All Wales Medicines Strategy Group

Grŵp Strategaeth Meddyginiaethau Cymru Gyfan

Final Appraisal Report

Nelarabine (Atriance®▼) for the treatment of T-cell acute lymphoblastic leukaemia and T-cell lymphoblastic lymphoma

GlaxoSmithKline UK

Advice No: 0909 – April 2009

Recommendation of AWMSG

Nelarabine (Atriance®▼) is recommended for restricted use within NHS Wales 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. Treatment should be restricted to patients in whom there is an intention to proceed to allogeneic stem cell transplantation, as it is not cost effective when used for palliation.

Nelarabine (Atriance®▼) is not suitable for shared care within NHS Wales.

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

This report should be cited as:

1.0 RECOMMENDATION OF AWMSG:

The AWMSG recommendation is based on: the Preliminary Appraisal Report, the Company Response to this, medical expert opinion, lay perspective and discussions at the AWMSG meeting.

Date: Wednesday, 29th April 2009

The recommendation of AWMSG is:

Nelarabine (Atriance®▼) is recommended for restricted use within NHS Wales 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. Treatment should be restricted to patients in whom there is an intention to proceed to allogeneic stem cell transplantation, as it is not cost effective when used for palliation.

Nelarabine (Atriance®▼) is not suitable for shared care within NHS Wales.

Additional note:

- Nelarabine (Atriance®▼) meets the AWMSG criterion for ultra-orphan drug status.
- AWMSG will review the evidence on the use of this medicine within a period of three years.

ABBREVIATIONS

ALL	Acute lymphoblastic leukaemia
AWMSG	All Wales Medicines Strategy Group
BMT	Bone marrow transplant
BNF	British National Formulary
BSA	Body surface area
BSC	Best supportive care
CI	Confidence interval
CR	Complete response
CNS	Central Nervous System
EMEA	European Medicines Agency
EPAR	European Public Assessment Report
FDA	US Food and Drug Administration
ICER	Incremental cost effectiveness ratio
ITT	Intention-to-treat
IV	Intravenous
LBL	Lymphoblastic leukaemia
NHS	National Health Service
NICE	National Institute for Health and Clinical Excellence
NMG	New Medicines Group
OS	Overall survival
PR	Partial response
PSA	Probabilistic sensitivity analysis
QALY	Quality-adjusted life year
SCT	Stem cell transplant
SPC	Summary of Product Characteristics
WMP	Welsh Medicines Partnership

2.0 PRODUCT DETAILS

2.1 Licensed indication

Nelarabine (Atriance®▼) is indicated 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[1].

Due to the small patient populations in these disease settings, the information to support these indications is based on limited data[1].

2.2 Dosing

Nelarabine must only be administered under the supervision of a physician experienced in the use of cytotoxic agents[1].

In patients aged 16 years and older, the recommended dose is 1,500 mg/m^2 administered by intravenous (IV) infusion over two hours on days 1, 3 and 5 and repeated every 21 days. In patients aged 21 years or younger, the recommended dose is 650 mg/m^2 administered by IV infusion over one hour daily for five consecutive days, repeated every 21 days. In clinical studies, the 650 mg/m^2 and 1,500 mg/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[1].

Limited data are available for patients below the age of four years. Insufficient numbers of patients aged 65 years and older have been treated with nelarabine to determine whether they respond differently to younger patients. Nelarabine has not been studied in patients with renal or hepatic impairment. See the Summary of Product Characteristics (SPC)[1] for full details.

2.3 Market authorisation date

22 August 2007[2].

2.4 UK Launch date

17 September 2007[2].

3.0 DECISION CONTEXT

Acute lymphoblastic leukaemia (ALL) and lymphoblastic lymphoma (LBL) are aggressive diseases that progress rapidly to a fatal outcome in the absence of effective therapy[3]. The T-cell lineage forms of the disease (T-ALL and T-LBL respectively) are less frequent, are considered higher risk and require more aggressive therapy, than B-cell forms. LBL is commonly considered the lymphomatous variant of ALL and current treatment for patients with T-LBL follows the same treatment strategy for T-ALL, with comparable results. Newly diagnosed patients are typically treated with induction chemotherapy and complete response (CR) rates of over 95% in children and 60-80% in adults are possible. Induction therapy is followed by additional cycles of multi-agent chemotherapy with the aim of long term disease control. However, approximately 25-30% of children experience relapse or are refractory to initial induction therapy and after first CR the majority of adult patients will eventually experience relapse. The cure rate of T-ALL and T-LBL in adults is lower than in children[3].

No consensus on the treatment of patients with relapsed or refractory disease exists, and therapy is largely individualised based on the nature of response to prior therapy[3]. Even in those achieving a second remission, the prognosis is poor when treated with

chemotherapy alone. Therefore, these patients are recommended for reinduction chemotherapy followed by allogeneic bone marrow transplantation (BMT) or stem cell transplantation (SCT). Long term event-free survival rates as high as 70% have been reported following BMT, but the probability of this in adult patients is lower than in children[3].

There are only limited available data on patients who have relapsed or have refractory disease following two or more prior induction attempts. Patients in second relapse would normally have received at least two multi-agent chemotherapy regimens without having reached a sufficiently stable remission of their disease. Clofarabine is the only single agent therapy licensed for the treatment of 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. It is not specifically licensed for use in adults, or in patients with LBL[4]. For many patients in second relapse, all established treatment options would therefore have been exhausted[3].

