrent or refractory T-ALL or T-LBL despite two previous induction regimens. The paediatric study involved 39 patients who were ≤21 years of age at initial diagnosis and who had a predicted life expectancy of at least 8 weeks. Patients received nelarabine as a 1-hour intravenous infusion at the licensed dose of 650mg/m^2 daily for the first 5 days of each 21 day cycle. Treatment was continued until disease progression, unmanageable toxicity, continued treatment with nelarabine was no longer deemed beneficial or treatment had been continued for two years. The adult study involved patients who were ≥16 years of age at initial diagnosis. Twenty-five patients received nelarabine as a 2-hour intravenous infusion at the licensed dose of 1.5g/m^2 on days 1, 3 and 5 of each 21 day cycle and 3 patients received a 2.2g/m^2 dose as per this treatment regimen (data from these subjects were included in all analyses). Patients were assessed for disease response on day 22 of cycle 1. If residual T-ALL / T-LBL were present, a second course of nelarabine was administered. If residual or recurrent T-ALL / T-LBL were still present after 2 treatment cycles the subject was withdrawn

from treatment. If complete remission was documented after the first or second cycle of treatment, 2 additional cycles were given as consolidation therapy. In both studies patients were permitted to receive full supportive care, including transfusions of blood and blood products, antibiotics and antiemetics.

Primary efficacy variables in each study included complete response with full haematological recovery (CR) and complete response with or without full haematological recovery (CR*). Patients who achieved a CR were also included in the patients who achieved a CR*. Secondary efficacy variables included survival (overall and 1-year), duration of response (defined as time from the date of response to the earliest of progression, death or last contact) and time to response. Efficacy data were reported for the 'all treated patients' population defined as those patients who received at least one dose of study drug. For overall survival (OS), patients who were lost to follow-up or who were alive at the end of the study were censored at their last contact date.

In the paediatric study, 97% of patients withdrew due mainly to progressive disease / no response (54% of patients). A CR was achieved in 13% of patients and a CR* in 23% of patients. The duration of CR* ranged from 6.4 to 36.4 weeks. There was a median OS of 13.1 weeks. Fourteen percent of patients survived 1-year. Stem cell transplant was performed in 4 out of 9 (44%) of the CR* patients.

In the adult study, the main reasons for discontinuation were progressive disease or relapse (43%) and no response to therapy (32%). A CR was achieved in 18% of patients and a CR* in 21% of patients. The duration of CR* ranged from 4 to 195.4 weeks, with a median duration of CR* of 24.5 weeks. There was a median OS of 20.6 weeks. Twenty nine percent of patients survived 1-year. Bone marrow transplant was performed in 2 out of 6 (33%) of the CR* patients.

Table: Response Rates and Survival from Two Phase II Clinical Studies

	Paediatric Study (≤ 21 years at diagnosis) Nelarabine 650mg/m^2 n=39	**Adult study Nelarabine 1.5g/m^2 n=28**
Complete response, n (%) [95% Confidence Intervals (CI)]	5 (13) [4 to 27]	5 (18) [6 to 37]
Complete response with or without haematological recovery, n (%) [95% CI]	9 (23) [11 to 39]	6 (21) [8 to 41]
Median overall survival, weeks [95% CI]	13.1 [8.7 to 17.4]	20.6 [10.4 to 36.4]
1-year survival, n (%) [95% CI]	5 (14) [3 to 26]	8 (29) [12 to 45]

*Other data were also assessed but remain commercially confidential.**

Summary of evidence on comparative safety

In the paediatric study, the most frequent adverse events were decreased haematological parameters: haemoglobin 38% (15/39), platelets 38% (15/39), white blood cells 36% (14/39) and neutrophils 28% (11/39). Most of these events were ≥ grade 3. Nervous-system disorders occurred in 28% (11/39) of patients. The most frequent serious adverse events were reported in the nervous system with peripheral sensory neuropathy and peripheral

motor neuropathy each occurred in 5.1% (2/39) of patients and convulsion in 2.6% (1/39) of patients.

