SCIENTIFIC DISCUSSION

1. Introduction

T-cell lymphoblastic leukaemia (T-ALL) and lymphoblastic lymphoma (T-LBL)

ALL and LBL are aggressive diseases that progress rapidly to a fatal outcome in the absence of effective therapy. LBL is commonly considered the lymphomatous variant of ALL in which extramedullary disease predominates in the presence of lesser involvement (< 25% marrow blasts) of the bone marrow compared with ALL. LBL represents approximately 30% of childhood and 3% of adult non-Hodgkin's lymphoma (NHL). An important subset of ALL and LBL is the T-cell lineage form of the disease (T-ALL and T-LBL, respectively) which is less frequent than B-cell lineage disease. The T-cell phenotype occurs in approximately 15-20% of children and 25% of adults with ALL and in approximately 10-20% of patients with Non-Hodgkin's lymphoma. Current treatment for patients with T-LBL follows the same treatment strategy for T-ALL, with comparable results.

Newly diagnosed ALL and LBL patients are typically treated with induction therapy consisting minimally of vincristine, prednisone, and anthracycline with or without asparaginase. Utilising modern risk adapted treatment plans in these patients; the complete response (CR) rate is > 95% in children and 60-80% in adults. Induction therapy is followed by additional cycles of multi-agent chemotherapy incorporating substances of different drug classes with the aim of long term disease control. The T-cell lineage forms of the disease (T-ALL and T-LBL) are considered high risk diseases requiring more aggressive therapy. Approximately 25-30% of children experience relapse or is refractory to initial induction therapy with a resultant poor prognosis. Children who relapse within 6 months of completion of initial therapy exhibit a 10% to 20% likelihood of long-term survival when treated with chemotherapy alone while those who relapse at over one year from completion of therapy have a 30% to 40% probability of long-term survival. The cure rate of T-ALL and T-LBL in adults is lower than in children. After first CR the majority of adult patients will eventually experience relapse.

Treatment of patients with relapsed or refractory T-ALL and T-LBL

Therapy of patients with relapsed or refractory disease is largely individualised based on the nature of response to prior therapy (e.g., achieve CR or not, timing of relapse following CR, total anthracycline dose received, any agent specific toxicity). No consensus for therapy has emerged. Clofarabine is the only currently approved agent in Europe for single-agent therapy in relapsed or refractory paediatric ALL (Commission decision dated 29 May 2006). However, most patients with first relapse will receive multi-agent combination re-induction therapy, which has demonstrated complete remission rates above 80% and ranging from 30-76% in clinical trials in children and adults, respectively. Even if achieving a second remission, patients have a poor prognosis when treated with chemotherapy alone. Thus, these patients are recommended for reinduction chemotherapy followed by allogeneic bone marrow transplantation (BMT) or stem cell transplantation for those who have an HLA-matched donor or autologous transplantation for those who do not. Long-term event free survival rates as high as 70% have been reported in children after BMT, whereas the probability for long-term survival in adult patients with relapsed ALL is lower, even with BMT. Therefore, the benefit of any new antileukaemic agent must be assessed in the context that only CR or at least a very substantial reduction in leukaemic blasts would be of therapeutic interest and that achievement of CR should be followed by additional chemotherapy and/or BMT when feasible.

There are only limited available data on patients who have relapsed or refractory disease following two or more prior induction attempts. No randomized trials have been performed in either paediatric or adult patients with relapsed or refractory T-ALL/T-LBL. 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. In many cases, all established treatment options would have been exhausted.

About the product

Atriance contains nelarabine, an antineoplastic agent that acts as DNA synthesis inhibitor (ATC code: L01BB07). Nelarabine is demethylated to the deoxyguanosine analogue ara-G and then

phosphorylated intracellularly to the active triphosphate ara-GTP. Accumulation of ara-GTP in leukaemic blasts and incorporation into DNA leads to inhibition of DNA synthesis and cell death. The acronyms used during the development of the medicinal product were nelarabine, coded 506U78 and GI262250.

2. Quality aspects

Introduction

Atriance is presented as a solution for infusion containing 5 mg of nelarabine (active substance) per ml. The excipients used in the preparation of Atriance are all well known excipients used in intravenous preparations such as sodium chloride, hydrochloric acid, sodium hydroxide and water for injections.

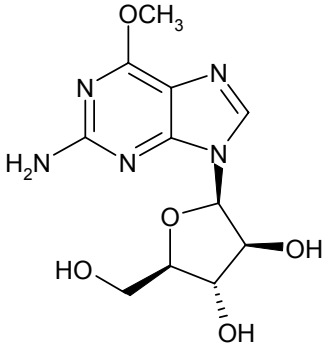
Atriance is a clear, colourless solution containing 5 mg/ml of nelarabine filled into clear glass vials. Each vial contains 250 mg of nelarabine.

Active Substance

The active substance is a pro-drug of the deoxyguanosine derivative 9-β-*D*-arabinofuranosylguanine (ara-G), which converts initially to ara-G *in vivo* and subsequently converts to the active 5'-triphosphate (ara-GTP).

Nelarabine is chemically designated as 9-β-D-arabinofuranosyl-6-methoxy-9H-purin-2-amine (CAS) or 2-amino-9-β-D-arabinofuranosyl-6-methoxy-9H-purine (IUPAC). The structure of nelarabine is shown in figure 1.

Figure 1: Chemical structure of nelarabine



Nelarabine is an ampholyte with an aqueous solubility of 8-9 mg/ml at 25°C over the pH range of 4 to 10. Its pKa is 2.5 and 12.1. It is a white to slightly colored, non-hygroscopic solid. There is only one known crystalline form of nelarabine, a crystalline anhydrate (non-solvate). Although it contains four adjacent chiral atoms in the sugar moiety, the route of synthesis is stereo-selective and therefore only one stereoisomer is synthesized. The median particle size volume diameter is in the range of 10-100 micrometers.

Since the drug product is a solution, solid-state and bulk properties of the drug substance have no impact on the drug product performance.

- Manufacture

Nelarabine is synthesised in one step from two starting materials followed by a purification step. Confirmation of the chemical structure of nelarabine was provided by elemental analysis and spectroscopic analysis of a large-scale batch from the proposed commercial route of nelarabine. The results from infrared spectroscopy, proton and ^{13}C nuclear magnetic resonance, mass spectrum, and single crystal x-ray crystallography confirmed the proposed chemical structure.

- Specification

The active substance specification includes tests for description, identification (IR spectroscopy), assay (HPLC), impurities (HPLC), water content (Karl Fisher), residue on ignition, specific optical rotation, residual protein (UV spectroscopy) and bacterial endotoxins.

The method for identification of nelarabine by IR was validated for specificity, the HPLC method for assay of nelarabine and impurities was validated for specificity, linearity, accuracy, precision, robustness, stability and detection limit. No validation was performed for the methods described in the PhEur.

Data was provided on one pilot scale batch and three production scale batches manufactured according to the proposed manufacturing process. In addition, data were also provided on 20 batches manufactured according to the previous routes of synthesis, used in the non-clinical and clinical studies. All the batches complied with the requirements in the active substance specification.

- Stability

Three production scale batches were stored at 30°C/65% RH for 24 months (long term storage conditions) and at 40°C/75% for 6 months (accelerated conditions). Additionally, photostability was presented for one batch of active substance manufactured at pilot. No significant changes were observed on storage.

The stability studies showed that the active substance is stable and confirm the proposed re-test period.

Medicinal Product

- Pharmaceutical Development

Initially the product was developed as lyophilized solid nelarabine. Each vial contained 200 mg of active substance in the form of sterile powder to be reconstituted with water for injections. The formulation was then further developed into a ready-to-use liquid injectable dosage form. The solubility of nelarabine in water and in sodium chloride was investigated. The effects of pH, light, temperature and terminal sterilization on the aqueous solution of nelarabine were also evaluated. Based on the results a 5 mg/ml solution of nelarabine in sodium chloride was prepared and the stability of this formulation was monitored. Sodium chloride was used to adjust the tonicity of the formulation and sodium hydroxide and hydrochloric acid were used to adjust the pH.

- Adventitious Agents

None of the excipients used in the formulation of nelarabine solution for infusion are of animal origin.

- Manufacture of the Product

The manufacturing process for nelarabine solution for infusion comprises (1) mixing of nelarabine, sodium chloride and water for injections (2) Filtration (3) pH adjustment (4) second filtration (5) filling of the solution into sterile vials (6) terminal sterilisation by a cycle which is F_0 controlled.

There are several in-process controls such as the determination of the bioburden prior to filtration, determination of the pH prior to filling, testing of the integrity of the sterilising filter pre- and post-filtration and the check of the fill weight at regular intervals throughout the filling operation.

The manufacturing process validation has been performed using three production scale batches. The nelarabine content and pH at key stages in the manufacturing process was evaluated. The results showed that the manufacturing process delivers the appropriate concentration and that no losses in content are seen at any point during the transfer, filtration or filling of the solution into vials. The steam sterilisation process was validated by performing heat penetration temperature monitoring in association with a bacterial spore challenge.

The manufacturing process was adequately validated. Batch analysis data on three production scale batches confirmed that the defined process reliably produces product which meets the proposed release specification.

- Product Specification

The specification for nelarabine solution for infusion include tests for appearance (visual examination), identification of nelarabine (UV and HPLC), assay (HPLC), impurities (HPLC), extractable volume, particulate contamination, pH, bacterial endotoxin and sterility.

All methods have been satisfactorily validated. The HPLC method was validated for specificity, linearity, accuracy, range, precision, robustness, stability and detection limits. The method for determination of the endotoxin in nelarabine was validated as well as the sterility test. All other methods are described in the PhEur and therefore validation was deemed to be unnecessary.

- Stability of the Product

Stability data were provided on four batches of drug product manufactured at the commercial site using the commercial process at production scale. The batches were stored at 30°C/65% RH for 24 months (long term storage conditions) and at 40°C/75% for 6 months (accelerated conditions) in the proposed packaging. The parameters assessed were the appearance, pH, bacterial endotoxins, sterility, extractable volume, assay, impurities and particulate contamination. Additionally, stability data for one batch exposed to light and freeze/thaw conditions was also provided. The results of all studies complied with the product specification in all batches and no changes were observed under photostability stress or freeze/thaw conditions.

In summary, the stability results support the shelflife and storage conditions as defined in the SPC.

Discussion on chemical, pharmaceutical and biological aspects

The active substance and finished product have been adequately described. The excipients used in the preparation of the finished product and the manufacturing process selected are typical of an intravenous preparation. The results of the tests indicate that the active substance and the finished product can be reproducibility manufactured and therefore the product should have a satisfactory and uniform performance.

At the time of the CHMP opinion, there was a minor unresolved quality issue having no impact on the Benefit/Risk ratio of the product. The applicant gave a Letter of Undertaking and committed to resolve this as a Follow Up Measure after the opinion, within an agreed timeframe.

3. Non-clinical aspects

Introduction

The pharmacology of nelarabine was investigated *in vitro* and *in vivo*. Except for a single-dose toxicity study in monkey, all pivotal non-clinical safety studies were carried out in compliance with GLP standards, as claimed by the applicant.

Pharmacology

- Primary pharmacodynamics

The pharmacodynamics of nelarabine has been characterized *in vitro*, in human leukaemic cell lines and *in vivo*, in a mouse tumour model.
The in-vitro potency and selectivity of cytotoxicity of nelarabine and ara-G have been investigated in a range of human haematopoietic cell lines. In these assays, the IC_{50} for cytotoxicity in human T-cell lines ranged from 0.31 to 4.4 μM for nelarabine and from 0.31 to 5.0 μM for ara-G (see Table 1). Generally, the IC_{50} values for cytotoxicity in B-cells with nelarabine and ara-G were at least 20-fold higher (>200 μM and >100 μM, respectively, with the exception of one study where the IC_{50} values were >10 μM, the maximum tested concentration), and for monocyte (THP-1) cells were >50 μM. In malignant haematopoietic cell lines of T-cell lineage, (CEM, HSB, and dCK deficient cell line, ACO611a), a B-cell line (WIL-2), and a stem cell line (DU528) exposed to varying concentrations (50, 100, 200 or 500 μM) of either agent for 4 or 24 hours and incubated at 37°C for 2 to 3 weeks, treatment with nelarabine or ara-G resulted in comparable, concentration-dependent cytotoxicity and

inhibition of subsequent outgrowth of malignant T-cells (see Table 2). T-cells deficient in dCK (AC0611a) and haematopoietic cell lines of stem cell or B-cell lineage did not show any substantial sensitivity to the cytotoxic effects of nelarabine or ara-G.

Table 1: IC_{50} values (μM) in malignant and normal human haematopoietic cell lines

Cell line	Lineage	Nelarabine		Ara-G	
		No. of independent assays	IC_{50} (μM)	No. of independent assays	IC_{50} (μM)
Bjab	B-cell	-	-	1	350
IM-9	B-cell	1	>10->200	1	>10->100
Raji	B-cell	-	-	1	28
SB	B-cell	-	-	1	35
Tral	B-cell	-	-	1	80
WIL-2	B-cell	-	-	1	170
K562	Erythroid	-	-	1	>1000
Monomac-6	Monocyte	1	0.8	1	0.8
THP-1	Monocyte	1	>50	1	>50
U937	Monocyte	5	1.0-3.9	5	0.44-1.0
HL60	Myeloid	-	-	1	130
KG-1	Myeloid	-	-	1	22
DU-528	Pre-T	-	-	1	0.44
Human bone marrow cells	Progenitor cells	2	2-8	2	0.7-4
ACO611a	T(dCK-)	-	-	1	9.0
CEM	T-cell	4	0.307-1.9	5	0.31-2.0
CEM $CD4^+$	T-cell	2	3.4-4.4	2	3.2-5.0
HSB	T-cell	-	-	1	0.75
MOLT-4	T-cell	5	0.70-1.6	6	0.45-2.3

Table 2: *In vitro* cytotoxicity to T-, B- and stem cells

Cell Line	Lineage	Log kill						
		Nelarabine (μM)				Ara-G (μM)		
		50	100	200	500	100	200	500
CEM	T-cell	-	4.4	5.1	5.2	4.2	5.1	5.2
HSB	T-cell	-	4.2	4.7	4.8	4.6	4.5	4.9
ACO6111a	T(dCK-)	-	0.5	0.17	0.7	0.8	0.6	1.3
WIL-2	B-cell	0	0	-	-	-	-	-
DU528	Stem	1.2	0.9	-	-	-	-	-

The role of ADA in the conversion of nelarabine to ara-G was investigated in similar assays using human leukaemic cell lines (CEM, MOLT-4, CEM-CD4+, U937 and IM-9) treated with nelarabine or ara-G (up to 200 μM). In the absence of ADA inhibitors, growth inhibition of human T-cell lines was observed with IC_{50} values of 0.31 to 3.4 μM for nelarabine and 0.31 to 5.0 μM for ara-G. In the presence of ADA inhibitors, there was a concentration-dependent increase in the IC_{50} values of nelarabine for growth inhibition of T-cell lines. At the highest ADA inhibitor concentration of 10 μM, there was a >7-fold increase in IC_{50} values of nelarabine. The increased IC_{50} values were noted for growth inhibition of both T-cell lines and macrophage/monocyte cell line (U937) sensitive to nelarabine, but not for the IM-9 B-cell line. In contrast, ara-G, in the presence of ADA inhibitors, retained its inhibitory activity with almost no change in IC_{50} values (0.31 to 5.0 μM), thus confirming the conversion of nelarabine to ara-G.