Nelarabine is a pro-drug nucleoside analogue that has been licensed under exceptional circumstances specifically for the treatment of adult and paediatric patients with T-ALL or T-LBL whose disease has not responded to or has relapsed following treatment with at least two chemotherapy regimens[3]. The company submission states that there are six paediatric/adult patients in Wales with T-ALL or T-LBL who fail to respond to a first line treatment regimen. The number of patients who fail to respond to second line treatment is unknown, but those meeting the licensed indication for nelarabine would therefore be estimated to be less than six patients per year, from the data available[2]. Nelarabine meets the AWMSG criterion for ultra-orphan status, as the diseases T-ALL and T-LBL have a combined prevalence of less than 1 in 50,000 in the UK (i.e. approximately 60 persons in Wales)[5].

4.0 EXECUTIVE SUMMARY

4.1 Review of the evidence on clinical effectiveness

The main evidence in support of nelarabine is derived from two non-comparative, phase II studies – the first conducted in children and young patients aged 21 years or less and the second in adults aged 16 years or more. Data presented in relation to the licensed indication and doses are only available from small sub-groups of these trials. In the first trial, 9/39 patients (23% of the sub-group) achieved complete response (CR), with or without full haematological recovery, of which four went on to receive SCT. In the second trial, 6/28 patients (21% of the sub-group) achieved CR, with or without full haematological recovery, of which the company submission reports two went on to receive BMT. Due to the small patient numbers involved, there would appear to be significant uncertainty in surrounding the rates of these important outcomes, and data on survival post-transplant are limited. However, the magnitude of response in patients whose disease has not responded to, or has relapsed, following treatment with at least two chemotherapy regimens is considered to be clinically meaningful. The adverse event profile of nelarabine was as expected for this class of agent in the treatment of leukaemia, with the exception of its neurotoxicity. As a result it is advised that patients must be closely monitored for neurological effects, and the company has committed to provide further safety data in this area.

4.2 Review of the evidence on cost-effectiveness

Cost utility analyses of nelarabine have been conducted within its licensed indication compared against best supportive care (BSC) in children and adults. Patient-level data from those patients meeting the licensed indication in the pivotal phase II trials are used to populate a Markov model.

In the base case analyses, when no constraints are placed on the maximum number of nelarabine cycles that can be received (as per the clinical trials), the model estimates the incremental cost per quality adjusted life year (QALY) gained in children to be £102,281. In adults, this is estimated to be £53,630.

As the number of patients involved in the provision of data is very small, there is significant uncertainty associated with the model inputs. The ability of nelarabine to increase the potential of patients to undergo SCT would appear to be a major driver of the model outputs, as would survival following SCT. The most unfavourable estimates of incremental cost effectiveness are achieved when it is assumed that SCT will not be possible following nelarabine treatment, and when only one cycle of nelarabine treatment is permitted. The incremental cost effectiveness ratios reduce substantially from the large values estimated in the base case analysis when less conservative assumptions of survival following SCT are used.

An indirect comparison has also been made between nelarabine and clofarabine, by adoption of the assumptions made in the AWMSG submission for clofarabine in the current nelarabine model. Using this approach, the incremental cost per life year gained with nelarabine is lower than that with clofarabine when each are compared with BSC. However, there are many limitations to this approach, which warrants caution in its interpretation.

5.0 LIMITATIONS OF DECISION CONTEXT

- Nelarabine was licensed under exceptional circumstances. Due to the rarity of the licensed indication, supporting data are incomplete. The two pivotal phase II studies upon which the licensed indication is based were single-arm studies involving small numbers of patients and there are no comparative trial data available.
- The sub-groups of patients who met the licensed indication for nelarabine in the pivotal trials had no central nervous system (CNS) malignancy.
- Nelarabine has not been studied in patients with hepatic or renal impairment and there were insufficient numbers of patients aged 65 years and over to determine if elderly patients respond differently to younger patients.
- The pivotal trials assessed nelarabine as a single agent. There are currently no data available in support of the use of nelarabine in multi-agent regimens.

6.0 SUMMARY OF THE EVIDENCE ON EFFICACY AND SAFETY

6.1 Clinical efficacy

The company submission describes two single-arm, phase II studies[6,7] that were used to support the licensing application for nelarabine[3]. One was conducted in children and young adults aged 21 years or less (study COG P9673)[6], and one was conducted in adult patients aged 16 years or more (study CALGB 19801)[7]. Both recruited patients with relapsed or refractory T-ALL or T-LBL with no stipulation on the number of prior

chemotherapy regimens[6,7]. Only results and data relating to the sub-groups of patients in these trials who met the licensed indication and doses of nelarabine are discussed below. Table 1A, Appendix 1 provides details of the study and a summary of the results.

6.1.1 Study COG P9673 in paediatric and young adult patients

Patients in this trial were stratified at baseline by the number of prior relapses and evidence of CNS involvement[3,6]. The protocol-defined primary endpoint was response rate, which was defined as CR (no evidence of remaining tumour and haematological recovery within one month after remission induction treatment), and partial response (PR) rates[3,6]. However, it was considered in the European Public Assessment Report (EPAR) that only CR, or at least a very substantial reduction in leukaemic blasts, would be of therapeutic interest in the assessment of new antileukaemic agents, and that achievement of CR should be followed by additional chemotherapy and/or transplant[3]. Therefore, the EPAR[3] and the company submission[2] present only the CR rates, rather than the CR plus PR rates.

Of the 153 patients enrolled, 39 met the subsequent licensed indication, had a predicted life expectancy of at least eight weeks, and received at least one dose of nelarabine at the recommended dose[2]. Nine of these patients achieved a CR (23%; 95% confidence interval [CI] 11% to 39%), of which five also achieved full haematological recovery (13%; 95% CI 4% to 27%). The median duration of response across all 39 patients was 12.3 weeks, and median overall survival was 13.1 weeks. Five of the 39 patients were alive at one year (14%; 95% CI 3% to 26%)[2,3].