In the adult study, 96% (27/28) of patients experienced at least one adverse event, the most frequent of which were decreased haematological parameters: haemoglobin 89% (25/28), platelets 68% (19/28) and neutrophils 57% (16/28). Nervous system disorders occurred in 61% (17/28) of patients. Serious adverse events, all of which were determined to be unrelated to nelarabine, were reported by 29% (8/28) of patients, with only dyspnoea occurring in more than one patient (11%, 3/28). Although 89% (25/28) of patients died following enrolment, no deaths were determined to be related to nelarabine.

The European Medicines Agency (EMEA) has indicated that there is a requirement to expand the safety database of nelarabine in children regarding neurological adverse reactions, and post–marketing safety data will be provided by the manufacturer.

*Other data were also assessed but remain commercially confidential.**

Summary of clinical effectiveness issues

There are no randomised, controlled clinical trials of nelarabine in the licensed indication. However, the EMEA states that the lack of randomised trials in this very heavily treated population is justified in view of the small size of the population of patients in second relapse. Even in the absence of adequately controlled trials, the EMEA concluded that nelarabine treatment achieved meaningful response rates and duration of response in a significant proportion of adult and paediatric patients, whose disease has not responded to or has relapsed following treatment with at least 2 chemotherapy regimens. The magnitude of the response was clinically relevant, allowing some patients to undergo stem cell transplantation.

The primary efficacy endpoint for both the adult and paediatric studies was complete response rate. This surrogate end point has been accepted by the EMEA as a suitable indicator of activity for cytotoxic agents and can be used in patients with acute leukaemia destined for transplantation, provided that it is supported by data on successful transplantation and, for example, leukaemia-free survival. Thus, complete response rate can be considered a reasonable surrogate for clinical benefit in the patient population under consideration.

To allow additional analysis, the response rates provided in this submission were determined independently by the manufacturer based on data provided by the Children's Oncology Group (COG) and the Cancer and Leukaemia Group B (CALGB). The rates provided by the manufacturer are somewhat lower than those reported by COG and CALGB for these studies due to a more conservative approach to analysis.

Quality of life was not evaluated in either the adult or paediatric study.

Summary of comparative health economic evidence

The manufacturer submitted a Markov model comparing nelarabine with best supportive care (BSC) for children and adults with T-cell acute lymphoblastic leukaemia and T-cell lymphoblastic lymphoma whose disease has not responded to, or has relapsed following, treatment with at least two chemotherapy regimens.

The clinical data for the nelarabine arm, particularly the probability of a stem cell transplant (SCT), came from the two phase II studies. Life expectancy after a SCT was estimated using censored data from the studies. BSC was assumed to be equivalent to the resources and costs of managing patients with ovarian cancer. Patients in this arm were never able to receive SCT. Other resource use and costs were from published Scottish sources and utilities from a prospective survey of similar patients treated in Wales.

The lowest base case result was with 3 cycles of nelarabine, with an incremental cost/QALY of £56,107 for adults and £43,717 for children. Sensitivity analyses showed the results were highly sensitive to survival after transplant and the probability of receiving this procedure. Changing survival to 10 years after a transplant reduced the incremental cost/QALY to £6,507 for children and £13,035 for adults.

An informal comparison with clofarabine using published data and the nelarabine model reported an incremental cost per life year gained in children for nelarabine compared to BSC care of < £9,000, compared to £23,514 per life year gained for clofarabine compared to BSC. These results assumed a life expectancy gain of over 64 years for children receiving a SCT compared to the 50.32 weeks assumed in the base case.

The main strengths of the economic evaluation include:

- Robust economic model with transparent and appropriate sources for clinical data, costs and utilities.
- Modelled clinical parameters reconciled to study outcomes.
- Results expressed as incremental cost/QALY so relevant to SMC decision making.
- Extensive sensitivity analyses.
- Informal comparison with clofarabine.

The main weakness was the absence of survival data post-transplant; in the base case, the survival data have been censored at the end of the studies and this seems unduly conservative.