Further *in vitro* studies of the role of ADA and the interaction of nelarabine and ara-G with adenosine kinase (AK), dGK, and dCK were conducted using purified mammalian enzymes. Ara-G was a good substrate for phosphorylation by dCK and dGK. In contrast, phosphorylation of nelarabine by dCK was not detected. Nelarabine was phosphorylated by mitochondrial dGK, but only at a low rate (4% of ara-G). Neither nelarabine nor ara-G was phosphorylated by AK.

The effects of nelarabine on intracellular ara-GTP formation was investigated in malignant CEM CD4+ T-cells incubated with ^{3}H-nelarabine or ^{3}H-ara-G in the presence or absence of the ADA inhibitor dCF. Nelarabine and ara-G caused comparable intracellular accumulation of ara-GTP (54.7 and 55.9 pmol/10^6 cells, respectively) whereas the ADA inhibitor blocked ara-GTP accumulation induced by nelarabine (6.9 pmol/10^6 cells), but not by ara-G (65.1 pmol/10^6 cells), suggesting that nelarabine is converted to ara-G at the nucleoside or the nucleoside monophosphate level. No phosphates of nelarabine were detected in these assays at the limit of quantification of 1 pmol/10^6 cells. Analysis of the media showed that 13% of nelarabine was converted to ara-G in the absence of dCF. Additionally, nelarabine was stable in media only in the presence of dCF, whereas ara-G was stable in the media in the presence or absence of dCF. The ability of ara-G to cause ara-GTP accumulation was also studied in normal bone marrow precursor cells and in malignant B- and T-cell lines, including the dCK-deficient derivative ACO611a cell line. In these studies, ara-G was found to cause ara-GTP accumulation in both T-cells and B-cells. However, intracellular ara-GTP levels were 20- to 40- fold higher in T-cells than in B-cells and ara-GTP was degraded much more rapidly in B-cells, resulting in sustained high concentrations of ara-GTP in T-cells. Ara-GTP accumulation in the -dCK ACO611a cell line was low, suggesting that in addition to dGK, dCK is involved in the phosphorylation of ara-G to ara-GTP. Ara-GTP accumulation was also low in normal marrow precursor bone cells and significant toxicity to these cells occurred only at very high concentrations of ara-G (1000 μM).

The effects of ara-G on DNA polymerase activity have been studied. Ara-GTP caused inhibition of DNA polymerase α, β, δ, ε, and γ, in that order of sensitivity, relative to K_m for dGTP (Ratio K_i:K_m), indicating that although ara-G can be phosphorylated by mitochondrial dGK, it is not likely to inhibit mitochondrial DNA polymerase γ.

In vivo, duplicate studies determined the effect of nelarabine and ara-G on growth inhibition of implanted tumour cells in nude SCID mice injected SC with 10^7 CEM (malignant T-cell line) cells/mouse. The day after tumour implant, the mice (n=3 to 8/group), were administered either PO or IP, daily doses of nelarabine at 150 or 300 mg/m^2 (50 or 100 mg/kg) for 25 consecutive days, or ara-G at 300 mg/m^2 (100 mg/kg) PO for 25 consecutive days or ara-G, PO, twice daily doses of 300 mg/m^2 (100 mg/kg) for a total dose of 600 mg/m^2/day (200 mg/kg/day) for 10 days. Euthanasia and tumour removal were carried out 64 to 68 days after tumour transplant. Solid tumours were visible 30 days after implantation in the control group. Tumour growth inhibition by nelarabine was dose-dependent with approximately 72% to 94% inhibition of implanted tumour cell growth following PO or IP administration at doses ≥150 mg/m^2/day for 25 days. PO administration of ara-G once daily for 25 days was equally effective in inhibition of implanted tumour cell growth in mice compared to the twice daily PO administration of ara-G for 600 mg/m^2/day for 10 days, with tumour weights of 11.3 and 7.1 % of control, respectively.

- Secondary pharmacodynamics

Limited *in vitro* and *in vivo* studies indicate that nelarabine and ara-G have antiviral properties against certain DNA viruses such as varicella zoster, cowpox and herpes simplex viruses.

- Safety pharmacology programme

No pharmacodynamic safety studies were performed.

- Pharmacodynamic drug interactions

No pharmacodynamic drug interaction studies were performed.

Pharmacokinetics

- Absorption-Bioavailability

The pharmacokinetics of nelarabine and ara-G were studied *in vivo* in the mouse and cynomolgus monkey using IV administration. Human *in vitro* systems were employed to determine the potential for interactions with plasma proteins, P-glycoprotein-mediated transport and cytochrome P450.

In all species, elimination of nelarabine from plasma occurred more rapidly than that of ara-G. Also, exposure to ara-G was greater than exposure to nelarabine in all species except in the rat. The PK parameters observed in the monkey showed the greatest similarity to those observed in humans. No difference was observed in plasma exposure to nelarabine or ara-G between day 1 and day 3 when nelarabine was administered IV to monkeys twice daily at a dose of 300 mg/m^2/dose. For both day 1 and day 3, systemic exposure to ara-G was approximately 6.5-fold higher than exposure to nelarabine (see table 3). In the 5- and 30-day toxicity studies, exposure was comparable between days 1 and 5 in the 5-day study and between days 3 and 28 of the 30-day study. There was no evidence for accumulation of nelarabine or ara-G. No substantial gender-related differences were observed.

Table 3: Principal PK parameters in the monkey following repeated IV doses of nelarabine

Study	**PK**	**Nelarabine**						**Ara-G**					
3-day 50 (600)[1]		**Day 1**			**Day 3**			**Day 1**			**Day 3**		
	$AUC_{(0-6)}$ (µM.h)	155.5			199.1			24.3			29.4		
	C_{max} (µM)	57.0			67.9			67.9			82.5		
	$t_{½}$ (h)	1.8			1.6			0.18			0.21		
	t_{max} (h)	0.5			0.6			0.083			0.083		
5-day		**Day 1**			**Day 5**			**Day 1**			**Day 5**		
		60 (720)[1]	150 (1800)[1]	300 (3600)[1]	60 (720)[1]	150 (1800)[1]	300 (3600)[1]	60 (720)[1]	150 (1800)[1]	300 (3600)[1]	60 (720)[1]	150 (1800)[1]	300 (3600)[1]
	$AUC_{(0-24)}$ (µM.h)	513.	1203	2721	582.0	1042	3320	248.0	407.0	1223	330.0	545.0	1608
	C_{max} (µM)	130.0	288.0	534.0	124.0	262.0	495.0	830.0	1113	2466	1065	1505	2528
	t_{max} (h)	0.5	0.8	1.0	0.5	0.9	1.5	0.07	0.07	0.07	0.07	0.07	0.07
28-day		**Day 3**			**Day 28**			**Day 3**			**Day 28**		
		10 (120)[1]	20 (240)[1]	40 (480	10 (120)[1]	20 (240)[1]	-	10 (120)[1]	20 (240)[1]	40	10 (120)[1]	20 (240)[1]	-
	$AUC_{(0-24)}$ (µM.h)	84.9	177.0	307.4	69.4	161.5	-	21.9	57.1	130.1	22.4	52.3	-
	C_{max} (µM)	24.7	50.6	93.3	24.1	51.3	-	65.0	141.2	396.4	66.7	175.7	-
	t_{max} (h)	0.5	0.5	0.5	0.5	0.5	-	0.07	0.07	0.07	0.07	0.07	-
	Cl (l/kg	0.40	0.37	0.43	0.38	0.41	-	-	-	-	-	-	-

1: dose in mg/kg [mg/m^2]

- Distribution

The tissue distribution of ^{14}C-nelarabine-related radioactivity was assessed in male and female pigmented mice following a single IV infusion of ^{14}C-nelarabine (300 mg/m^2), using whole body autoradiography. The ^{14}C-related material was rapidly and widely distributed into the tissues. In most tissues, the concentrations of radioactivity were highest immediately after the end of the infusion period (10 minutes). Tissues with high levels of radioactivity were kidney, gall bladder, liver and spleen. Low levels of radioactivity were measured in the central nervous system and were generally at the limit of quantification (0.28 µg eq of nelarabine/g) by 14 days after dosing. No selective association of ^{14}C-nelarabine-related radioactivity with melanin-containing tissues was observed. Radioactivity declined relatively slowly (quantifiable levels at 35 days after dosing).

- Metabolism

The *in vitro* metabolism of nelarabine and ara-G was investigated by incubating the ^{14}C-labelled molecules with mouse, rabbit, monkey and human hepatocytes. In incubations of human hepatocytes with nelarabine, the metabolites observed were ara-G, uric acid, xanthine and allantoin. Similarly, following incubations with ara-G, uric acid, xanthine and allantoin were observed. In general, metabolites observed in human hepatocytes were also observed in the mouse, rabbit or monkey hepatocytes.
The *in vivo* metabolism of nelarabine was investigated in male and female mice (300 mg/m^2) and cynomolgus monkeys (1200 mg/m^2) after an IV administration of ^{14}C-nelarabine. Selected samples of plasma, urine, bile (male mouse and monkey only) and faeces obtained from excretion studies were analysed using radio-HPLC and LC/MS/MS to quantify and identify the major metabolites of nelarabine. In the plasma of mice, ara-G and allantoin were the major radioactive components circulating with smaller amounts of nelarabine and uric acid. In the monkey, ara-G was the major radioactive component circulating in plasma; nelarabine was a minor component. In mice, unchanged nelarabine represented approximately 22% to 28% of the administered dose in urine, ara-G approximately 19% to 22% and allantoin represented approximately 20% to 24% of the dose. Three other minor urinary metabolites, uric acid, guanine and xanthine, collectively accounted for less than 3% of the dose. In monkeys, unchanged nelarabine represented approximately 4 to 12% of the administered dose in urine. Ara-G was the most prominent metabolite in urine, accounting for approximately 45 to 60% of the administered dose. Two minor metabolites observed were allantoin and xanthine. The metabolites detected in the faeces and bile were similar to those detected in urine but the amounts were very low and accounted for <6% of the total administered dose. In general, there were no notable differences in metabolic profile between males and females.

- Excretion

Following IV administration of ^{14}C-nelarabine to male and female mice (300 mg/m^2) and cynomolgus monkeys (1200 mg/m^2); the predominant route of excretion was *via* the urine in both species (62 to 75% and 63 to 69% of the dose excreted by this route in mice and in monkey, respectively). Less than 6% of the dose was excreted in the faeces and bile. The majority of the recovered radioactivity was excreted within 48 hours in mice and 96 hours in monkeys. For the mouse, approximately 4% of radioactivity remained in the carcasses at the end of the study (96 hours) indicating some retention of radioactivity in the body. Studies conducted in male bile duct cannulated animals revealed that biliary secretion was a minor route of elimination, accounting for <2% of the IV dose in both mice and monkeys.

- Pharmacokinetic drug interactions

The protein binding of nelarabine and ara-G (6, 60 and 600 μM) was investigated in human plasma by ultrafiltration. Low binding to human plasma proteins was observed for both nelarabine (7.02 to 19.6%) and ara-G (9.78 to 24.4%). When incubated with pooled human liver microsomes *in vitro*, nelarabine and ara-G (up to 100 μM) did not inhibit the activities of the major human hepatic cytochrome P450 enzymes (CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6 and CYP3A4). Likewise, neither nelarabine nor ara-G (up to 300 μM) caused any apparent increase in mean mRNA expression or catalytic activities for CYP1A2, 2B6 or 3A4 in human hepatocytes. *In vitro,* no inhibition of human P-glycoprotein (P-gp)-mediated transport was observed with either nelarabine or ara-G (up to 100 μM). Nelarabine and ara-G were not substrates for human P-gp and both compounds showed low passive membrane permeability.

Toxicology

- Single dose toxicity

Single-dose toxicity studies were carried out in mice and cynomolgus monkeys and are summarised in Table 4.

Table 4: Summary of single-dose toxicity studies

Species	Dose in mg/kg (mg/m^2)	Route	Max. non-lethal dose in mg/kg (mg/m^2)	Major findings
Mouse (n = 6/sex/dose)	0, 300 (900), 400 (1200), 500 (1500), 600 (1800)	IV bolus injection	600 (1800)	Reduced body weight gain in females (1200 mg/m^2) and above transient sedation in males and females (1800 mg/m^2)
Monkey (n = 1F)	100 (1200), 200 (2400), 300 (3600), 400 (4800), 500 (6000)	IV infusion under ketamine sedation administered on consecutive days	500 (6000)	Transient augmentation of ketamine-induced sedation at 4800 mg/m^2 and above

- Repeat dose toxicity (with toxicokinetics)

The potential toxicity of nelarabine was investigated in repeat-dose IV studies of 5 or 30 days duration. The 5-day studies were conducted in mice (600 to 1800 mg/m^2/day) and in ketamine-sedated cynomolgus monkeys (720 to 3600 mg/m^2/day). The 30-day study was carried out in the non-sedated monkey (120 to 480 mg/m^2/day). The dose of 300 mg/kg/day (3600 mg/m^2/day) was chosen as the maximum dose in the final 5-day study (death of ketamine-sedated female monkeys observed in three non-GLP studies at 500 and 400 mg/kg, i.e. 6000 and 4800 mg/m^2). The design of the final mouse and monkey studies is summarised in Table 5.

Table 5: Design of the final repeat-dose toxicity studies

Species (strain)	Method of administration	Animals/ sex/group	Dose mg/kg/day [mg/m^2/day]	Duration of dosing
Mouse (CD-1)	Intravenous (bolus)	6	0 [0]; 200 [600]; 300 [900]; 400 [1200]; 500 [1500]; 600 [1800]	5 days
Monkey (cynomolgus)	Intravenous (infusion) Under ketamine sedation	2[1]	0 [0]; 60 [720]; 150 [1800]; 300 [3600]	5 days
Monkey (cynomolgus)	Intravenous (infusion)	3[2]	0 [0]; 10 [120]; 20 [240]; 40 [480]	30[3] days

[1] 2 males and 2 females served as control for the 150 and 300 and additional 2 males and 2 females were included as control for the 60 mg/kg/day group; [2] An additional 2 males and 2 females were included in the control and the 40 mg/kg/day groups; [3] Dosing was terminated for the 40 mg/kg/day group after 23 days due to neurotoxicity.