In those five patients who achieved CR with full haematological recovery, the duration of response ranged from 4.7 weeks to 36.6 weeks. Three patients who achieved a CR with full haematological recovery and one patient who achieved CR with incomplete haematological recovery subsequently underwent SCT[2]. The rates of successful engraftment in these patients is unclear from the available data, as haematological recovery data for patients who underwent transplant are not available specifically for patients who received the licensed dose of nelarabine. However, it appears from data presented in an appendix to the company submission that overall survival in these patients ranged from 16.6 weeks to 57.4 weeks[2].

6.1.2 Study CALGB 19801 in adult patients

Of the 40 patients enrolled in this study, 28 had received two or more prior inductions and their results provide the efficacy data[3,7]. The primary endpoint was CR with full haematological recovery, which was achieved in five patients (18%; 95% CI 6% to 37%). One further patient achieved CR without haematological recovery. The duration of response across the six patients who achieved CR with or without full recovery ranged from 4.0 weeks to more than 195 weeks. Median overall survival across all 28 patients was 20.6 weeks, and eight patients were alive at one year (29%; 95% CI 12% to 45%)[3].

The company submission reports that four patients subsequently underwent transplantation, although only two of these had achieved a CR with or without haematological recovery following nelarabine treatment[2]. Haematological recovery data following transplant is reportedly available for only three of the four patients, which indicate that two patients achieved neutrophil recovery[2]. Survival data following transplant is limited due to the censoring of data from patients who underwent transplantation. Survival data are provided for patients who received one prior induction before receiving nelarabine treatment[2], but not for the group of patients meeting the licensed indication.

6.1.3 Points to note from the above trials

- The results were determined by the company based on the trial data provided by the Children's Oncology Group (COG) and Cancer and Leukaemia Group B (CALGB)[2]. The company approach to the analyses is more conservative than that used by these groups.
- The number of patients involved in the provision of data in relation to important outcomes of CR and subsequent SCT or BMT in these trials is small and subject to uncertainty. A small variation in the absolute number of patients achieving a CR or receiving SCT, due to chance or otherwise, would have a large impact on the relative estimates of these outcomes.
- In the 39 patients who met the licensed indication for nelarabine in study COG P9673, 24 received one cycle, 10 received two cycles and five received more than two cycles of nelarabine. Eight of 15 patients receiving two or more cycles of treatment achieved a CR compared with one out of 24 of those who received one cycle of treatment. In the 28 patients providing data for nelarabine in study CALGB 19801, 11 received one cycle, 11 received two cycles and six received more than two cycles of nelarabine. Two of 11 patients receiving two cycles of treatment and four of six patients receiving more than two cycles of treatment achieved a CR compared with none of those who received one cycle of treatment. The company interprets such data to mean that one cycle of nelarabine treatment is insufficient to generate a response[2].
- Across the entire study COG P9673 population, the majority of which did not meet the licensed indication or use the licensed dose for nelarabine, it is reported that 43 patients underwent transplantation following nelarabine treatment. Haematological recovery data are available for 21 of these patients, of which 20 had documented neutrophil recovery[2]. Recovery data does not distinguish between the different doses; therefore it is difficult to make conclusions for the licensed nelarabine dosage in the approved indication.
- The sub-groups of patients who met the licensed indication for nelarabine in these trials had no CNS malignancy and had adequate hepatic and renal function. There were insufficient numbers of patients aged 65 years and over to determine if elderly patients respond differently to younger patients[1].
- The company acknowledges that there are some limitations to the interpretation of non-comparative data, such as the inability to rule out selection bias, but considers that it would have been unethical to employ a placebo arm in these studies[2].

6.2 Safety

The major dose-limiting adverse effect of nelarabine is neurotoxicity[1]. Both pivotal phase II study protocols were amended to reduce the dose of nelarabine (to the current licensed doses) following the development of neurological events[3]. These events may include severe somnolence, CNS effects including convulsions, and peripheral neuropathy ranging from numbness and paresthesias to motor weakness and paralysis. Full recovery from these events has not always occurred with cessation of nelarabine. Therefore, the SPC recommends close monitoring for neurological events and advises that nelarabine must be discontinued at the first sign of neurological events of grade 2 or greater[1]. Delaying subsequent dosing is an option for managing other toxicities, including haematological toxicity. Leukopenia, thrombocytopenia, anaemia, and neutropenia have been associated with nelarabine therapy and complete blood counts including platelets must be monitored regularly[1].

The company submission reports that, in study COG P9673 (paediatric and young adult patients), the most frequent adverse events in the subgroup of 39 patients meeting the licensed indication, regardless of cause, were decreases in haemoglobin

(38%), platelet counts (38%), white blood cell counts (36%) and neutrophil counts (28%)[2]. The majority of these were of grade 3 or greater. Six (15%) patients experienced gastrointestinal disorders and five (13%) infections. Eleven patients (28%) experienced nervous system disorders. The most frequently reported serious adverse events were CNS related and included; peripheral sensory and motor neuropathy, both reported in two patients (5%)[2]. One patient was reported to have withdrawn due to toxicity[2].

In study CALGB 19801 (adult patients), the company submission reports that the most frequent adverse events in the subgroup of 28 patients providing data were decreases in haemoglobin (89%), platelet counts (68%) and neutrophil counts (57%). Fifteen patients (54%) experienced gastrointestinal disorders, eight (29%) patients experienced infections, and nine (32%) and six (21%) patients experienced peripheral sensory and motor neuropathy, respectively. The most frequently reported serious adverse event was dysponea, which occurred in 3 (11%) patients[2]. Two patients were reported to have withdrawn due to adverse events[2].

The EMEA indicates that there were no deaths attributed to nelarabine alone[3].