In conclusion, nelarabine is an orphan drug and there are limitations in the data but the manufacturer has presented a good quality analysis that shows cost-effectiveness is highly dependent on patients receiving SCT in the nelarabine arm and the assumed survival after the procedure. However, the manufacturer's estimate of survival with treatment in the base case seemed pessimistic and using more optimistic estimates improved the ICER considerably. The informal analysis of clofarabine and nelarabine uses data from different patients groups and does have some limitations. but the comparative clinical data and relative prices suggest that nelarabine is likely to be at least as cost-effective as clofarabine, both compared to BSC.

Summary of patient and public involvement

Patient Interest Group Submissions: Rarer Cancers Forum; The Lymphoma Association.

Additional information: previous SMC advice

After review of a full submission, the Scottish Medicines Consortium (SMC) issued advice on 8th December 2006 that 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.

Additional information: comparators

For adult patients with T-ALL / T-LBL there are no direct comparators for use after second relapse and patients would receive 'best-supportive care'. For paediatric T-ALL 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, clofarabine is a comparator product. There is no alternative treatment to nelarabine for paediatric patients with T-LBL.

Cost of relevant comparators

Drug	Dose regimen	Cost per cycle (£)	Cost for three cycles[a] (£)
Nelarabine	1,500mg/m^2 on days 1, 3 and 5 and repeated every 21 days (adults and adolescents aged 16 years and older).	**7,326**	**21,978**
	650mg/m^2 for 5 consecutive days, repeated every 21 days (children and adolescents aged 21 years and younger).	**4,440**	**13,320**
Clofarabine	52mg/m^2/day for 5 consecutive days, repeated every 2 to 6 weeks (children ≤21 years).	24,000*	72,000*

Doses are for general comparison and do not imply therapeutic equivalence. Costs from the Monthly Index of Medical Specialities (MIMs) on 5th December 2007. Costs calculated using a body surface areas of 1.73m^2 and 1.25m^2 for adults and children, respectively. Calculations assume that unused drug will be discarded and a whole number of vials will be used. [a]Three cycles used as mean days of therapy in adult and paediatric clinical studies indicate an average of 2 to 3 cycles per patient. * Costs do not include the 0.9% sodium chloride infusion bags that are used during administration of clofarabine.

Additional information: budget impact

The manufacturer estimated that in year one, assuming no limits on the number of cycles per patient, the budget impact would range from £72k to £107k, depending on the response to treatment. Savings from lower supportive care costs would offset some costs giving a net increase in cost of £53k and £79k. By year 5, the budget impact would have increased to £362k or £535k depending on treatment response, with net cost impacts of £267k and £393k. This estimate includes palliative care use. Acceptance for restricted use means that the budget impact is likely to be less than the estimate.

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 16th January 2008.

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.

** Agreement between the Association of the British Pharmaceutical Industry (ABPI) and the SMC on guidelines for the release of company data into the public domain during a health technology appraisal: http://www.scottishmedicines.org.uk/*

The undernoted references were supplied with the submission. The reference shaded grey is additional to those supplied with the submission.

DeAngelo DJ, Yu D, Johnson JL, Coutre SE, Stone RM, Stopeck AT, Gockerman JP, Mitchell BS, Appelbaum FR, Larson RA. Nelarabine induces complete remissions in adults with relapsed or refractory T-lineage acute lymphoblastic leukemia or lymphoblastic lymphoma: Cancer and Leukemia Group B study 19801. Blood 2007;109:5136-5142.

Berg SL, Blaney SM, Devidas M, Lampkin TA, Murgo A, Bernstein M, Billett A, Kurtzberg J, Reaman G, Gaynon P, Whitlock J, Krailo M, Harris MB. Phase II study of nelarabine (compound 506U78) in children and young adults with refractory T-cell malignancies: a report from the Children's Oncology Group. J Clin Oncol 2005;23:3376-3382.

European Medicines Agency. Atriance European Public Assessment Report Scientific Discussion. Available at: http://www.emea.europa.eu.

Committee for Medicinal Products for Human Use (CHMP) guideline on the evaluation of anticancer medicinal products in man. European Medicines Agency, December 2005 (cpmp/ewp/205/95 rev.3).