In the mouse study, decreased activity was noted in a majority of males and females given 600 mg/kg/day. Shallow breathing and ptosis were noted, but decreased over time. The onset of the clinical signs was approximately 2 to 26 minutes following dosing, with animals recovering by 1 to 5 hours after dosing. A single incidence of hypothermia and tremors was noted in one male given 600 mg/kg/day. One female given 500 mg/kg/day died on post dose day 8 and two females given 600 mg/kg/day died by post dose days 7. Dehydration, high carriage, and partially closed eyes were noted prior to death. Macroscopic findings of red lungs and tarry material in stomach, duodenum, jejunum, ileum, coecum and colon were noted in one female given 600 mg/kg/day and found dead on post dose day 5. The LD_{10}, LD_{50} and LD_{90} values calculated from this study for males and females combined were 1638, 2170 and 2702 mg/m^2/day, respectively.
In the monkey, administration of 300 mg/kg/day of nelarabine for 5 consecutive days caused severe neurotoxicity that was lethal in 3 of 4 monkeys. An identical regimen of 150 mg/kg/day resulted in no mortality, but 2 of 4 monkeys showed reversible neurotoxicity. Reversible neurotoxicity was also seen in 3 of 4 monkeys given 60 mg/kg/day. Clinical signs in this group were moderate, but persisted 21, 36 and 57 days into the post dose observation period. Clinical signs of neurotoxicity included seizures, convulsions, muscle tremor and weakness, in-coordination, ataxia, depth perception deficits, and unresponsiveness. No microscopic lesions were observed in central or peripheral nervous system tissues to correlate with this observed neurotoxicity. Clear decreases in total white blood cell values, body weight, and food consumption were noted in all treated groups. Histopathological changes were seen in the high dose group, and were characterized by maturation arrest of intestinal epithelial cells and depletion of lymphoid organs, reversible in surviving animals. Neurotoxicity was dose-limiting. Onset of clinical neurotoxicity was dose-dependant, beginning immediately after the dosing period in individual animals at the highest dose and as late as post dose day 10 and 13, in animals from the low

and mid-dose groups, respectively. All signs of neurotoxicity were reversible at all dose levels tested. A no-effect level was not determined.
In the 30-day study in non-sedated monkeys, neurotoxicity manifested clinically after 19 doses as coarse muscle tremors and seizures lasting about 30 seconds in 2 monkeys given 480 mg/m^2/day and one monkey given 240 mg/m^2/day. After 23 doses, 6 monkeys given 480 mg/m^2/day and 2 monkeys given 240 mg/m^2/day had tremors and/or seizures and dosing was stopped for the 480 mg/m^2/day monkeys. During the recovery period, clinical signs were completely reversible in the 20 mg/kg/day group, but only partially reversible in the 480 mg/m^2/day group. Within 3 weeks after the dosing period, surviving clinically affected monkeys showed improvement as muscle tremors lessened and the general body condition improved. However, no further clinical improvement occurred during the rest of the recovery period. Laboratory findings comprised decreased RBC parameters, platelet counts, neutropenia and monocytopenia and reduced cholesterol, glucose and creatinine levels in high-dose animals. There were no treatment-related macroscopic changes. Neurotoxicity that was evident clinically as tremors and seizures at 480 mg/m^2/day was accompanied by histopathologic changes of white matter degeneration and vacuolation in brain and spinal cord in 3 of the 10 monkeys. These lesions occurred only at 480 mg/m^2/day and persisted through the recovery period.
In monkey, systemic exposure (AUC values) to nelarabine and ara-G were dose-proportional and did not show any gender differences; neither nelarabine nor ara-G accumulated over the dosing period. Neurotoxicity was unrelated to nelarabine exposure, but generally correlated with greater exposure to ara-G.

- Genotoxicity

The mutagenic potential of nelarabine at concentrations from 100 to 5000 μg/ml was investigated in 3 hour incubations in the presence and absence of rat liver S9-mix in mouse lymphoma L5178Y/TK cells. The relative total growth at the highest concentration of 5000 μg/mL during the 3-hour treatments was 14% (in the absence of S9-mix) and 11% (in the presence of S9-mix). Both small and large colony mutants were observed in cultures treated with nelarabine in the presence and absence of S9-mix, as well as in the positive controls. With nelarabine an increase in the frequency of both small and large colonies was observed. The increase in frequency of small colonies is consistent with damage to multiple loci on chromosome 11, in addition to loss of the TK locus.

- Carcinogenicity

Carcinogenicity studies were not conducted with nelarabine.

- Reproduction Toxicity

Studies assessing effects on fertility were not conducted as adverse effects on fertility would be expected from the class of cytotoxic nucleoside analogue drugs. No undesirable effects were seen in the testes or ovaries of monkeys given nelarabine intravenously at doses up to approximately 32% of the adult human dose on an mg/m ^{2} basis for 30 consecutive days.

A conventional embryo-foetal developmental toxicity study was conducted in the rabbit. As expected from its mechanism of action, nelarabine caused maternal and foetal toxicity when given to pregnant rabbits as an 8-hour daily intravenous infusion at doses of 354, 1180 or 3540 mg/m^2/day during the period of major organogenesis. Maternal toxicity was seen at 3540 mg/m^2/day as evidenced by mortality, abortion, adverse clinical signs, decreased body weight gains and corrected body weight gains and lower food consumption. There was no evidence of treatment-related embryolethality. Foetotoxicity was evidenced at 3540 mg/m^2/day by low foetal weights and at all levels by indications of delayed skeletal ossification. Increased incidences of foetal abnormalities were seen in all nelarabine-treated groups, including cleft palates at 3540 mg/m^2/day, absent pollices at doses ≥1180 mg/m^2/day and absent gall bladders, accessory lung lobes and fused/extra sternebrae at all doses. Effects at 354 mg/m^2/day were thus limited to increased incidences of minor anomalies and common skeletal variants. Toxicokinetic data were obtained in the course of this study. On the last day, the AUC in the low-dose group averaged 90.8 μM.h, corresponding to a safety margin of 0.2 in adult humans.

A segment III study and studies in juvenile animals were not conducted.

- Local tolerance

Studies of local tolerance are limited to a haemolysis and protein flocculation study and a conventional eye irritation test (both negative).

- Other toxicity studies

Antigenicity: Nelarabine tested negative in a conventional guinea pig test for delayed hypersensitivity. No Immunotoxicity or dependence studies were conducted with nelarabine.

Ecotoxicity/environmental risk assessment

An evaluation of the potential risk to the environment from the storage, use and disposal of nelarabine has not been performed.

Discussion on the non-clinical aspects

Pharmacology

Nelarabine is a water-soluble pro-drug of the deoxyguanosine analogue 9-β-*D*-arabinofuranosylguanine (ara-G). The IC_{50} for cytotoxicity in human T-cell lines ranged from 0.31 to 4.4 μM for nelarabine and from 0.31 to 5.0 μM for ara-G. Generally, the IC_{50} values for cytotoxicity in B-cells with nelarabine and ara-G were at least 20-fold higher. *In vivo*, proof of concept was established in studies determining the effect of nelarabine and ara-G on growth inhibition of implanted malignant T-cell line in mice. Tumour growth inhibition by nelarabine was dose-dependent with approximately 72% to 94% inhibition of implanted tumour cell growth following PO or IP administration of nelarabine at doses ≥150 mg/m^2/day for 25 days. PO administration of ara-G once daily for 25 days was equally effective in inhibition of implanted tumour cell growth in mice compared to the twice daily PO administration of ara-G for 600 mg/m^2/day for 10 days, with tumour inhibition values of 89% and 93%, respectively. The mechanism of action was investigated in human leukaemic cell lines treated with nelarabine or ara-G in the absence or presence of adenosine deaminase inhibitors, or using purified enzymes. Taken together, these studies indicated that nelarabine is demethylated by adenosine deaminase to form ara-G. Ara-G is then phosphorylated by cellular dCK or dGK to ara-GMP, which on subsequent phosphorylation is converted to active ara-GTP. Ara-GTP accumulates to significantly higher levels and for longer duration in T-cells than in other cell types including B-cells and inhibits DNA synthesis by chain termination of DNA polymerase α, β, δ, ε, and γ, in that order, leading to T-cell death. Limited studies of secondary pharmacodynamics revealed no clinically relevant findings. Safety pharmacology studies were not conducted, as these are not required for cytotoxic anticancer drugs unless they have a novel mode of action (ICH S7A Note for Guidance on safety pharmacology studies for human pharmaceuticals CPMP/ICH/539/00, 16 November 2000). No pharmacodynamic drug interaction studies were conducted, which was considered acceptable.

Pharmacokinetics

The pharmacokinetics of nelarabine and ara-G was studied *in vivo* in mice and cynomolgus monkeys using IV administration, which is the proposed clinical route. Human *in vitro* systems were employed to determine the potential for interactions with plasma proteins, P-glycoprotein-mediated transport and cytochrome P450. Validated methods of adequate sensitivity were used to quantify the concentrations of nelarabine, ara-G and ^{14}C-labelled material in biological samples. Following a single IV administration, the plasma half-life of nelarabine was shorter (30 minutes in the monkey) than that of ara-G (about 4 hours in the monkey) and systemic exposure to ara-G was greater than exposure to nelarabine in all species, except in rats. In monkeys and adult humans, the plasma half-life of nelarabine was 30 and 17 minutes, respectively, and that of ara-G, 228 and 181 minutes, respectively. Following repeated IV administration of nelarabine, systemic exposures to both nelarabine and ara-G in monkeys were generally dose-proportional. There were no substantial changes in exposures over

time, no evidence for accumulation of nelarabine or ara-G, and no apparent gender-related differences in exposure on repeat dosing for up to 28 days in the monkey. Nelarabine is rapidly and widely distributed, followed by a slow elimination attributable to the incorporation of nucleotide metabolites into nucleic acids. The principal metabolic pathway involves the O-demethylation of nelarabine by adenosine deaminase to form ara-G. Hydrolysis of nelarabine and ara-G results in the formation of the naturally occurring purine nucleotides methylguanine and guanine, respectively. These are then de-methylated and/or de-aminated to xanthine and further oxidized to uric acid and allantoin. Urinary excretion was the major route of elimination of nelarabine, accounting for approximately 62 to 75% (mice) and 63 to 69% (monkey) of the administered dose. Faecal and biliary elimination were very minor routes of excretion in mice and monkeys (<6% of the administered dose). Excretion in milk was not investigated. At concentrations representative of those in human plasma, less than 25% protein binding of nelarabine or ara-G was observed, indicating that neither is substantially bound to human plasma proteins. Neither nelarabine nor ara-G was inhibitors or substrates for human P-gp. Nelarabine and ara-G showed little potential for inhibition of CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6 and CYP3A4 in human liver microsomes. Taken together, these studies suggest that nelarabine and ara-G are unlikely to interact with other drugs.

Toxicology

In conventional single-dose toxicity studies using IV administration, the maximum non-lethal dose was 1800 mg/m^2 in mice and 6000 mg/m^2 in cynomolgus monkeys. The noteworthy clinical findings were reduced body weight gain in female mice and sedation in either species.

Repeat-dose toxicity studies included 5-day studies in mice at doses of 600 to 1800 mg/m^2/day and in ketamine-sedated cynomolgus monkeys at doses of 720 to 3600 mg/m^2/day and a 30-day study in non-sedated monkeys at doses of 120 to 480 mg/m^2/day. In mice, clinical findings comprised tremors, decreased activity and death. Macroscopic findings were either negative or unspecific, and histopathology was not performed. The LD_{10}, LD_{50} and LD_{90} values calculated from this study for males and females combined were 1638, 2170 and 2702 mg/m^2/day, respectively. In monkeys, the critical effect was neurotoxicity characterized by seizures, muscle tremor and weakness, in-coordination, ataxia, depth perception deficits and unresponsiveness, which occurred in males and females given ≥720 mg/m^2/day for 5 days or at ≥240 mg/m^2/day for up to 30 days, but not in monkeys given 120 mg/m^2/day for 30 days. Clinical neurotoxicity occurred earlier the higher the dose and was only partially reversible at 480 mg/m^2/day given for 23 days. No histopathologic lesions were observed in central or peripheral nervous system tissues of monkeys given nelarabine for 5 days, but white matter degeneration and vacuolation in brain and spinal cord were noted in 3 of 10 monkeys dosed at 480 mg/m^2/day for 23 days. These CNS lesions occurred only at 480 mg/m^2/day and were still present 2 months after dosing was stopped. Other main findings in the 5- and 30-day repeat-dose studies in monkeys indicate that nelarabine also targets the mitotically active cells in bone marrow, lymphoid organs and intestinal tract, resulting in secondary effects whose incidence and severity increased with time and dose. All of these reversed during recovery. One high dose female (out of 4 animals given 3600 mg/m^2/day) in the 5-day study had minimal epicardial fibrosis and minimal myocarditis. Mild multifocal degeneration of the myocardium was observed in 1 low dose male (out of 6 animals) and in 1 mid dose female (out of 6 animals) and 1 high dose female (out of 10 animals) in the 30-day study. Similar effects were not observed in the controls. However, since neither the frequency nor the severity of these effects correlated with exposure, they are unlikely to be treatment-related (see SPC section 5.3). The repeat-dose mice study did not include toxicokinetics. In monkeys, AUC values for both nelarabine and ara-G were dose-proportional and showed no sex difference or signals of accumulation. A no-effect level was not determined for effects attributable to toxicity to mitotically active cells in bone marrow, lymphoid organs and intestinal tract. The NTEL for neurotoxicity in the monkey was 120 mg/m^2/day. Neurotoxicity was unrelated to nelarabine exposure but generally correlated with greater exposure to ara-G. The safety margin for neurotoxicity was well below 1, whether based on ara-G exposure (AUC values) or nelarabine dose expressed in mg/m^2. As such, treatment with nelarabine is expected to result in potentially serious adverse events relating to haematological, gastrointestinal and/or nervous system disorders. Like other nucleoside analogue antimetabolites, nelarabine was genotoxic in a mouse lymphoma assay. Carcinogenicity studies were not conducted and are not required for anticancer drugs.

Although non-clinical studies of toxicity to reproduction are not required for anticancer drugs, nelarabine was tested for embryo-foetal developmental toxicity in a conventional segment II test in rabbits. There was an increased incidence of malformations at exposures ≥354 mg/m^2/day, corresponding to a safety margin well below 1 in adult humans. As such, nelarabine is a potential teratogen. Nelarabine should not be used during pregnancy unless clearly necessary. If a patient becomes pregnant during treatment with nelarabine, they should be informed of the possible risk to the foetus. Both sexually active men and women should use effective methods of contraception during treatment and for at least three months following cessation of treatment. The effect of nelarabine on fertility in humans is unknown. Based on the pharmacological action of the compound, undesirable effects on fertility are possible. Family planning should be discussed with patients as appropriate. It is unknown whether nelarabine or its metabolites are excreted in human breast milk. The excretion of nelarabine in milk has not been studied in animals. However, because of the potential for serious adverse reactions in infants, breastfeeding should be discontinued (see SPC sections 4.6 and 5.3). No studies were performed in juvenile animals and there are no data on pharmacokinetics in juvenile animals.

Gross and microscopic examination of the site of IV administration was included in the repeat-dose monkey studies and indicated that nelarabine is well tolerated. A haemolysis and protein flocculation study and a conventional eye irritation test were both negative. There are no studies of immunotoxicity. This is considered justified as reversible immunotoxicity is a well-known class effect of cytotoxic nucleoside analogues. The drug substance contains six compound-related impurities whose specification level is above the applicable qualification threshold (0.05%). No details have been provided on the structure of these impurities, or on their levels in the batches used in pivotal animal safety studies. Given the serious nature of the proposed indication and the fact that nelarabine itself is highly toxic, it was nevertheless considered unwarranted to request that these be qualified. An environmental risk assessment was not conducted since at the time of submission the current draft CHMP guideline exempted orphan drugs from this requirement. Meanwhile, this exemption has been eliminated from the final guideline. The latter, however, was not planned to come into effect until 1st December 2006. It was therefore deemed acceptable that no environmental risk assessment is submitted. At all events, the small size of the target patient population precludes any significant environmental exposure to the drug.