7.0 SUMMARY OF CLINICAL EFFECTIVENESS ISSUES

7.1 Comparator medications

Clofarabine is licensed for use in children with ALL (B- or T-cell type) 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[4]. There is no approved or standard therapy for the treatment of adults with T-ALL/T-LBL or for the treatment of children with T-LBL who have failed other currently available treatments. Palliative care would be the alternative for many patients[2].

7.2 Effectiveness considerations

- Nelarabine is the only drug licensed for use in adults with T-ALL/T-LBL or children with T-LBL who have relapsed or are refractory after receiving at least two prior regimens.
- Nelarabine was licensed under exceptional circumstances by the EMEA on the basis that the indication for which nelarabine is intended is encountered so rarely that the company could not reasonably be expected to provide comprehensive data on its clinical efficacy and safety. In the absence of adequately controlled trials, nelarabine treatment achieved a meaningful response rate 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 two chemotherapy regimens. The magnitude of the response was clinically relevant, allowing some patients to undergo a SCT[3].
- Only non-comparative data from small sub-groups of patients are available in support of nelarabine, and important outcomes such as CR rates, successful transplant rates and OS are subject to some uncertainty.
- The safety profile of nelarabine is considered by the EMEA to be similar to that of other nucleoside analogues and haematological toxicity is considered to be as expected in the setting of leukaemia treatment. However, the risk of neurotoxicity is a particular concern[3]. The SPC states that patients must be closely monitored for signs of neurological toxicity and that treatment should be discontinued in those experiencing events of grade 2 or greater severity[1]. The

company is required to provide further safety data from a post-marketing surveillance study in children.

- Nelarabine has not been studied in patients with hepatic or renal impairment.
- There were insufficient numbers of patients aged 65 years and over to determine if elderly patients respond differently to younger patients.
- Patients in the subgroups of the trials who met the licensed indication did not have central nervous system involvement. The SPC states that patients treated previously or concurrently with intrathecal chemotherapy or previously with craniospinal irradiation are potentially at increased risk for neurological adverse events and therefore concomitant intrathecal therapy and/or craniospinal irradiation is not recommended[1].
- The pivotal trials assessed single agent nelarabine. There are currently no data available in support of the use of nelarabine in addition to other chemotherapeutic agents.
- The company submission contains an "informal" comparison between study COG P9673 of nelarabine and the pivotal phase II trial of clofarabine (study CLO-212)[9]. There are important differences in the patient populations in these two trials, their prior therapies, and the definitions of overall response rates that have been used to assess outcomes. Both studies were non-comparative, which effectively renders this a comparison of observational data. Any such comparison is subject to significant uncertainty and the company acknowledges that it is inappropriate to make such indirect comparisons between clofarabine and nelarabine based on these trials[2]. Therefore, this is not further discussed here.

8.0 REVIEW OF HEALTH ECONOMIC EVIDENCE

8.1 Overview of the key economic issues for AWMSG to consider

The key economic issue for AWMSG to consider is whether any additional benefits offered by nelarabine over the relevant comparator(s) justify any additional costs and, if so, whether the total budgetary impact of supporting the use of nelarabine is acceptable.

8.2 Description and critique of the company's submission

The company submission[2] describes separate cost utility analyses of nelarabine in its licensed indication compared against best supportive care (BSC) in children and adults. A Markov model has been developed, in which the key driver of effectiveness is increased potential for patients to undergo SCT, and subsequently improved survival. Following initiation of the first cycle of therapy, patients who respond (experience complete response with or without full haematological recovery) may receive SCT, BSC or further treatment with nelarabine. The first, second and subsequent cycles of therapy are modelled as separate states. Patient-level data from those patients meeting the licensed indication in the two pivotal phase II trials, described in section 6, are used to provide transition probabilities.

As the number of patients providing data is very small, there is significant uncertainty associated with the model inputs, especially in relation to the probability of receiving SCT and duration of survival. In the base case analysis, survival is based on mean data from the pivotal trials, which was censored and is considered to be a conservative approach by the company. Sensitivity analyses indicate that the model is sensitive to these inputs, and different assumptions of survival following SCT significantly reduce the incremental cost effectiveness ratios (ICERs) from the large values estimated in the base case analysis. The model is also sensitive to the maximum number of cycles of

treatment that are permitted, with the most favourable ICER being achieved with more than one cycle of treatment. The model has been provided to WMP.

An indirect comparison has also been made between nelarabine and clofarabine, by adopting the assumptions made in the AWMSG submission for clofarabine[10] in the current nelarabine model. There are many limitations to this, which warrants caution in its interpretation.

8.3 Population

Patient-level data from the pivotal phase II studies in patients aged ≤21 years (COG P9673)[6] and patients aged ≥16 years (CALGB 19801)[7] are used in the model. Only data relating to patients who had received two or more prior chemotherapy regimens in study COG P9673 have been used in the analysis in children[2], as per the licensed indication for nelarabine[1]. For the analysis in adults, data relating to patients who had received two or more prior anticancer therapies in study CALGB 19801 (28 patients) rather than two or more prior chemotherapy regimens (27 patients) has been used in the model[2].

8.4 Perspective and time horizon

The model considers the cost utility of nelarabine from the perspective of NHS Wales and uses a lifetime horizon of analysis. A cycle length of three weeks, equivalent to one nelarabine treatment cycle is used.

8.5 Comparator

The main model compares nelarabine against BSC[2]. The company justifies this on the basis that there is no approved or standard therapy for the treatment of adults with T-ALL/T-LBL or for the treatment of children with T-LBL who have failed other currently available treatments[2].

Clofarabine is licensed for the treatment of ALL (either B- or T-cell type) 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[4]. Following appraisal by AWMSG in 2007, clofarabine was recommended for use within NHS Wales within its licensed indication but only in patients in whom there is an intention to proceed to SCT[10]. In the company submission for nelarabine, an indirect comparison of nelarabine and clofarabine has been discussed (see section 8.10.3).