4. Clinical aspects

Introduction

The clinical programme of nelarabine comprised four phase I pharmacokinetic and safety studies, involving patients with various relapsed or refractory haematological malignancies, including non-T-cell disease (PGAA1001, PGAA1002, PGAA1003, PGAA1005). Three pivotal phase II studies were submitted. Studies PGAA2001 and PGAA2002 were two independent pivotal studies, conducted in collaboration with the National Cancer Institute (NCI), aimed to assess the efficacy of nelarabine in paediatric and adult patients with refractory acute T-cell lymphoblastic leukaemia or lymphoblastic lymphoma. Study PGAA2003 was a multi-centre study to assess the safety and the efficacy of nelarabine in patients with chronic lymphocytic leukaemia who failed previous Fludarabine therapy. Seven small phase II open label studies (CALGB69803, MDACC 86, CALGB59901, SWOG S0010, COG AALL00P2, MDACC 430, TRC9701) and compassionate use phase II protocols were submitted as non-pivotal safety studies and involved patients with haematological malignancies. The Clinical trials were performed in accordance with GCP as claimed by the applicant. The applicant has provided a statement to the effect that clinical trials conducted outside the community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

Nelarabine treatment is for intravenous use only and is administered undiluted. It must only be administered under the supervision of a physician experienced in the use of cytotoxic agents. Nelarabine. The recommended dose in adults and adolescents (aged 16 years and older) of nelarabine is 1,500 mg/m ^{2} administered intravenously over two hours on days 1, 3 and 5 and repeated every 21 days. In children and adolescents (aged 21 years and younger), the recommended dose of nelarabine is 650 mg/m^2 administered intravenously over one hour daily for 5 consecutive days, repeated every 21 days. Both regimens have been studied in the age range 16 to 21 years in clinical

trials and the safety and efficacy were similar. Therefore, for these patients, the prescribing physician should consider which regimen is appropriate. Nelarabine must be discontinued at the first sign of neurological events of National Cancer Institute Common Terminology Criteria Adverse Event (NCI CTCAE) grade 2 or greater. Delaying subsequent dosing is an option for other toxicities, including haematological toxicity (see SPC section 4.2 and 4.4).

Pharmacokinetics

Methods for the determination of nelarabine and ara-G in plasma, urine, and cerebrospinal fluid have been validated using reverse-phase HPLC analysis and UV detection. An LC/MS/MS method for the determination of nelarabine and ara-G in plasma was validated. A method for the determination of arabinosylguanine triphosphate (ara-GTP) and fludarabine triphosphate (F-ara-ATP) in human cells has been validated using an HPLC assay. Ara-GTP and F-ara-ATP were extracted from human cells by protein precipitation using perchloric acid. Extracts were analyzed using HPLC with UV absorbance detection at 256 nm. Full validation reports documenting acceptable levels of detection, quantification, accuracy and precision have been submitted. Pharmacokinetic analyses were performed using standard non-compartmental analysis. Standard pharmacokinetic statistical analyses have been applied.

- Absorption

Nelarabine is administered as an i.v. solution. Therefore, this section is not applicable.

- Distribution

After i.v. administration, nelarabine is rapidly converted to ara-G. Based on cross study analysis, using dose-corrected data from 107 adults and 30 paediatric patients, the mean volume of distribution at steady state (Vss) for nelarabine was 115 l/m2 in adults and 89.4 l/m2 in paediatric patients. Mean Vss/F for ara-G was 44.8 l/m2 in adults and 32.1 l/m2 in paediatric patients. The mean in vitro protein binding of nelarabine and ara-G in human plasma was < 25% that was independent of concentration over a concentration range of 6 and 600 μM.

- Elimination

After IV administration of ^{14}C-nelarabine in animals, urinary excretion accounted for the majority of elimination (62-75% of dose in mice, 63-69% in monkey). Less than 6% of the dose was excreted in faeces and bile. These data suggest that the primary clearance of nelarabine is by metabolism followed by excretion in urine. Renal excretion accounted for approximately 5% and 23% of the administered dose for nelarabine and Ara-G, respectively.
With human hepatocytes, ara-G, uric acid, xanthine and allantoin were the metabolites observed for nelarabine; uric acid, xanthine and allantoin were the metabolites observed for ara-G. The results from metabolism studies indicate that the principal route of metabolism for nelarabine in preclinical studies was O-demethylation by adenosine deaminase to form ara-G, which underwent hydrolysis to form guanine. In addition, some nelarabine was hydrolyzed to form methylguanine, which was O-demethylated to form guanine. Guanine was N-deaminated to form xanthine, which was further oxidized to yield uric acid.

- Dose proportionality and time dependencies

In cross-study analysis, nelarabine and ara-G AUC0-t and AUCinf values were examined for dose proportionality for adult and pediatric patients separately, with dose expressed either in total mg and in mg/m^2. In adult patients, AUC0-t and AUCinf data were available from 53 to 98 patients, having received nelarabine doses ranging from 200 to 2900 mg/m^2. In pediatric patients, AUC0-t and AUCinf data were available from 16 to 24 patients, having received nelarabine doses ranging from 100 to 2350 mg/m^2. In adult patients, the results of the power model were reasonably consistent with dose proportionality for both nelarabine and ara-G with dose expressed in either mg or mg/m^2. In pediatric patients, the results for ara-G were consistent with dose proportionality. However, the results for nelarabine were less than dose proportional. Based on these results, data obtained with various doses

were combined, correcting the relevant PK parameters for a dose of 1500 mg/m^2, for evaluation of potential predictors of pharmacokinetics.
Single dose pharmacokinetic data for nelarabine, ara-G and ara-GTP obtained from cross-study analysis of study PGAA1001, 1002, 1003 and 1005 were analyzed in 124 patients for nelarabine, 100 patients for ara-G, and 51 patients for intracellular ara-GTP, for which data were dose-normalized to 1500 mg/m^2. Pharmacokinetic data in pediatric patients, receiving the nelarabine 650 mg/m^2 infused over 1 hour were obtained from a preliminary analysis of the ongoing clinical study AALL00P2. Pharmacokinetics obtained from this study was compared to those of the cross-study analysis. The data obtained in 6 pediatric patients in study AALL00P2 were in line with results obtained in the other PK studies, applying a different dosage (data not shown).
In study PGAA1003, full nelarabine and ara-G pharmacokinetics were obtained at day 1 and day 5. Analysis of time-dependence comparing day 1 and day 5, based on dose-corrected parameters in adults indicated that no clinically relevant accumulation occurred for nelarabine and ara-G upon repeated infusion of nelarabine at day 1, 3 and 5.

- Special populations

No specific clinical trials were conducted to investigate the PK of nelarabine, ara-G, or intracellular ara-GTP in special populations. The relationship between PK parameters and covariates was explored by stepwise regression analysis. Covariates of interest (study, age, gender, race, BSA, disease category, baseline calculated CrCl) were included in the full model of regression analysis. Study was included to account for differences between the studies such as number of days of dosing (3 days vs. 5 days), schedule of dosing (daily x5, daily x3, alternate day dosing), duration of infusion (1 hour vs. 2 hours), study population.

Impaired renal function: Baseline creatinine clearance (CrCl) was not a significant covariate for nelarabine PK. Ara-G clearance was related to baseline CrCl, being 7% lower in subjects with baseline calculated CrCl of 50 to 80 ml/min compared to subjects with CrCl >80ml/min (p=0.036).

Gender: Gender was not a significant covariate for nelarabine and ara-G PK. However, dose-normalized intracellular ara-GTP AUC0-t and Cmax were 4.2 and 2.1 times higher (p=0.020 and p=0.074), respectively, in adult females than in adult males (AUC0-t 3752 vs. 896 µmol.h/l, respectively and Cmax 158 and 74.2 µmol/l, respectively).
Ethnic groups: Ethnic groups were not found to be a significant covariate on nelarabine, ara-G and ara-GTP pharmacokinetics.

Weight: Nelarabine and ara-G Vss were influenced by BSA, with reduced Vss at lower BSA (p= 0.009 and <0.001, respectively). Ara-G Cl/F was significantly correlated with BSA (p<0.001). Similar correlations were observed for weight.
Elderly: Nelarabine, ara-G and ara-GTP PK in elderly subjects (>65 years of age) were not statistically different from PK in the adult population.

Children: PK data were compared between patients of less than 18 years of age, patients of 18-65 years old and patients more than 65 years old. Age was not found to be a significant variable for nelarabine, and ara-G PK.

- Pharmacokinetic interaction studies

In vitro, nelarabine and ara-G did not inhibit the activities of the major hepatic cytochrome enzymes (CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, and CYP3A4) up to the highest concentration tested, i.e. 100 µM. Nelarabine and ara-G showed no inhibition of human P-glycoprotein (P-gp)-mediated efflux of [3H]-digoxin at concentrations of 0.3 to 100 µM. Additionally, nelarabine and ara-G were not found to be substrates for human P-gp. Both compounds showed low passive membrane permeability in these assays.

In vivo data were assessed from an open-label Phase I PK/PD study (PGAA1005) to determine the effect of fludarabine on intracellular concentrations of 9-β-D-arabinofuranosylguanine triphosphate

(ara-GTP) in 13 patients with refractory leukemia. Patients received nelarabine at a dose of 1200 mg/m^2 administered as a 2-hour infusion on Days 1, 3, and 5. Fludarabine was administered 4 hours before the nelarabine infusion at a dose of 30 mg/m^2 infused over 30 minutes on days 3 and 5 in course 1 and on days 1, 3, and 5 on second and subsequent courses. The effect of fludarabine administration on intracellular ara-GTP exposure was assessed by comparing AUC_{0-48} values on days 1 and 3 of the study. Because of the observed accumulation of ara-GTP with this dosing schedule, day 3 AUC_{0-48} values were corrected for carryover from the day 1 dose assuming linear PK behavior. There was no significant difference between the day 1 AUC_{0-48} and the corrected day 3 AUC_{0-48} values for intracellular ara-GTP (geometric mean values of 3957 and 4062 µM.h, respectively), demonstrating that fludarabine administration before nelarabine on day 3 did not affect the intracellular accumulation of ara-GTP.

- Discussion on clinical pharmacokinetics

The pharmacokinetics of nelarabine, ara-G and intracellular ara-GTP has been well studied in the target population including 40 patients below the age of 18. The results presented were consistent across the studied populations. Maximum concentrations of ara-G were achieved at the end of intravenous infusion of nelarabine, and tended to be higher than nelarabine Cmax. This is consistent with a rapid conversion from nelarabine to ara-G as indicated by the short t½ of nelarabine. In adult patients, after infusion of 1500 mg/m^2 nelarabine over two hours, mean plasma nelarabine C_{max} and AUC_{inf} values were 13.9 µM (81%) and 13.5 µM.h (56%) respectively. Mean plasma ara-G C_{max} and AUC_{inf} values were 115 µM (16%) and 571 µM.h (30%), respectively. Intracellular C_{max} for ara-GTP appeared within 3 to 25 hours on day 1. Mean (%CV) intracellular ara-GTP C_{max} and AUC values were 95.6 µM (139%) and 2214 µM.h (263%) at this dose (see SPC section 5.2). In paediatric patients, after infusion of 400 or 650 mg/m^2 nelarabine over one hour in 6 paediatric patients, mean (%CV) plasma nelarabine C_{max} and AUC_{inf} values, adjusted to a 650 mg/m^2 dose, were 45.0 µM (40%) and 38.0 µM.h (39%), respectively. Mean plasma ara-G C_{max} and AUC_{inf} values were 60.1 µM (17%) and 212 µM.h (18%), respectively. Nelarabine and ara-G were extensively distributed throughout the body based on combined Phase I pharmacokinetic data at nelarabine doses of 104 to 2900 mg/m^2. For nelarabine, mean (%CV) V_{SS} values were 115 l/m^2 (159%) and 89.4 l/m^2 (278%) in adult and paediatric patients, respectively. For ara-G, mean V_{SS}/F values were 44.8 l/m^2 (32%) and 32.1 l/m^2 (25%) in adult and paediatric patients, respectively. *In vitro* protein binding of nelarabine was less than 25%. Upon repeated administration (either a daily or a day 1, 3, 5 schedule), nelarabine did not accumulate. Dose proportionality with respect to AUC exposure was apparent with the exception of nelarabine in the paediatric population for which less than expected increases were observed. Nelarabine and ara-G appeared dose-proportional with respect to C_{max} in adults while less than dose-proportional in paediatric patient. Intracellular ara-GTP concentrations in leukaemic blasts were quantifiable for a prolonged period after nelarabine administration. Intracellular ara-GTP accumulated with repeated administration of nelarabine. On the day 1, 3, and 5 schedule, C_{max} and $AUC_{(0-t)}$ values on day 3 were approximately 50% and 30%, respectively, greater than C_{max} and $AUC_{(0-t)}$ values on day 1. The PK of nelarabine, ara-G and intracellular ara-GTP was characterized by a moderate between subject variability for the primary active metabolite Ara-G and a large variability for nelarabine and intracellular ara-GTP. Nelarabine Cl and Vss values showed greater between-day variability (53% and 73%, respectively) than ara-G Cl/F and Vss/F values (15% for both). The population pharmacokinetic model provided intra-individual variability estimates of 23% for nelarabine clearance and 13% for intracellular ara-GTP apparent clearance.

The results from metabolism studies indicate that the principal route of metabolism for nelarabine in preclinical studies was O-demethylation by adenosine deaminase to form ara-G, which underwent hydrolysis to form guanine. In addition, some nelarabine is hydrolysed to form methylguanine, which is O-demethylated to form guanine. Guanine is N-deaminated to form xanthine, which is further oxidized to yield uric acid. Nelarabine and ara-G are rapidly eliminated from plasma with a half-life of approximately 30 minutes and 3 hours, respectively. The excretion of nelarabine is mainly through urine, primarily as metabolites. Urinary excretion of nelarabine and ara-G accounted for 5.3% and 23.2% of the dose, respectively. Because the timecourse of intracellular ara-GTP was prolonged, its elimination half-life could not be accurately estimated.

No specific studies were performed in special populations. Stratified analysis identified BSA as a major predictor of PK. Gender has no effect on nelarabine or ara-G pharmacokinetics. Intracellular ara-GTP C_{max} and $AUC_{(0–t)}$ values at the same dose level was 2 to 3 fold greater on average in adult female than in adult male patients. Ethnic groups had no apparent effect on nelarabine, ara-G, or intracellular ara-GTP pharmacokinetics (see SPC section 5.2). Clinical pharmacology data in children below the age of 4 was limited. Combined phase I PK data at nelarabine doses of 104 to 2900 mg/m ^{2} indicated that Cl and V_{ss} values for nelarabine and ara-G are comparable between the two groups (see SPC section 4.2 and 5.2). No data were available in hepatically impaired patients. These patients should be treated with caution (see SPC section 4.2). The PK of nelarabine and ara-G has not been studied in renally impaired or haemodialysed patients. Nelarabine is excreted by the kidney to a small extent (5 to 10% of the administered dose) whereas ara-G is excreted by the kidney to a greater extent (20 to 30% of the administered nelarabine dose). The mean apparent clearance (Cl/F) of ara-G was about 7% lower in patients with mild renal impairment (Cl_{cr} = 50 to 80 ml/min) than in patients with normal renal function (Cl_{cr} > 80 ml/min), see SPC section 5.2. No data were available to provide a dose advice for patients with Cl_{cr} less than 50 ml/min. Patients with renal impairment must be closely monitored for toxicities when treated with nelarabine (see SPC sections 4.2 and 5.2). In elderly patients, decreased renal function, which is more common in the elderly, may reduce ara-G clearance (see section 4.2).

Nelarabine and ara-G did not inhibit the activities of the cytochrome P450 enzymes (CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, and CYP3A4). Nelarabine and ara-G showed no inhibition of human P-glycoprotein and were not found to be substrates for human P-gp in vitro. Concomitant treatment with fludarabine does not appear to influence the intracellular ara-GTP exposure. From a theoretical point of view, concomitant treatment with potent adenosine deaminase inhibitors such as pentostatin is not recommended as the efficacy of nelarabine may be reduced and/or the adverse event profile of either active substance may be change (see SPC section 4.5).

Pharmacodynamics

- Mechanism of action

Nelarabine, a water-soluble prodrug of ara-G, is a deoxyguanosine analogue. Nelarabine is rapidly demethylated by adenosine deaminase in the peripheral blood to ara-G. *In vitro* studies and biochemical studies have demonstrated that intracellular ara-G is phosphorylated via deoxycytidine kinase (dCK) and deoxyguanosine kinase (dGK) to the 5'-monophosphate, which undergoes further phosphorylation to the active 5'-triphosphate, 9-β-D-arabinofuranosylguanine triphosphate (ara-GTP). Ara-GTP is incorporated into deoxyribonucleic acid (DNA) and acts as a chain terminator stopping further DNA synthesis, which results in cell death. *In vitro*, T-cells are more sensitive than B-cells to the cytotoxic effects of nelarabine.

- Primary and Secondary pharmacology

No human pharmacodynamic studies were performed.

A cross-study pharmacodynamic analysis was performed to investigate the relationships between plasma nelarabine, plasma ara-G, or intracellular ara-GTP exposure and neurotoxicity. A concentration-effect relationship was identified between intracellular ara-GTP Cmax and AUC(0-t) and neurotoxicity.

Intracellular ara-GTP concentrations were quantified in 51 patients with leukaemic blast counts of >10,000/µl. Dose-normalized intracellular ara-GTP AUC(0-t) and Cmax values were influenced by gender (2- to 3-fold higher in adult female patients than in adult male patients). Other potential factors (age, race, body surface area, baseline calculated creatinine clearance, disease category, study) did not appear to influence intracellular ara-GTP exposure. In study PGAA1001, median intracellular ara-GTP Cmax values were 139 µM in patients who responded and 46 µM in patients who did not respond. In study PGAA1003, median intracellular ara-GTP Cmax values were 292 µM in patients who responded and 100 µM in patients who did not respond. In study PGAA1005, median intracellular ara-GTP Cmax values were 835 µM in patients who responded and 40 µM in patients who did not respond (see PK interaction studies and clinical efficacy/dose response studies regarding

the design of these studies). A cross-study PD analysis was performed to look for relationships between plasma nelarabine or ara-G pharmacokinetics or intracellular ara-GTP exposure and clinical response. Intracellular ara-GTP exposure in leukaemic blasts was higher in patients who responded than in patients who did not respond. No relationship was seen between nelarabine or ara-G plasma exposure and response.

One combination study was performed to examine interactions with other medicinal products or substances, i.e., of nelarabine and fludarabine (study PGAA1005). No effect on nelarabine, ara-G, or intracellular ara-GTP pharmacokinetics was observed after fludarabine administration on Day 3.
In vitro cytotoxicity studies have demonstrated concentration-dependent increases in the growth inhibitory IC50 values for nelarabine in the presence of adenosine deaminase ADA inhibitors. The ADA inhibitors studied had no effect on the IC50 values for ara-G. Pentostatin (deoxycoformycin), an anti leukemic drug, is also a potent inhibitor of ADA (see discussion on clinical pharmacokinetics).

- Discussion on clinical pharmacodynamics

Cross-study analyses were performed combining the data from study PGAA1001, study PGAA1002, and study PGAA1003 to evaluate potential relationships between plasma exposure of nelarabine or ara-G or intracellular exposure of ara-GTP and response using logistic regression models. Intracellular ara-GTP exposure in leukemic blasts was higher in patients who responded than in patients who did not respond. No relationship was seen between nelarabine or ara-G plasma exposure and response. This result is consistent with the suggestion that the intracellular generation of ara-GTP is responsible for the cytotoxic effects seen with nelarabine.
The dose-limiting toxicity of nelarabine observed across the Phase I program was grade 3 and grade 4 neurotoxicity affecting both the central and peripheral nervous systems. Central nervous system toxicities included somnolence, seizures, dizziness, confusion, and ataxia. Peripheral nervous system toxicities included hypoesthesia, paresthesia and pain in extremities, peripheral neuropathy, and Guillain-Barré like syndrome.
The Guillain-Barré like syndrome was observed in study PGAA1001 (dosing for 5 consecutive days). The Guillain-Barré like syndrome was observed in 5 of 93 patients. It was not reversible. The polyradiculopathy behaved like a chronic demyelinating neuropathy. Each of the cases of Guillian-Barré-like syndrome was considered possibly related to the administration of nelarabine. Three cases occurred within 22 days (range: 7 to 22 days) of the initial dose of nelarabine. One of the five cases occurred at the recommended Phase II dose of 1200 mg/m^2 (adult patient). All other cases were at doses greater than 1200 mg/m^2. Besides nelarabine, factors that influence CNS function, like medication, exposure to neurotoxic chemotherapeutic agents, prior CNS radiation as well as electrolyte imbalances, may have contributed also to the neurotoxicity as observed.

Clinical efficacy

- Dose response studies

A total of 181 patients (142 adults of more than 17 years old, 39 paediatric patients of less than 17 years old) received at least one dose of nelarabine across 4 phase I studies (studies PGAA1001, PGAA1002, PGAA1003, PGAA1005). The median dose was 1360 mg/m2 (range: 104 - 2900 mg/m2). The total number of cycles administered was 361, with a median number of cycles of one (range: 1 - 16) and a mean of 2 cycles. The maximum tolerated dose (MTD) was determined based on observed dose-limiting toxicities using three different dosing schedules: daily dosing for 5 consecutive days (study PGAA1001), daily dosing for 3 consecutive days (study PGAA1002), and alternate day dosing on Days 1, 3, and 5 (study PGAA1003).

Study **PGAA1001** was a stratified, dose escalation, open-label, phase I PK study to determine the MTD of nelarabine when administered as a 1-hour intravenous infusion on a once-daily schedule for 5 consecutive days. Patients were enrolled into one of four groups: adult leukemia (stratum 1), paediatric leukemia (stratum 2), adult lymphoma (stratum 3), and paediatric lymphoma (stratum 4). Ninety-three patients, including 65 adults (i.e. ≥18 years of age at the time of first dose) and 28 paediatric patients (i.e. <18 years of age at the time of first dose) were enrolled and received at least one dose of nelarabine. Doses (5, 10, 20, 40, 60, and 75 mg/kg) were increased (increments from 25 to 100%)

until the MTD (the dose at which 2/6 or 3/6 patients experienced grade 3/4 toxicity) was reached. The schedule was amended because of grade 3 and 4 neurotoxicity in adult (40 mg/kg) and paediatric patients (≥60 mg/kg). All patients who had received doses ≥40 mg/kg had their subsequent doses lowered to 1200 mg/m^2 once daily for 5 days. Patients who had no evidence of intolerable myelosuppression or other grade 3/4 toxicity during the 21-day period after initiation of therapy, was eligible to receive a subsequent course of therapy of 1200 mg/m^2 once daily for 5 days. Clinical activity of nelarabine was observed in 35% (33/93) of patients. Complete responses occurred in 7 adult patients with T-cell ALL/LBL, T-cell chronic lymphocytic leukemia (CLL), T-cell lymphoproliferative disorder (LPD), chronic myelogenous leukemia (CML), and CML in blast crisis and 6 paediatric patients with T-cell ALL/LBL. Partial responses occurred in 18 adult patients with T-cell ALL/LBL, T-cell CLL, T-cell non-Hodgkin's lymphoma (NHL), other T-cell diseases, and B-cell ALL, B-cell CLL/B-cell prolymphocytic leukemia (PLL), and B-cell NHL. Partial responses occurred in 2 paediatric patients with T-cell ALL/LBL and T-cell NHL.

Study **PGAA1002** was a dose escalation (1200, 1500, 1800, 2200, and 2500 mg/m²), open-label, safety and PK study initially planned to evaluate the MTD of nelarabine administered as an intravenous infusion over 2 hours daily for 3 consecutive days in adult (≥18 years) and paediatric (<18 years) patients with refractory haematologic malignancies; 27 patients (17 adult; 10 paediatric patients) were enrolled and received at least one dose of nelarabine.
Based on clinical results in study PGAA1001 (grade 3/4 non-hematological toxicity), the protocol was amended to change the administration of nelarabine to 900, 1200, or 1500 mg/m^2 by intravenous infusion over a 2-hour period once daily for either 3 or 5 consecutive days in paediatric patients and for 3 consecutive days in adult patients. Dose escalations in the adult patients receiving 1200 mg/m^2 and 1500 mg/m^2 were terminated because of possibly drug-related grade 3/4 non-hematological toxicity. The 900 mg/m^2 dose was recommended for phase II studies. Clinical activity of nelarabine was observed in 14.8% (4/27) of patients. A complete response occurred in 2 patients (1200 mg/m^2 and 1500 mg/m^2) with T-cell ALL/LBL and 1 patient (900 mg/m^2) with T-cell non-Hodgkin's lymphoma (NHL). A partial response occurred in one patient (900 mg/m^2) with T-cell ALL/LBL.

Study **PGAA1003** was an open-label, dose escalation (1200, 1500, 1800, 2200, and 2500 mg/m²), safety and PK study to determine the MTD of nelarabine when administered as a 2-hour intravenous infusion on a day 1, 3, and 5 schedule, repeated every 21 to 28 days, in adult (≥18 years) and paediatric (<18 years) patients with refractory hematologic malignancies; 48 patients (46 adults; 2 paediatric patients) were enrolled and received at least one dose of nelarabine. An amendment was made to the protocol to include higher nelarabine dose levels (2900, 3300, 3800, 4400, and 5000 mg/m²) at the same dosing schedule, as MTD was not observed with the previous doses. Dose-limiting toxicities were observed at the 2900 mg/m² dose level in adult patients (2/2 patients with grade 3 ataxia). Unresolved grade 1 and 2 clinically significant peripheral neuropathy was observed in 2/11 adult patients at the 2500 mg/m² dose level. The MTD of nelarabine administered on a Day 1, 3, and 5 schedules every 21-28 days in adult patients was 2200 mg/m²/dose. The 2200 mg/m² dose was recommended for further studies. Dose escalations in paediatric patients were incomplete because of a lack of available patients. Clinical activity of nelarabine was observed in 18.7% (9/48) of patients. Nelarabine demonstrated clinical activity in adult and paediatric patients with refractory T-cell (T-cell ALL/LBL, T-cell PLL, T-cell NHL) and B-cell (B-cell CLL, B-cell NHL) hematologic malignancies.

- Main studies

Two study reports of open-label non-comparative phase II studies pertinent to the claimed indication were submitted. Study PGAA2001 was a Phase II study to evaluate nelarabine in paediatric patients (≤21 years of age at diagnosis) with refractory or relapsed T-lineage acute lymphoblastic leukaemia (ALL) or lymphoblastic lymphoma (LBL). Study PGAA2002 was a Phase II study to evaluate nelarabine in adult patients (≥16 years of age at diagnosis) refractory or relapsed T-lineage acute lymphoblastic leukaemia (ALL) or lymphoblastic lymphoma (LBL).
These two studies were sponsored by the National Cancer Institute (NCI) and conducted by the Cancer and Leukemia Group B (CALGB), and the Children's Oncology Group (COG).

Study PGAA2001 (paediatric)

Methods

Study Participants

This was a phase II, two-stage, open label, multicentre clinical trial. The main inclusion criteria were patients ≤ 21 years of age at diagnosis with refractory or recurrent T-ALL or T-NHL, a predicted life expectancy of ≥ 8 weeks, Karnofsky Performance Status (KPS) ≥ 50, no severe infection, adequate hepatic (bilirubine ≤ 1.5mg/dL; SGPT < 5xN) and renal function (creatinine normal for age or creatinine clearance or GFR ≥ 60ml/min/1.73m^2). Exclusion criteria were pregnant or lactating females and baseline ≥ grade 2 neurotoxicity.

Treatments

Nelarabine was administered at a dose of 400 mg/m^2, 650 mg/m^2, 900 mg/m^2, or 1200 mg/m^2 (depending on strata assignment and date of enrollment) as a 1hour infusion daily for 5 days (see protocol amendments in section "*conduct of the study*"). Cycles were to be repeated every 21 days or until the occurrence of one or more of the following: disease progression, unmanageable toxicity, continued treatment with nelarabine was no longer deemed beneficial, or treatment had continued for two years. Patients in Strata 02, 03 and 04 could also receive triple intrathecal therapy consisting of cytarabine, methotrexate and hydrocortisone.
All patients were to be pre-treated with allopurinol beginning a minimum of one day prior to the first cycle of treatment with nelarabine. In the presence of a high initial WBC (>50,000/µl), organomegaly, or initial hyperuricemia, hydration was to be initiated with 2400-3000 ml/m^2/day IV fluids containing sodium bicarbonate (NaHCO3), to maintain urine pH ≥ 6.5. Potassium containing solutions were to be avoided during tumor lysis. Antiemetics, antibiotics, blood and platelet transfusions or other necessary medical and supportive care was to be used as indicated. Prophylactic TMP/SMZ was to be administered in two divided doses on 3 consecutive days each week, if hepatic toxicity >grade2 was noted. Alternative pneumocystic carinii pneumonia prophylaxis was to be substituted for patients discontinuing TMP/SMZ therapy.
Follow up information was to be collected at completion of protocol therapy, every six months until four years from registration, and annually thereafter unless the patient subsequently entered another study or died. Off protocol therapy follow-up included information on survival, relapse, late effects events, and additional anti-cancer therapy.

Objectives

The primary objective was to evaluate the efficacy (response rate: CR and PR, complete and partial response) of nelarabine administered as a one-hour infusion daily for 5 days in pediatric patients with relapsed or refractory T-ALL or T-NHL. Secondary objectives were to evaluate the safety, duration of response and time to response in paediatric patients and to correlate the pharmacology of nelarabine, and ara-G nucleotides with clinical response

Outcomes/endpoints

The primary endpoint was response rate i.e., complete response (CR) defined as no evidence of remaining tumour and haematological recovery within one month after remission induction treatment, and partial response (PR). The study population includes all patients that received at least one dose of study drug.
CR was defined as bone marrow blast counts ≤5%, no evidence of disease, and full recovery of peripheral blood counts (i.e., ANC >1500/µl, platelets >100 000/µl, Hgb ≥10 g/dl for patients less than 2 years of age, Hgb ≥11 for patients ≥2 years of age).
CR* was defined as bone marrow blast counts ≤5% and no other evidence of disease but incomplete haematologic recovery. These patients may have had hypocellular bone marrow or peripheral haematology parameters not normalised.

A partial bone marrow response was defined as bone marrow blast percents less than or equal to 25% occurring at any time on the study.
CRh* was defined as bone marrow blast counts ≤5%, no other evidence of disease, and partial recovery of peripheral blood counts (i.e., ANC >500/µl, platelets >50 000/µl, Hgb ≥ 7 g/dl).
Independent review of bone marrow aspirates or biopsies took place in patients who achieved a haematological response. Marrow specimens appeared not available from all responding patients. The available specimens were scored as M1 (bone marrow with blast counts ≤5%), M2 (marrow required blast counts ≤25%) or M3 (blast counts >25%).

The secondary outcome measures included duration of response, measured from the date of response assessment to relapse, death, or last date of contact. Treatment with additional anti-cancer therapy was not a criterium for termination of response. Relapse was determined by occurrence or reoccurrence of disease in bone marrow, peripheral blood blasts, CSF or extramedullary disease. If the patient either did not have disease in one of these sites or had achieved response at one of these sites, then relapse was appearance or reappearance of disease at that site. For bone marrow this was > 5% blasts, for peripheral blood blasts or CSF this was blasts > 0%. Extramedullary relapse was signs of disease in the spleen, liver, lymph nodes, mediastinal mass, testes or other site. If the patient showed disease at one of these sites but was stable or improved, relapse was defined as progressive or increasing disease at that site.
From patients that proceeded to SCT after a nelarabine induced remission, the time in remission afterwards was included in the calculation of duration of response.

Time to Response was defined as the elapsed time from treatment start to response date.

Overall survival (OS) was defined as the elapsed time from treatment start date to death. Patients who were alive at the end of the study reporting period were censored at date of last contact.