8.6 Clinical inputs

8.6.1 Efficacy data

8.6.1.1 Nelarabine efficacy

For the analysis in children, the probabilities of response or non-response to nelarabine are based on data relating to patients who had received two or more prior chemotherapy regimens in study COG P9673[6]. The company submission states that the data is more conservative than that published, one reason being that the company has used an all-patients-treated approach to the statistical analyses[2]. The number of patients experiencing CR, with or without haematological recovery, and the number of patients receiving one, two or more cycles of nelarabine treatment, is verifiable from the EPAR[3] and SPC[1]. Four of the nine patients who achieved a CR (with or without haematological recovery) subsequently underwent SCT[3]. It would appear from data presented in an Appendix to the company submission that overall survival in these patients ranged from 16.6 weeks to 57.4 weeks[2].

For the analysis in adults, the probabilities of response or non-response to nelarabine are based on data relating to patients who had received two or more prior induction

therapies, rather than specifically chemotherapy regimens. Data are therefore based on 28 patients who had received two prior induction therapies, rather than 27 patients who had specifically received two prior chemotherapy regimens. The company submission reports that two out of the six patients who had previously received two or more prior induction therapies and achieved CR underwent SCT[2]. It should be noted that, as the actual number of patients providing these data is small, a small change in the number of patients experiencing a particular outcome would have a potentially significant impact on the probabilities of that outcome.

In both analyses, the number of patients providing data in relation to the third and subsequent cycles of nelarabine treatment is small. The company considers these to be insufficient to provide reliable transition probabilities, and therefore has assumed a geometric series. Again, these would appear to be subject to some uncertainty due to the very small number of patients providing data.

Survival data has been censored at the end of the trial, and there are few data informing survival following SCT. In the base case analysis, survival is based on trial-derived data, which the company submission indicates is conservative. Sensitivity analyses have been conducted around survival following SCT. The company submission also refers to additional evidence from a secondary care database that uses data from the population of Cardiff, which it suggests is consistent with the trial-derived survival data[2].

8.6.1.2 BSC efficacy
The comparator in the main model is BSC. The source of assumed efficacy data (survival) for treatment with BSC is unclear.

8.6.2 Adverse events
Adverse events are not specifically considered as clinical inputs. They appear to have been assumed to be included in the utility weights that have been used in the model.

8.6.3 Utility weights
Health-related quality of life data and utility weights specific to treatment with nelarabine are lacking. Therefore, several sources have been used to provide estimates. For patients not responding to nelarabine treatment, or untreated patients, a utility weight of 0.64 is assumed (not verified), reportedly based on data from patients with lymphoid leukaemia reported in the Health Outcomes Data Repository (HODaR) database in Cardiff[2]. The HODaR database is used to collect health-related quality of life and utility data from secondary care patients treated in Cardiff via the SF-36 and EQ-5D questionnaires[2].

For patients undergoing SCT, a utility value of 0.92 is assumed, based on a study in patients with acute myeloid leukaemia (AML)[11]. It is then assumed that, for patients responding to nelarabine but not undergoing SCT, a utility weight midway between the two values above (a value of 0.78) would be appropriate. For patients on nelarabine, this is assumed to be associated with disutility due to adverse events. A utility value of 0.42 is applied for one week to represent disutility during treatment, based on the same study in AML[11]. However, some adverse events such as neurological effects have been found to be irreversible following nelarabine treatment[1] (see section 6.2). In addition, the utility weights in that study were derived from physicians rather than patients[11], which may introduce some uncertainty into the estimates. Utility weights are explored in sensitivity analyses, including the application of the reduced utility value for the full duration of treatment to represent irreversible adverse events with nelarabine treatment.

8.7 Healthcare resource utilisation and cost

8.7.1 Treatment costs

Nelarabine drug cost is based on body surface area (BSA) and dose. In the model, it is assumed that adults have a BSA of 1.73m^2 and children a BSA of 1.25m^2, and that each receive the dose recommended in the SPC[1] (see section 2.2), with vial wastage. Administration costs are assumed to be the costs for a day case ALL, based on 2006-7 NHS reference costs[12]. This is assumed to include neurological monitoring as recommended by the SPC[1].

The costs of SCT are based on a weighted (by the number of finished consultant episodes on which the data are derived) average of adult and child BMT costs as included in 2006-7 NHS reference costs[12]. Due to a lack of data, the costs of BSC are assumed to be the same as those that were employed for BSC in the clofarabine submission to AWMSG in 2007[10]. These costs were based on ovarian cancer costs from 2001 and include medication, hospital, district nurse and GP contact costs. However, even after inflation to near-current prices, there would clearly be a significant degree of uncertainty in the assumption of these costs for the treatment of adults and children with T-ALL/T-LBL. The company has provided supplementary sensitivity analyses to explore the impact of the assumed costs of BSC (see section 8.10.1).

8.7.2 Adverse event costs

Adverse events are not specifically considered separately.

8.7.3 Other resource use and costs

N/A

8.8 Discounting

The company submission states that censoring of data resulted in a relatively short analytic time horizon and, therefore, costs and outcomes have not been discounted[2]. However, it is also reported that the maximum reported survival in the relevant population of the trials was almost four years and the mean survival of adult patients undergoing SCT was almost 94 weeks[2]. Discounting would therefore seem to be appropriate.

8.9 Results

8.9.1 Base-case analysis

8.9.1.1 In children

When no constraints are placed on the maximum number of cycles of nelarabine that can be received (as per the clinical trials), the model estimates the incremental cost per QALY gained for nelarabine treatment compared with BSC to be £102,281. This is based on a mean of 1.66 treatment cycles with nelarabine at an incremental cost of £20,408 (£25,909 nelarabine vs. £5,501 BSC) and a gain of 0.20 QALYs (0.37 nelarabine vs. 0.17 BSC)[2].