Sample size

Stage 1 required > 4/20 evaluable patients with early marrow response, in order to enrol an additional 17 evaluable patients in stage 2 (see statistical methods), with a type 1 error rate of 0.094 and statistical power of 0.903. After a protocol amendment to update the assumptions of the null and alternative hypotheses, the sample size calculations were amended. The alternative hypothesis for the early marrow response rate was reduced from 40% to 35% and corresponding changes were made to patient accrual needed for stage 1 and stage 2. Stage 1 required >3/19 evaluable patients with early marrow response, to enrol an additional 14 evaluable patients in stage 2 with type 1 error rate of 0.096 and statistical power of 0.904.

Randomisation and blinding

Study PGAA2001 was an open label study with no randomisation process. Seventy-eight Children's Oncology Group (COG) institutions in the US, Canada, and Australia participated in this study, enrolling between 1 and 6 patients per institution.

Statistical methods

A two-stage design was used to determine if there was sufficient activity to warrant complete enrolment in a given stratum. An interim futility analysis was planned after the first 19 evaluable patients. If less than 4 of the first 19 evaluable patients experienced response, enrolment was to be terminated. If there were 3 or fewer responders from the first 19 evaluable patients enrolled in either stratum 01 or 02 (see participant flow), that data would have supported the null hypothesis. If four or more patients experienced a response rate enrolment was to continue.

The null hypothesis of a response rate of ≤ 15% was tested against the alternative hypothesis of a response rate of ≥ 35%. Following an amendment to the protocol the alternative hypothesis for the early marrow response rate was increased from 30% to 40%, the null hypothesis for the early marrow response rate was increased from 10% to 20%; the alpha level was reduced from 0.55 to 0.09.

Results

Participant flow

Patients were entered into one of the following four strata based on presentation of disease:
Stratum 01: T-ALL or T-NHL in first relapse (>25% bone marrow blasts, with or without concomitant extramedullary relapse - other than central nervous system [CNS]).
Stratum 02: T-ALL or T-NHL in second or later relapse (>25% bone marrow blasts, with or without concomitant extramedullary relapse - other than CNS).
Stratum 03: T-ALL or T-NHL with positive bone marrow and CSF (>5% bone marrow blasts and CNS 2 or 3 involvement); CNS 2: subjects with <5 WBC/mm^3 and positive cytology; CNS 3: subjects with ≥ 5 WBC/mm^3 and positive cytology.
Stratum 04: Extramedullary relapse and <25% bone marrow blasts in the bone marrow (excluding isolated CNS relapse). Strata 03 and 04 were introduced as an amendment to the protocol. Stratum 03 was opened with the goal of accruing data from patients with neurological complications. Stratum 04 was added to gain insight in treatment of extramedullary disease without bone marrow or CNS involvement.

A total of 70 paediatric patients were treated with nelarabine in strata 1 and 2. In Stratum 01, 29% (9/31) of patients were withdrawn to receive bone marrow transplants. In Stratum 02, 13% (5/39) of patients were withdrawn in order to receive SCT. The study population includes all patients that received at least one dose of study drug.

Table 6: Reason for discontinuation study participation (Study PGAA2001 - stratum 01 and 02)

Reason for Ending Study Participation	**Patients, n (%)**	
	Stratum 01 N=31	**Stratum 02 N=39**
Completed study[a]	1 (3)	1 (3)
Toxicity	1 (3)	1 (3)
Relapse	3 (10)	3 (8)
Progressive Disease/No Response	14 (45)	21 (54)
Other	2 (6)	0
Bone Marrow Transplant	9 (29)	5 (13)
Wrong diagnosis/Ineligible	0	3 (8)
Death	0	4 (10)
Unknown	1 (3)	1 (3)

a. According to the definition in the protocol, completion of treatment was defined as two cycles for Stratum 01 patients receiving up-front window therapy, otherwise up to two years of nelarabine was allowed.

Conduct of the study

Six amendments to the protocol were made during the study. The first amendment included a dose reduction from 1200mg/m^2 to 900 mg/m^2 due to grade 4 neurotoxicity. The protocol was also revised to update the assumptions of the null and alternative hypotheses and to provide more stringent criterion for testing the hypotheses. Amendment 2 included a dose of 30mg/kg for infants of less than one year of age. Amendment 3 dealt with updates on the toxicity section. The fourth amendment included a dose reduction from 900 mg/m^2/day to 650 mg/m^2/day x 5 days for all patients over 1 year of age and 20 mg/kg for infant up to one year, due to reports of Guillain-Barre-like syndrome. The protocol also amended the assumptions of the null and alternative hypotheses, and hence the sample size calculations. Amendment 5 involved a dose reduction for Strata 03 and 04 to 400 mg/m^2. This dose was planned for use in future study. Amendment 6 was introduced to collect post stem cell transplant engraftment data on patients who received nelarabine and then subsequently received a bone marrow transplant. The "completed" status of the study was withdrawn and the status was redefined as "Treatment Completed".

Baseline data

Patients were allocated to stratum based on the number of prior inductions reported by investigators. All patients in stratum 01 had received one prior induction and all patients in stratum 02 had received more than 1 prior induction (see table 7):

Table 7: Prior Anti-Cancer Therapies in study PGAA2001

	Patients, n (%)	
	Stratum 01 N=31	**Stratum 02 N=39**
Type of Prior Therapy, n (%)		
Chemotherapy	31 (100)	39 (100)
Radiation	9 (29)	25 (64)
Surgery	6 (19)	7 (18)
BMT	2 (6)	8 (21)
Prior Inductions, n (%)		
1	31 (100)	NA
2	NA	27 (69)
3	NA	7 (18)
4	NA	2 (5)
5	NA	2 (5)
Unknown	NA	1 (3)
NA = not applicable		

Prior Stem Cell Transplants (SCT)
For Stratum 01, 6% (2/31) of patients had prior SCT; one patient had allogeneic bone marrow SCT, one patient had both prior allogeneic and autologous bone marrow SCT.
For Stratum 02, 21% (8/39) patients had prior SCT; 13% (5/39) had prior allogeneic bone marrow SCT, one patient had an allogeneic transplant of unknown type, and 5% (2/39) had prior autologous bone marrow SCT.

Table 8: Baseline demographic characteristics in study PGAA2001

Demographic Characteristic	**Stratum 01 N=31**	**Stratum 02 N=39**
Age at Enrollment (yrs)		
N	31	39
Mean	11.56	11.45
Median	11.47	10.87
Range	3.2 – 21.7	2.5 – 20.0
Age Group (yrs)		
2mo – 2yrs	0	2 (5)
3 – 12yrs	18 (58)	21 (54)
13 – 16yrs	9 (29)	10 (26)
17 – 21yrs	4 (13)	6 (15)

Age at Initial Diagnosis (yrs)		
N	31	39
Mean	9.9	10.1
Median	9.8	9.5
Range	2.3 – 18.4	1.8 – 19.6
Gender, n (%)		
Female	4 (13)	14 (36)
Male	27 (87)	25 (64)
Race, n (%)		
White	19 (61)	25 (64)
Black	6 (19)	3 (8)
Hispanic	5 (16)	7 (18)
Asian	1 (3)	2 (5)
Other	0	2 (5)

Seventy patients included in the original strata 01 and 02 were treated with a dose of nelarabine of 650 mg/m2. A total of 61% (19/31) and 38% (15/39) of patients received at least 2 cycles of nelarabine, in stratum 01 and 02, respectively (see table 9).

Table 9: Number of treatment cycles in study PGAA2001

Cycle	**Patients, n (%)**	
	Stratum 01 N=31	**Stratum 02 N=39**
1	31 (100)	39 (100)
2	19 (61)	15 (38)
3	8 (26)	5 (13)
4	6 (19)	3 (8)
5	4 (13)	1 (3)
6	2 (6)	1 (3)
7	1 (3)	0

Table 10: Baseline diseases characteristics in study PGAA2001

Baseline Characteristic	**Patients, n (%)**	
	Stratum 01 N=31	**Stratum 02 N=39**
Diagnosis at Baseline		
ALL	28 (90)	31 (79)
LBL	3 (10)	8 (21)
KPS		
0-40	1 (3)	1 (3)[b]
50	1 (3)	4 (10)
60	0	3 (8)
70	2 (6)	5 (13)
80	6 (19)	7 (18)
90	12 (39)	8 (21)
100	9 (29)	8 (21)
Response to Most Recent Induction Therapy		
CR	20 (65)	17 (44)
<CR	9 (29)	22 (56)
Unknown	2 (6)	0
Site of Disease at Baseline		
Bone Marrow		
Yes	31 (100)	36 (92)
No	0	2 (5)
Unknown	0	1 (3)
CNS		
Yes	1 (3)	1 (3)
No	27 (87)	32 (82)
Unknown	3 (10)	6 (15)
Extra medullary		
Yes	10 (32)	17 (44)
No	18 (58)	15 (38)
Unknown	3 (10)	7 (18)

Outcomes and estimation

Response rate

In stratum 01, 42% of patients (13/31) achieved a CR and 48% of patients (15/31) of patients achieved a CR*. In stratum 02, 13% (5/39) of patients achieved CR and 23% (9/39) reached CR* (table 11). The 5 patients who achieved a CR are also included in the 9 patients who achieved a CR*.

Table 11: Response rate in study PGAA2001

Response	Stratum 01 N=31	Stratum 02 N=39
CR, n (%)	13 (42)	5 (13)
95% CI	[25,61]	[4,27]
CR* , n (%)	15 (48)	9 (23)
95% CI	[30, 67]	[11, 39]
CRh*, n (%)	15 (48)	8 (21)
95% CI	[30, 67]	[9, 36]

Among the 70 patients in strata 01 and 02, 31 were not in remission from the disease (<CR) after their most recent prior induction regimen. Of these 31, 26% (8/31) of patients achieved CR. 35% (11/31) of patients whose previous induction failed (<CR) reached CR*.

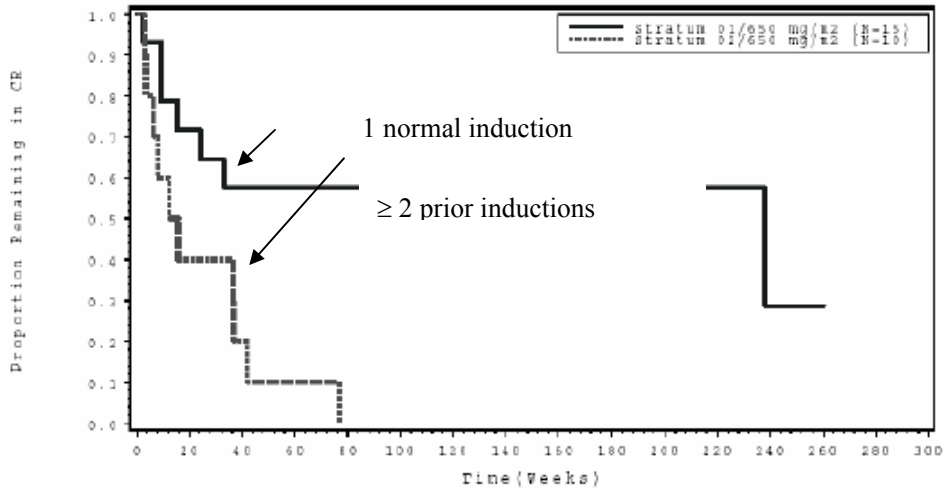
Table 12: CR and CR* rates for patients whose prior induction failed (study PGAA2001)

	Stratum 01 N=9	Stratum 02 N=22	Total N=31
CR, n (%)			
Complete response (CR)	4 (44)	4 (18)	8 (26)
95% CI	[14,79]	[5,40]	[12,45]
CR* + CR, n (%)			
CR* + CR	5 (56)	6 (27)	11 (35)
95% CI	[21,86]	[11,50]	[19,55]

Duration of Response

In stratum 01, the median duration of response was 273.3 weeks. For the 13 patients who achieved a CR, the duration ranged from 0.9 to >260 weeks; 13/15 patients reached a CR or CR* and received SCT. In stratum 02 the median duration of response was 12.3 weeks. For the 5 patients who achieved a CR, the duration ranged from 4.7 to 36.4 weeks; 4/9 patients reached at least a CR* and received SCT.

Figure 2: Duration of CR for strata 01 and 02 (study PGAA2001)



Survival

The median overall survival was 33.3 weeks (95% CI: 24.1, 93.6) in stratum 01 and 13.1 weeks (95% CI: 8.7, 17.4) in stratum 02. The one year survival rate was 33% in stratum 1 and 14% in stratum 02 (see table 13). Among the five patients alive at one year, three responded to nelarabine (one each of CR, CRh*, and mCR), and two of these three received a subsequent allogeneic bone marrow transplant. The third patient had received a transplant prior to receiving nelarabine. Two patients alive at one year had a marginal marrow PR while on nelarabine. One of these patients did go on to transplant. Among patients who achieved a CR on nelarabine, survival ranged from 16.6 to 57.4 weeks.

Table 13: Overall survival for strata 01 and 02 (study PGAA2001)

	Stratum 01 N = 31	**Stratum 02 N = 39**
Median OS (weeks) [95% CI]	33.3 wks [24.1, 93.6]	13.1 wks [8.7, 17.4]
Survival at 1 year (%) [95% CI]	33% [16%, 50%]	14% [3%, 26%]

Study PGAA2002 (Adults)

Methods

Study Participants

This was a phase II, open label, multicentre clinical trial. The main inclusion criteria were patients ≥ 16 years of age with a diagnosis of relapsed or refractory T-lineage ALL or LBL. Leukemia or lymphoma cells must have expressed at least two of the following cell surface antigens: CD1a, CD2, CD3 (surface or cytoplasmic), CD4, CD5, CD7, and CD8. Leukemia cells must also have been negative for myeloperoxidase or Sudan Black B. If the only T cell markers present were CD4 and CD7, the leukemic cells were to lack myeloid markers, CD33 and /or CD13 (results of TdT assay were to be included if performed).

Treatments

Nelarabine was administered as an undiluted IV infusion over 2 hours at a dosage of 1500 mg/m^2 on days 1, 3 and 5 of a 21 day cycle. Three subjects received a starting dose of 2200 mg/m^2/day.
The adult dose was decreased from 2200 mg/m^2 to 1500 mg/m^2 on the day 1, 3, 5 schedule due to neurological events observed in subjects on another trial (study PGAA2003). Three subjects received a total of four cycles of the higher dose. Patients were permitted to receive full supportive care including transfusions of blood products, antibiotics and anti-emetics. Hormones (including dexamethasone and other steroidal anti-emetic agents, other chemotherapeutic agents, filgrastim, sargramostim, and erythropoietin were prohibited.

Objectives

The primary objective was to determine the efficacy (response rate) of nelarabine given at a dose of 1500 mg/m^2/day on an alternate day schedule (days 1, 3, 5) in adult patients with refractory or relapsed T-ALL or LBL. Secondary objectives were to evaluate the safety of nelarabine administered on this schedule, the impact of nelarabine therapy on survival. Time to response was also evaluated.

Outcomes/endpoints

The primary endpoint was response rate (CR, CR* and PR). Response was measured using established clinical and hematologic (blood and bone marrow) response criteria.
CR for ALL was defined as: ANC >1500/µl, no circulating blasts, platelets >100,000/µl, bone marrow blast counts ≤5%, no evidence of disease. CR for LBL was defined as: disappearance of all

measurable disease, signs, symptoms, and biochemical changes related to the tumor and appearance of no new lesions.
PR for ALL was defined as: bone marrow blast percents less than or equal to 25% occurring at any time on the study. PR for LBL a reduction of ≥50% in the sum of the products of the perpendicular diameters of all measurable lesions. No new lesions could appear and no existing lesion could enlarge. Independent review of bone marrow aspirates or biopsies took place in patients at different stage of therapy.
Regarding the definitions of CR* and of the secondary endpoints (i.e. duration of response, time to response and overall survival), see section "Outcomes/endpoints" of study PGAA2001.