8.9.1.2 In adults

When no constraints are placed on the maximum number of cycles of nelarabine that can be received (as per the clinical trials), the model estimates the incremental cost per QALY gained for nelarabine treatment compared with BSC to be £53,630. This is based on a mean of 1.89 treatment cycles with nelarabine at an incremental cost of £19,571 (£25,072 nelarabine vs. £5,501 BSC) and a gain of 0.36 QALYs (0.58 nelarabine vs. 0.21 BSC)[2].

8.9.2 Secondary analyses

The company submission also presents the model outputs by the maximum number of cycles of nelarabine treatment received[2].

In children, when the maximum number of cycles of nelarabine is restricted to one, the incremental cost per QALY gained is estimated to be £187,095. This is due to the very low rates of treatment response observed in the clinical trials for patients who received only one cycle of treatment. When the maximum number of cycles is two or more, the results are similar to the base case analysis, reflecting the fact that few patients received more than two cycles of treatment in the clinical trials[2].

In adults, at a maximum of one treatment cycle, the incremental cost per QALY gained is estimated to be £157,835. At a maximum of two or more cycles of treatment the results are similar to the base case analysis[2].

8.10 Sensitivity and scenario analyses

8.10.1 One-way sensitivity analyses

The company submission presents the results of 24 different sensitivity analyses for each for the evaluations in children and adults[2]. Those related to the survival of patients following SCT have the largest impact on the model outputs. These, and those analyses around other key assumptions, are briefly discussed below.

The assumed costs of BSC in the base case analysis would seem to be a significant source of uncertainty. The company has provided supplementary sensitivity analyses in which the costs of BSC are explored within the range of £0 to three times the value used in the base case analysis. These indicate that the model is relatively insensitive to the assumed costs of BSC.

The range of costs in the NHS reference costs that were used to estimate the cost of SCT in the model was wide. Between the maximum and the minimum NHS reference costs for this procedure, the ICER ranges from £74,256 to £125,422 in children and £49,951 to £70,736 in adults[2].

Utility values were explored within the range of $\pm$20%. For children, the ICER ranged from £80,770 to £162,607, and for adults it ranged from £43,131 to £78,323[2]. The company has provided supplementary sensitivity analyses in which the lower utility value (0.42) is applied to all patients for the duration of nelarabine treatment, to explore the impact of prolonged disutility associated with irreversible adverse effects. This resulted in ICERs of £149,077 in children and £82,205 in adults; however, this represents an extreme scenario, as most patients in the clinical trials did not experience irreversible adverse events due to nelarabine treatment.

The ability of nelarabine to increase the potential of patients to undergo SCT would appear to be a major driver of the model outputs. When nelarabine is assumed to permit life extension only and no patients are able to undergo SCT following nelarabine treatment, the ICER increases to £189,521 per QALY gained in children and £73,376 per QALY gained in adults[2]. This would suggest that nelarabine is less cost effective if there is no intention to offer SCT to patients (e.g. if used with only palliative intent).

Survival following SCT is also a driver of the model outputs and the company submission considers that a conservative approach has been used in the base case analysis. If survival following SCT was two years, the ICER in children is estimated to reduce to £51,169, and to £50,594 per QALY gained in adults. The corresponding ICERs at five years are £21,811 and £26,388, and at 10 years are £11,872 and £15,539 per QALY gained, respectively. When survival is set to normal life expectancy (based on Welsh life tables) in patients who survive more than one year following SCT, the ICERs are £25,523 in children and £11,318 per QALY gained in adults[2]. Costs and

outcomes have, appropriately, been discounted at 3.5% per annum for these analyses[2].

8.10.2 Probabilistic sensitivity analysis

Probabilistic sensitivity analysis (PSA) has not been conducted as the company considered that characterising the uncertainty around the input parameters would be challenging given the limited clinical data that are available[2]. However, the value of PSA is arguably greatest when parameter uncertainty is highest.

8.10.3 Scenario analysis - comparison with clofarabine

The company submission[2] presents a discussion of the model outputs when the input parameters are adjusted to reflect the assumptions used in the AWMSG submission for clofarabine[10]. The base-case analysis for clofarabine assumed normal life expectancy for patients who had survived one year following SCT, and registry data were used to provide estimates of mean survival for untreated patients[10]. Patients treated with nelarabine are assumed not to accrue BSC costs after cessation of treatment, and utility values in this analysis are set to unity (which implicitly assumes no impact of adverse effects, etc., and results are reported as costs per life year gained). Costs and outcomes are discounted at 3.5% per annum.

When no constraint is placed on the maximum number of cycles of nelarabine treatment, the incremental cost per life year gained in children is estimated to be £20,640. In adults, it is estimated to be £7,898. The company submission[2] notes that these estimates are lower than the incremental cost per life year gained that was estimated for clofarabine (£22,226)[10].

There are many limitations to this type of indirect comparison, which mean that the results should be interpreted with great caution. The main clofarabine study that provided efficacy data for the clofarabine submission was conducted in a paediatric population with ALL (i.e. patients could have either B- or T-cell type ALL). In addition, the definitions of overall response differed between studies. The nelarabine company submission acknowledges that it is inappropriate to make indirect comparisons between the main clofarabine and nelarabine clinical trials[2]. This would extend to an economic model based on these trial-derived data.

8.11 Review of published evidence on cost-effectiveness

Standard literature searches conducted by WMP have not identified any published evidence on the cost-effectiveness of nelarabine.