Sample size

A sample size of 35 patients was based on the primary endpoint of complete response rate. Criteria for response rate were described in the protocol as a null hypothesis consisting of a CR probability of ≤10% versus an alternative hypothesis consisting of a CR probability of ≥30%, with a type I and II errors of 5% and 10%. Although the planned sample size was 35 patients, a total of 39 patients were treated (α = 7%; 1-β = 93%).

Randomisation and blinding

Study PGAA2002 was an open label study with no randomisation process.

Statistical methods

Per protocol, should the data indicate that the true response is at least 30% the drug will be considered active. If the data indicate that the true response rate is no better than 10% the drug will be considered inactive. 95% CIs for response rates were calculated using the exact binomial method. Because of small sample sizes, analysis using Kaplan-Meier methods were not done. Overall survival for all treated patients and by number of prior induction was summarised using Kaplan-Meier product limit methods. Survival at one year was summarised by number of prior inductions and by response to most recent prior therapy.

Results

Participant flow

Forty adults were enrolled in study PGAA2002 and all but one received at least one dose of the study drug. Thus 39 patients were included in this analysis population. Reasons for discontinuation were progressive disease or relapse (n=14, 36%) and no response to therapy (n=14, 36%). Three patients (8%) withdrew due to adverse events. Two (5%) patients completed the 6 cycles of nelarabine treatment.

Conduct of the study

The protocol was amended once, to reduce the dose from 2200 mg/m^2/day to 1500 mg/m^2/day, to reduce the risk of neurotoxicity. In addition, patients with pre-existing grade 2 or greater neuropathy were deemed ineligible for enrolment.

Baseline data

Patients were assigned to two strata, based on the number of prior inductions (1 prior induction vs. ≥2 prior inductions). Twenty-eight patients (72%) had undergone ≥2 prior attempts at induction and 11 (28%) had received 1 prior induction (see table 14). Most patients were male (82%) and most were white (69%). Median and mean age at the time of the study entry were 34 and 35 years, respectively. The age range was 16 to 66 years for all treated patients and 16 to 65 years for patients with ≥2 prior inductions. Thirty-three patients (85%) were >21 years of age at the time of enrolment.

Table 14: Patients baseline characteristics by number of prior inductions (Study PGAA2002)

Baseline Characteristic	Patients, n (%)		
	1 Prior Induction N=11	≥2 Prior Inductions N=28	Total N=39
Diagnosis			
ALL	9 (82)	17 (61)	26 (67)
LBL	2 (18)	11 (39)	13 (33)
Response in most recent induction therapy			
CR	9 (82)	11 (39)	20 (51)
<CR	2 (18)	17 (61)	19 (49)
Extramedullary Disease at Baseline			
Yes	6 (55)	20 (71)	26 (67)
No	5 (45)	7 (25)	12 (31)
Unknown	0	1 (4)	1 (3)
History of CNS Leukemia			
No	11 (100)	24 (86)	35 (90)
One Occurrence	0	3 (11)	3 (8)
>One Occurrence	0	1 (4)	1 (3)
Diagnosis			
T-ALL	9 (82)	17 (61)	26 (67)
T-LBL	2 (18%)	11 (39)	13 (33)
Performance Status			
0 (Fully Active)	4 (36)	7 (25)	11 (28)
1 (Ambulatory)	4 (36)	13 (46)	17 (44)
2 (In bed <50% of time)	2 (18)	4 (14)	6 (15)
3 (In bed >50% of time)	1 (9)	4 (14)	5 (13)

All patients enrolled had received extensive prior treatment with anti-cancer therapy and prior multi-agent chemotherapy (see table 15).

Table 15: Prior therapies by number of prior inductions (Study PGAA2002)

Therapy	Patients, n (%)		
	1 Prior Induction N=11	≥ 2 Prior Inductions N=28	Total N=39
All Therapies	**10 (91)**	**27 (96)**	**37 (95)[a]**
Chemotherapy	10 (91)	27 (96)	37 (95)
Limited Radiation (<50% portion of body)	1 (9)	8 (29)	9 (23)
Extensive Radiation (≥50% portion of body)	1 (9)	4 (14)	5 (13)
Bone Marrow Transplant	1 (9)	4 (14)	5 (13)
Surgery	1 (9)	2 (7)	3 (8)
Immunotherapy	0	2 (7)	2 (5)

[a] Although all patients received prior chemotherapy, the Prior Therapy Form was not submitted for 2 patients and their results are not included in the table.

Outcomes and estimation

Response rate

A total of 5/28 (18%) patients with ≥2 prior inductions achieved a CR (confirmed one month later). One additional patient had no evidence of disease and achieved full hematologic recovery. However, this response was of short duration and, therefore, did not meet the definition of CR. This patient's best response was a CR*. Thus, 6 (21%) patients with ≥2 prior inductions achieved at least a CR*.
A total of 2/11 (18%) patients with 1 prior induction achieved a CR (confirmed one month later). One additional patient withdrew without demonstrating platelet and absolute neutrophil count (ANC) recovery in order to receive a cord blood transplant. Thus, the CR* rate was 27% for patients with 1 prior induction (see table 16).

Table 16: CR and CR* by number of prior Inductions (Study PGAA2002)

Response	1 Prior Induction N=11	≥2 Prior Inductions N=28	Total patients N=39
CR, n (%)	2 (18)	5 (18)	7 (18)
95% CI	[2,52]	[6,37]	[8,34]
CR*, n (%)	3 (27)	6 (21)	9 (23)
95% CI	[6,61]	[8,41]	[11,39]

CR = Complete response; CR* = Complete response with or without hematologic recovery.

Eleven of 26 patients (42%) with ALL and 5/13 patients (38%) with LBL experienced responses (CR + PR). Of the 28 patients with ≥2 prior inductions, 17 failed to respond (<CR) to their most recent induction regimen. Of those, 3 (18%) patients experienced a complete response with nelarabine (confirmed 1 month later). Of the 2/11 patients who failed to respond to their single prior induction, none did respond to nelarabine.

Duration of response

The duration of CR of six patients with ≥ 2 prior remission inductions ranged from 15.1 to > 195.4 weeks. One additional patient achieved CR* lasting for 4 weeks. Two patients were still in remission at the date of last contact. One of these patients proceeded to a pre-SCT conditioning regimen while still in a nelarabine-induced CR and remained in a CR for at least 156.3 weeks. Another patient remained in a prolonged CR (195.4+ weeks) without subsequent anti-cancer therapy following treatment with 3 cycles of nelarabine. Prior to enrolment, this patient had relapsed after two multi-agent induction regimens, surgical resection and autologous stem cell transplantation.
Three patients who had 1 prior induction achieved a CR but did not receive a transplant. Their durations of response lasted 212, 29.4, and 18.9 weeks.

Table 17: Duration of CR and CR* for individual patients (Study PGAA2002)

Number of Inductions	Duration of CR (weeks) of individual patients	Duration of CR* (weeks) of individual patients
1 Prior Induction	212.0	215.0
	51.0	53.4
	n/a	4.7
≥2 Prior Inductions	18.9	18.9
	15.1	15.1
	29.4	30.1
	156.3+	156.3+
	195.4+	195.4+
	n/a	4.0

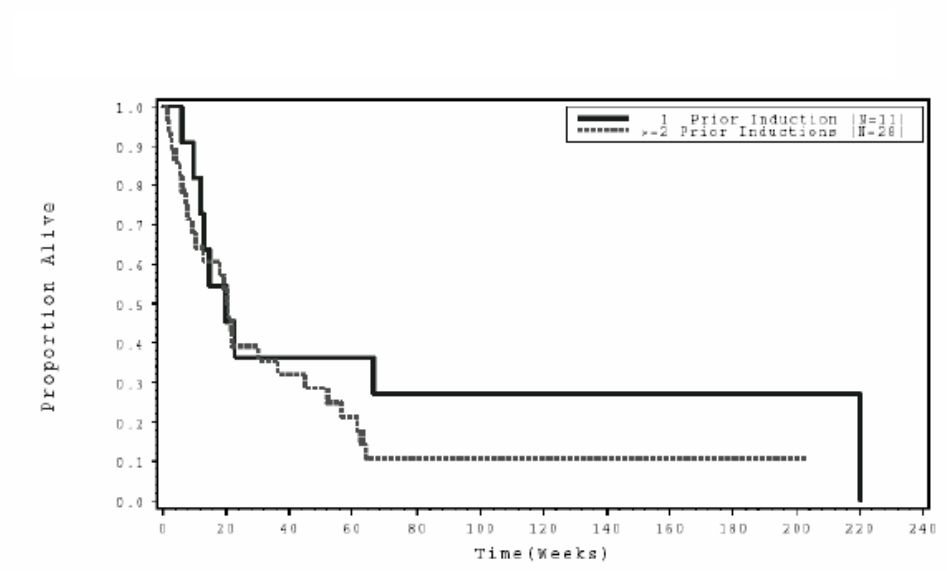
Survival

Eighteen percent of patients who received 1 prior induction, and 11% of patients who received ≥2 prior inductions were censored. The survival curves for the two prior induction groups are shown in Figure 3. The one year survival rate for all treated patients was 31% with a 95% CI of 16% to 45%. Of the 28 subjects with ≥2 prior inductions, 8 (29%) were alive at one year (see table 18).

Table 18: Survival at one year by number of prior inductions (Study PGAA2002)

Survival	1 Prior Induction N = 11	≥ 2 Prior Inductions N = 28	Total N = 39
Median OS (weeks) [95% CI]	20.1 weeks [12.0, 220]	20.6 weeks [10.4, 36.4]	20.4 weeks [12.9, 36.4]
Survival at 1 year [95% CI]	36% [8%, 65%]	29% [12%, 45%]	31% [16%, 45%]

Figure 3: Overall survival by number of prior inductions (Study PGAA2002)



Post nelarabine transplants and engraftment

Upon request from FDA, engraftment data were retrospectively collected from participating institutions that performed transplants on patients enrolled in study PGAA2002. Seven patients went on to transplant. Engraftment data for 6/7 patients were collected and entered into the database. Two patients who did not respond to nelarabine subsequently received BMTs.
Myeloid engraftment occurred in 3/7 transplanted patients on days 10, 11 and 18 post-transplant. One patient died shortly after transplant before engrafting. Engraftment data for one patient were unknown. Myeloid engraftment was not reported in the remaining two transplanted patients. Both were alive < 3 years after transplant, indicating engraftment had occurred at some unknown time.

- Supportive study

Treatment Referral Center Protocol (TRC 9701), was a phase II, open-label multi-centre study to investigate the safety and efficacy of nelarabine in patients with relapsed or refractory T-cell ALL or T-cell LBL. The study was conducted by NCI, CTEP. It was ongoing at the time of the marketing authorisation application. On 28 January 2005, 26 patients with relapsed or refractory T-ALL/T-LBL had been treated, 24 of whom were evaluable for response: 3/24 CRs had been reported (CR rate of 12.5%).

An expert report on the results of an interim analysis of an ongoing collaborative research trial with nelarabine (GMALL study 06/99 and study 07/03) was provided during the assessment. A total of 68 patients received nelarabine 650mg/m^2 on days 1-5 (adolescents 15-17 years) or nelarabine 1500mg/m^2 on days 1, 3 and 5 (adults). Patients suffered from T-ALL or T-LBL which was primary refractory, refractory to at least two induction regimens, or had relapsed following stem cell transplantation. Complete responses were achieved in 30 patients (44%), with an unconfirmed complete response in an additional patient; 77% (24/31) of these patients were transferred to stem cell transplantation with 29% survival at 3 years.

- Analysis performed across trials and studies in special populations

No Analysis across trials or studies in special populations was provided in this application.

- Discussion on clinical efficacy

In paediatric patients, since the maximal tolerated dose (MTD) could not be determined (lack of available patients) for the daily dosing for 3 consecutive days schedule and the alternate-day schedule (phase I studies PGAA1002, PGAA1003), the 5 consecutive day schedule was selected and further investigated in the paediatric phase II pivotal study. During this study, the initial dose of 1200 mg/m^2 was later reduced to 650 mg/m^2 due to grade 4 neurotoxicity. In adult patients, the day 1, 3, 5 schedule was preferred, based on the benefit-risk ratio observed in phase I studies.
Both dosing schedules were studied in patients 16 to 21 years of age, as patients in this age range could enrol in either the adult (study PGAA2002) or paediatric (study PGAA2001) pivotal phase II studies. In study PGAA2002, 6/39 patients who were treated with 1500 mg/m^2 on the day 1, 3, 5 schedule were 16 to 21 years of age (range: 16-66 years; mean: 35 years). In study PGAA2001, 10/84 patients who received a dose of 650 mg/m2 given daily x5 were 16 to 21 years of age (range: 2.5 to 21.7 years; mean: 11.9 years). Dose recommendations are reflected in section 4.2 of the SPC.

The application was based on two phase II open-label studies to evaluate the safety and efficacy of nelarabine in patients with relapsed or refractory T-ALL/T-LBL.
Study PGAA2002 was performed in patients ≥ 16 years of age with refractory or recurrent T-ALL (67% of patients) or T-LBL (33% of patients), and received 1500 mg/m^2 of nelarabine as an IV infusion over 2 hours, on days 1, 3 and 5 of a 21 day cycle. The primary endpoint was response rate i.e., complete response (CR defined as no evidence of remaining tumour, and haematological recovery within one month after remission induction treatment), and partial response (PR). Of the 39 patients who received nelarabine, 19 patients (49%) were refractory to their most recent prior induction therapy, 31% had isolated bone marrow disease at baseline, 11% had a history of CNS leukaemia.
Among the 28 patients with ≥2 prior inductions, 5 (18%) achieved a CR and 6 (21%) achieved at least a CR*. Among the 11 patients with 1 prior induction, 2 (18%) achieved a CR and 3 (27%) achieved a CR*. Response (CR + PR) was observed in 11/26 (42%) patients with ALL and 5/13 (38%) patients with LBL. The duration of CR and CR* ranged from 15.1 to 212.0 weeks, and from 4 to 215 weeks, respectively. The median survival was 20.1 weeks (95% CI: 12.0 to 220 weeks) for patients with one prior induction, 20.6 weeks (95% CI: 10.4 to 36.4 weeks) for patients with ≥2 prior inductions, 20.4 weeks (95% CI: 12.9 to 36.4 weeks) for all treated patients.
CR rate was considered as a relevant endpoint for approval. The CHMP considers that only CR, or at least a very substantial reduction in leukaemic blasts, is of therapeutic interest for new antileukaemic agent used in second- or third line therapy, and that achievement of CR should be followed by additional chemotherapy and/or SCT when feasible. However, only one patient received a stem cell transplantation and had a CR of 156+ weeks at the latest follow-up. One patient received a SCT during early relapse after nelarabine and later died of graft-versus-host disease. Without observing the outcome of transplantation, the question of unpredicted post-transplantation toxicities caused by prior exposure to nelarabine was raised. The results of an interim analysis of an ongoing collaborative research trial conducted in 68 patients (expert report provided) showed that 24 patients with CR went on to stem cell transplantation and 29% of these patients were alive after 3 years. These data support that stem cell transplantation is feasible after nelarabine treatment and there are no indications that the substance adversely affects the outcome of the transplantation.