9.0 REVIEW OF EVIDENCE ON BUDGET IMPACT

9.1 Description and critique of the company's submission

A range of sources have been used to derive estimates of UK incidence of T-ALL and T-LBL, and the rates of relapse following first-line treatment. Welsh estimates have been derived from the UK population as a whole. The company has presented two scenarios of uptake of nelarabine based on assumed rates of relapse/resistance to second-line treatment. It is assumed that the incidence of these diseases is constant over the five year time horizon, that there are no restrictions on the maximum number of cycles that patients may receive (estimates are based on patients receiving the same number of cycles of treatment as in the pivotal clinical trials), and that all treatment is received by patients within year. The small number of patients estimated to be eligible for treatment in Wales is potentially subject to significant annual variation, and sensitivity analyses indicate that the estimated budget impact is very sensitive to very small changes in patient numbers.

9.2 Perspective and time horizon

The budget impact analysis is conducted from the perspective of NHS Wales and considers a time horizon of five years[2].

9.3 Data sources

9.3.1 Incident and prevalent cases

The company submission uses data from UK charities and various publications to estimate the number of patients with T-ALL and T-LBL in the UK. The proportion of patients who suffer relapses or are refractory is based on several studies of outcomes in patients with these types of cancers and it appears that some assumptions are made with regards to relapse rates in adults being the same in children. Using UK population estimates, the company submission estimates that there are six incident cases of T-ALL/T-LBL in Wales each year[2].

9.3.2 Projected rate of adoption and market share

The proportion of patients who fail to respond to second-line treatment is unknown; therefore, the company employs two scenarios to estimate the number of patients eligible for nelarabine. In the first (A), the company submission states that response to second line treatment is 30-35%, which would imply that failure with second-line treatment is be 65-70%. However, the number of patients listed as being potentially eligible for treatment implies the reverse (i.e. that the failure rate with second-line treatment is 30-35%). In the second scenario (B), it is assumed that relapse rate is 50%. These assumptions would translate into two to three patients being potentially eligible for nelarabine treatment each year, and the company submission assumes that all eligible patients would start nelarabine[2].

It is assumed that there would be no change in this annual number of patients over the five-year time horizon, although the company submission also states that, as the mean average number of patients is low, there could be substantial annual variations[2].

9.3.3 Costs and resource use

The actual costs assumed in the budget impact analysis are based on the estimated patient numbers as calculated to two decimal places, rather than rounding to whole patients numbers. This has been explored in supplementary sensitivity analyses (see section 9.5). The costs that are considered for nelarabine are the acquisition costs of nelarabine and the costs of administration, and the costs of BSC are taken from the cost utility analysis. There is some significant uncertainty in the assumed costs of BSC, which are based on a 2001 estimate of ovarian cancer costs, as discussed in section 8.7.1[2].

9.4 Results

In scenario A (second-line treatment failure rate of 30-35%), the cost of nelarabine is estimated as £49,986 each year on the basis of no restriction in the maximum number of cycles received. The cost of BSC is estimated as £10,892, producing a net budget impact of £39,094 each year.

In scenario B (second-line treatment failure rate of 50%), the cost of nelarabine is estimated as £74,014 each year on the basis of no restriction in the maximum number of cycles received. The cost of BSC is estimated as £16,118, producing a net budget impact of £57,896 each year.

These estimates assume that patients receive nelarabine treatment within year and for the same mean number of cycles as observed in the clinical trials (1.66 cycles in

children and 1.89 cycles in adults)[2]. Any restrictions imposed on the use of nelarabine may potentially reduce this impact.

The company submission notes that, in children with ALL the acquisition cost of clofarabine is £24,000 per 5-day cycle for a patient with BSA of 1.25m^2, which would be repeated every two to six weeks. This compares with £3,774 per treatment cycle for nelarabine, which would be repeated every three weeks. The company suggests that in paediatric patients with T-ALL, the use of nelarabine instead of clofarabine would potentially result in a saving of £20,226 per treatment cycle. On the basis of the use of nelarabine as in the base case analysis, the company submission estimates direct savings with nelarabine of £30,863 per patient treated; however, these estimates should be viewed with caution due to the limitations of this type of indirect comparison. The company appropriately note that the average number of patients estimated to be eligible for either nelarabine or clofarabine is very low and could be subject to substantial annual variations.

9.5 Sensitivity analysis

The company submission describes the net cumulative cost impact of nelarabine compared with BSC over the entire five years, based on several of the scenario analyses conducted for the cost effectiveness section[2]. These scenarios represent either increases or decreases in the cost of nelarabine, or changes in the number of patients progressing to subsequent cycles of therapy. These appear to be of limited informative value and results are as would be expected from increasing or decreasing the costs of nelarabine.

Supplementary sensitivity analyses have been provided by the company to explore the impact of rounding the number of patients estimated to be eligible for treatment with nelarabine. When the number of patients is rounded from two decimal places to the nearest whole number, the impact on the budget impact estimates is minimal. When patient number estimates are all rounded up or all rounded down, the budget impact estimates vary significantly, by as much as 50%. This reflects how sensitive the budget impact analysis is to small changes in assumed patient numbers.

9.6 Table of comparative unit costs

There is no approved or standard therapy for the treatment of adults with T-ALL/T-LBL or for the treatment of children with T-LBL who have failed other currently available treatments. Clofarabine is licensed for use in children with ALL (B- or T-cell type)[4].

	Usual doses	**Approximate drug acquisition cost per cycle of treatment*[13]**
Nelarabine	Adults: 1,500mg/m^2/day on days 1, 3 and 5, repeated every 21 days[1]	£7,326
	Children: 650mg/m^2/day on 5 consecutive days, repeated every 21 days	£4,440
Clofarabine	Children: 52mg/m^2/day on 5 consecutive days, repeated every 2 to 6 weeks[6]	£24,000
This table does not imply therapeutic equivalence of the agents or doses. * based on body surface area of 1.73m^2 for adults and 1.25m^2 for children, and whole number of vials required to fulfil recommended dose with vial wastage. Other administration costs excluded.		

10.0 ADDITIONAL INFORMATION

10.1 Guidance and audit requirements

- At present there is no nationally accepted standard therapy for patients meeting the licensed indication for nelarabine.
- Nelarabine should be administered under the supervision of a physician experienced in the use of cytotoxic agents[1]. It would not be suitable for shared care.

10.2 Related advice

The National Institute for Health and Clinical Excellence (NICE) issued guidance on improving outcomes for haemato-oncology cancer in 2003[14] and on improving outcomes with children and young people with cancer in 2005[15]. A date for review of this guidance has not yet been confirmed.

10.3 Previous AWMSG advice

AWMSG issued guidance on the use of clofarabine (Evoltra®) in June 2007[10]. The guidance states that clofarabine is recommended for use within NHS Wales for the treatment of 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 a patient in whom there is an intention to proceed to SCT 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[10].

10.4 Ongoing studies

The company submission contains brief details of eight ongoing trials of nelarabine that are likely to provide evidence within the next 12 months[2]. These explore the use of nelarabine either alone or in combination with other anticancer agents in newly diagnosed and relapsed/refractory patients. Only one is specifically listed as being a randomised, comparative trial, and this is being conducted in newly diagnosed patients with B- or T-ALL (UK ALL 14)[2].

10.5 Patient organisation information

A patient organisation submission by Leukaemia Care, and the Lymphoma Association was provided to AWMSG members.

GLOSSARY

Incidence:
The rate at which new cases occur in a population during a specified period[16].

Prevalence:
The proportion of a population that are cases at a point in time[16].

Karnofsky performance status:
This scoring tool attempts to quantify the general well being of patients. The Karnofsky score runs from 100 to 0, where 100 is "perfect" health and 0 is death.

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Appendix 1. Additional Clinical Information

Table 1. Prospective studies of nelarabine in T-ALL/T-LBL – patients meeting licensed indication and doses

Ref	Study type	No. patients	Inclusion criteria	Baseline characteristics	Treatment regimens	Outcomes
2,3,6 COG P9673	Single-arm, phase II study (Paediatric and young adult patients)	Total enrolled n=153 Meeting licensed indication and licensed dose n=39	Age ≤ 21 years Refractory or recurrent T-cell malignancy Karnofsky performance status >50% Predicted life expectancy ≥8 weeks Adequate hepatic and renal function No severe infection No neurotoxicity (≥ grade 2) No CNS malignancy	Mean age: 11.45 years Male: 64% Race white: 64% T-ALL: 79% T-LBL: 21% No. prior inductions: 2: 69% 3: 18% >3: 13% Prior SCT: 21% Prior BMT: 5%	Nelarabine licensed dose in paediatric and young adult patients: 650mg/m^2 daily by IV infusion on days 1-5, repeated every 21 days Treatment permitted for up to 2 years	**Primary endpoint (Response rate):*** CR with full haematological recovery: 5/39 (13%, 95% CI 4% to 27%) CR with or without full haematological recovery: 9/39 (23%, 95% CI 11% to 39%) **Other outcomes:** Median duration of response: 12.3 weeks Duration of response in patients achieving CR with full haematological recovery: 4.7 weeks to 36.4 weeks Median OS: 13.1 weeks 1-year survival: 5/39 (14%, 95% CI 3% to 26%) Received SCT: 4/9 patients who achieved CR with or without full haematological recovery received SCT.†
2,3,7 CALGB 19801	Single-arm phase II study (Adult patients)	Total enrolled n=40 Received one dose of study drug and had ≥2 prior inductions n=28	Age ≥ 16 years Refractory or relapsed T-cell malignancy Leukaemia or lymphoma cells expressing ≥2 of the following cell surface antigens: CD1a, CD2, CD3 (surface or cytoplasmic), CD4, CD5, CD7, and CD8 Leukaemia cells negative for myeloperoxidase or Sudan Black B histochemical stains Adequate renal function No neuropathy ≥ grade 2 No CNS malignancy	Mean age: 34 years Male: 82% Race white: 61% T-ALL: 61% T-LBL: 39% No. prior inductions: 2: 36% 3: 32% >3: 32% Prior BMT: 14%	Nelarabine licensed dose in adult patients: 1.5g/m^2 daily by IV infusion on days 1,3 and 5, repeated every 21 days	**Primary endpoint:** CR with full haematological recovery**:** 5/28 (18%, 95% CI 6% to 37%) **Other endpoints:** CR with or without full haematological recovery: 6/28 (21%, 95% CI 8% to 41%) Duration of response: CR with full haematological recovery: 15.1 to >195 weeks CR with or without full haematological recovery: 4 to >195 weeks Median OS: 20.6 weeks 1-yr survival: 8/28 (29%, 95% CI 12% to 45%) Received transplant†: Company submission reports 4 patients in the relevant population subsequently received transplant, of which only 2 had achieved CR with or without haematological recovery. Engraftment data available for only 3 of the 4 patients.

BMT=bone marrow transplant, CNS=central nervous system, CR=complete response, OS=overall survival, PR=partial response, SCT=stem cell transplant
*The primary endpoint of response rate was defined as CR (no evidence of remaining tumour and haematological recovery within one month after remission induction treatment), and PR. However, only the CR data are provided in the EPAR (and the company submission), on the basis that it was considered in the EPAR that only CR, or at least a very substantial reduction in leukaemic blasts, would be of therapeutic interest in the assessment of new antileukaemia agents, and that achievement of CR should be followed by additional chemotherapy and/or transplant[3]..
†Retrospective data collection