The duration of CR observed in study PGAA2002 was considered clinically relevant as it would give patients a good chance to find an unrelated donor for stem cell transplantation.
Patients with active CNS disease (evidence of CNS leukaemia and/or lymphoma that would require intrathecal or craniospinal radiation therapy) and patients with pre-existing neuropathy of grade 2 or greater at the time of registration regardless of case were not eligible for study PGA2002. A warning was included in section 4.4 of the SPC for patients treated previously or concurrently with intrathecal chemotherapy or previously with craniospinal irradiation, as these patients are potentially at increased risk for neurological adverse events (see also safety assessment). In addition, dose modification recommendations are included in section 4.2 of the SPC in case of neurological events.
Study PGAA2001 was conducted in patients ≤21 years of age with refractory or recurrent T-ALL or T-LBL, and a predicted life expectancy of ≥ 8weeks. The starting dose of 1200 mg/m^2 was reduced to 900 mg/m^2 due to grade 4 neurotoxicity, and then to 650 mg/m due to reports of Guillain-Barre-like syndrome. The primary endpoint was response rate i.e., complete response (CR) defined as no evidence of remaining, and partial response (PR). Partial response was observed in 24/70 (34%) paediatric patients, and 18 (26%) reached CR. Within the population that responded, the number of prior remission induction therapies did not show an impact on the efficacy of nelarabine. In the group of patients with ≥2 prior inductions, 4/9 patients who reached CR* received SCT.
The supportive data provided (expert report from an external investigator), although only applicable for an adult patient population (19-81 years), indicated the option for successful treatment with stem cell transplantation following treatment with nelarabine.

Clinical safety

- Patient exposure

Safety data for nelarabine have been derived from four phase I studies (181 patients) and three pivotal phase II studies (227 patients). Altogether 459 patients, including 329 men and 130 women, from 0.6 to 83 years, with ALL (41%), CLL (26%), and LBL (15%), were included in the safety analysis. Supportive data from 522 patients from NCI studies, which were ongoing or just completed at the time of the assessment, were also were also included in this analysis (see summary table 19).
Separate analyses were provided from the phase II pivotal studies PGAA2001 (84 paediatric patients receiving 650 mg/m^2 on days 1-5 of a 21-day cycle) and PGAA2002, and pivotal safety phase II study PGAA2003 study (103 adult patients with refractory Chronic Lymphocytic Leukaemia receiving 1500 mg/m^2 on days 1, 3, and 5 of a 21-day cycle). Study PGAA2002 included 39 adult patients. In the safety analysis 3 patients were withdrawn. These patients received the 2200 mg/m2 dose regimen, which was later reduced to the recommended 1500 mg/m2 dose regimen due to neurotoxicity reported in study PGAA2003. Similarly, study PGAA2003 included 87 adult patients, of whom 67 received the recommended 1500 mg/m2 dose regimen and were included in the safety analysis. In study PGAA2003, the starting dose was reduced by protocol amendment from 2200 to 1500 mg/m2 after 2 of the first 20 patients had SAEs of ascending sensory neuropathies, one grade 3 demyelisation and one grade 3 paresthesia. Administration of doses was delayed because of haematological toxicity, infection, inter-current illness, and at the discretion of the investigator.
In the adult phase II studies, the mean number of days on therapy was 76.5. Most patients (72%) received treatment with nelarabine for at least 2 cycles; 6% of patients in study PGA2002 and PGAA2003 received a total of 6 cycles.

In the paediatric study, the mean number of days on therapy for the 650 mg/m^2 dose group was 60 days in stratum 01 and 46 days in stratum 02. The maximum number of days on therapy was 301 in the 900 mg/m^2 dose group in stratum 02.

Table 19: Summary of exposure by protocol (COG P9673=PGAA2001; CALGB 19801=PGAA2

	PGAA1001[a] (N=94)	PGAA1002 (N=27)	PGAA1003 (N=48)	PGAA1005 (N=13)	COG P9673 (N=151)	CALGB 19801 (N=39)	PGAA2003 (N=87)	Total (N=459)
Cumulative dose (mg/m^2)								
n	94	27	48	13	150	39	87	458
Mean	10919.9	5434.5	11887.9	7069.5	5979.2	9251.3	13319.3	9284.2
Standard deviation	10557.44	3760.24	7516.81	4381.72	5826.18	5304.98	8502.70	8110.26
Median	7599.8	3766.5	9914.1	6083.7	3521.9	8993.6	9125.7	6820.9
Minimum	517.2	2596.4	3578.7	3300.0	370.0	4290.7	4440.0	370.0
Maximum	63322.3	19225.1	35254.2	17823.5	40223.9	26914.3	44283.8	63322.3
Days on Therapy								
n	94	27	48	13	151	39	87	458
Mean	54.8	34.0	54.3	67.3	55.2	67.8	85.9	61.0
Standard deviation	70.07	35.40	42.87	63.07	47.23	70.81	52.95	56.78
Median	33.0	26.0	39.0	61.0	33.0	56.0	67.0	44.0
Minimum	4.0	7.0	7.0	5.0	4.0	10.0	5.0	4.0
Maximum	414.0	182.0	238.0	242.0	372.0	451.0	243.0	451.0

a. One (1) subject in study PGAA1001 was enrolled twice (subject numbers 101437 and 103584).

- Adverse events

In the pivotal studies conducted in adults patients (PGAA2002 and PGAA2003) receiving nelarabine 1500 mg/m^2, most patients (90%) had at least 1 possibly drug-related adverse event (ADR) (see table 20). The most common drug-related AEs were fatigue (39%), nausea (31%) and hematological disorders; i.e., decreased hemoglobin (25%), decreased platelet count (21%), and decreased neutrophil count (20%), and somnolence (20%). Notable differences between study PGAA2002 and study PGAA2003 included hematological disorders, such as decreased hemoglobin (72% vs. 0%), decreased neutrophil count (58% vs. 0%), and decreased platelet count (61% vs. 0%) and nervous disorders, such as somnolence (0% vs. 31%), peripheral sensory neuropathy (33% vs. 0%), asthenia (0% vs. 25%), hypo-aesthesia (0% vs. 24%), paresthesia (0% vs. 16%), and somnolence (0% vs. 31%). Those differences between studies in the incidences of these events could be explained by the differences in reporting procedures.

Table 20: Summary of most frequent ADRs (at least 10% total) by maximum grade (adult patients enrolled in PGAA2002 and PGAA2003 and treated with nelarabine 1500 mg/m^2)

System Organ Class	Number (%) of patients					
	Maximum Grade					Total
Preferred Term	Unknown	1	2	3	4+[a]	
Any Event	**2 (2)**	**71 (69)**	**66 (64)**	**41 (40)**	**19 (18)**	**93 (90)**
Gastrointestinal Disorders	**1 (1)**	**32 (31)**	**23 (22)**	**3 (3)**	**0**	**50 (49)**
Diarrhoea	0	9 (9)	3 (3)	0	0	12 (12)
Nausea	0	18 (17)	14 (14)	0	0	32 (31)
Vomiting	1 (1)	7 (7)	6 (6)	1 (1)	0	15 (15)
General Disorders and Administration Site Conditions	**0**	**32 (31)**	**32 (31)**	**10 (10)**	**2 (2)**	**61 (59)**
Asthenia	0	6 (6)	10 (10)	0	1 (1)	17 (17)
Fatigue	0	18 (17)	13 (13)	8 (8)	1 (1)	40 (39)
Pyrexia	0	3 (3)	9 (9)	2 (2)	0	14 (14)
Laboratory Investigations	**0**	**12 (12)**	**18 (17)**	**15 (15)**	**15 (15)**	**33 (32)**
Haemoglobin decreased	0	7 (7)	12 (12)	5 (5)	2 (2)	26 (25)
Neutrophil count decreased	0	1 (1)	5 (5)	5 (5)	10 (10)	21 (20)
Platelet count decreased	0	3 (3)	7 (7)	6 (6)	6 (6)	22 (21)
Musculoskeletal and Connective Tissue Disorders	**1 (1)**	**17 (17)**	**5 (5)**	**5 (5)**	**0**	**27 (26)**
Myalgia	0	6 (6)	3 (3)	1 (1)	0	10 (10)
Nervous System Disorders	**1 (1)**	**47 (46)**	**29 (28)**	**7 (7)**	**2 (2)**	**64 (62)**
Dizziness	0	12 (12)	6 (6)	0	0	18 (17)
Hypo-aesthesia	1 (1)	3 (3)	10 (10)	2 (2)	0	16 (16)
Paresthesia	0	7 (7)	4 (4)	0	0	11 (11)
Peripheral sensory neuropathy	0	6 (6)	6 (6)	0	0	12 (12)
Somnolence	0	19 (18)	2 (2)	0	0	21 (20)

a - Grade 5 events were reported in the Grade 4+ column and are included in the count.

In the paediatric studies, the majority of ADRs were hematological abnormalities (see table 21). Of the non-hematological AEs, the two most frequent ADRs reported at the 650 mg/m^2 dose were increased transaminase (12%), decreased blood potassium (11%), vomiting (10%), and decreased blood albumin (10%).

Table 21: Summary of most frequent ADRs (at least 4 patients total) by maximum grade (Study PGAA2001, 650 mg/m^2 dose group

Number (%) of patients					
System Organ Class	**Dose Group 650 mg/m2; N=84**				
Preferred Term	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4+[a]**	**Total**
Any Adverse Event	**22 (26)**	**33 (39)**	**51 (61)**	**37 (44)**	**65 (77)**
Laboratory Investigations	**13 (15)**	**18 (21)**	**40 (48)**	**34 (40)**	**52 (62)**
Haemoglobin decreased	5 (6)	4 (5)	19 (23)	4 (5)	32 (38)
WBC decreased	1 (1)	5 (6)	12 (14)	14 (17)	32 (38)
Neutrophil count decreased	1 (1)	0	8 (10)	22 (26)	31 (37)
Platelet count decreased	4 (5)	1 (1)	4 (5)	16 (19)	25 (30)
Transaminases increased	5 (6)	2 (2)	3 (4)	0	10 (12)
Blood potassium decreased	2 (2)	2 (2)	3 (4)	2 (2)	9 (11)
Blood albumin decreased	1 (1)	2 (2)	4 (5)	1 (1)	8 (10)
Blood bilirubin increased	0	0	6 (7)	1 (1)	7 (8)
Blood calcium decreased	3 (4)	2 (2)	1 (1)	1 (1)	7 (8)
Blood creatinine increased	3 (4)	2 (2)	0	0	5 (6)
Blood glucose decreased	1 (1)	1 (1)	3 (4)	0	5 (6)
Blood magnesium decreased	2 (2)	1 (1)	2 (2)	0	5 (6)
Nervous System Disorders	**8 (10)**	**10 (12)**	**9 (11)**	**3 (4)**	**23 (27)**
Peripheral sensory neuropathy	0	0	5 (6)	0	5 (6)
Headache	2 (2)	1 (1)	1 (1)	0	4 (5)
Somnolence	1 (1)	2 (2)	1 (1)	0	4 (5)
Hypoesthesia	1 (1)	1 (1)	2 (2)	0	4 (5)
Neuropathy peripheral	0	3 (4)	1 (1)	0	4 (5)
Gastrointestinal Disorders	**4 (5)**	**7 (8)**	**0**	**1 (1)**	**12 (14)**
Vomiting	3 (4)	5 (6)	0	0	8 (10)

Infections & Infestations	**2 (2)**	**2 (2)**	**6 (7)**	**4 (5)**	**13 (15)**
Infection	1 (1)	0	2 (2)	1 (1)	4 (5)

a - Grade 5 events were reported in the Grade 4+ column and are included in the count Three (3) patients had a fatal event. Fatal events included neutropenia and pyrexia (n = 1), status epilepticus/seizure (n = 1), and fungal pneumonia (n = 1). The status epilepticus was thought to be related to treatment with nelarabine. All other fatal events were unrelated to treatment wit nelarabine.

Nervous system ADRs

The most common nervous system ADRs in the adult phase II studies for patients who received the 1500 mg/m^2 dose were somnolence (20%), dizziness (17%), hypo-aesthesia (16%), peripheral sensory neuropathy (12%), paresthesia (11%), and ataxia (8%). With the exception of peripheral motor neuropathy (0 in women, 8% in men), peripheral sensory neuropathy (4% in women, 15% in men) and headache (14% in women, 4% in men), the incidence of nervous system ADRs did not appear to vary according to gender. Most nervous system ADRs were evaluated as grade 1 or 2. Grade 3 events (ataxia (N=2), convulsion (N=1), hemiparesis (N=1), hypoesthesia (N=2), loss of consciousness (N=1), peripheral neuropathy (N=1) were reported for 7% in patients and grade 4 events (cerebral haemorrhage (N=1), coma (N=1), depressed level of consciousness (N=1), intracranial haemorrhage (N=1), leukencephalopathy (N=1) were reported for 2% in patients.
In the pivotal paediatric study PGAA2001, at least one nervous system AER was reported in 48 patients (32%); 80% of nervous system disorders were resolved and 19% did not resolved. Because of the rather short survival time, the long-term consequences could not be given. The most frequent nervous system ADR in the 650 mg/m^2 dose group were peripheral sensory neuropathy (6%), headache (5%), somnolence (5%), hypoesthesia (5%), and peripheral neuropathy (5%).

Table 22: Summary of nervous system ADRs by dose (study PGAA2001)

	Number (%) of patients			
Nervous System Disorders Preferred Term	**400 mg/m^2 N=49**	**650 mg/m^2 N=84**	**900 mg/m^2 N=18**	**Total N=151**
Any AEs	**20 (41)**	**23 (27)**	**5 (28)**	**48 (32)**
Headache	8 (16)	4 (5)	1 (6)	13 (9)
Somnolence	4 (8)	4 (5)	1 (6)	9 (6)
Hypoesthesia	2 (4)	4 (5)	1 (6)	7 (5)
Neuropathy peripheral	2 (4)	4 (5)	1 (6)	7 (5)
Paresthesia	3 (6)	3 (4)	1 (6)	7 (5)
Peripheral sensory neuropathy	1 (2)	5 (6)	1 (6)	7 (5)
Motor dysfunction	2 (4)	3 (4)	1 (6)	6 (4)
Tremor	2 (4)	2 (2)	2 (11)	6 (4)
Peripheral motor neuropathy	1 (2)	3 (4)	0	4 (3)
Ataxia	2 (4)	2 (2)	0	4 (3)
Convulsion	1 (2)	2 (2)	0	3 (2)
Nervous system disorder	0	3 (4)	0	3 (2)
Lethargy	1 (2)	1 (1)	1 (6)	3 (2)
Encephalopathy	0	1 (1)	1 (6)	2 (1)
Cerebellar syndrome	1 (2)	0	0	1 (1)
Facial palsy	1 (2)	0	0	1 (1)
Hyporeflexia	0	1 (1)	0	1 (1)
Lethargy	1 (2)	1 (1)	1 (6)	3 (2)
Myoclonus	0	0	1 (6)	1 (1)
Neurotoxicity	0	0	1 (6)	1 (1)
Sensory loss	0	1 (1)	0	1 (1)
Status epilepticus	0	1 (1)	0	1 (1)

Additional exploratory neurotoxicity analysis

Exploratory analyses were undertaken using the integrated database for the four phases I and three phase II trials to identify predisposing factors associated with neurological events. The results show that neurological AEs were reported for 267 of the 459 subjects evaluated. Most were grade 2 or lower. The most prevalent grade ≥3 neurological events were ataxia (3%) and somnolence (3%), followed by peripheral neuropathy (2%), hypoesthesia (2%), confusional state (2%), convulsion (2%), and abnormal gait (2%).

Possible risk factors were found to be related to the occurrence of neurological events. These included increase in prescribed cycle dose in mg/m2 and any event (any grade and grade ≥3), mental status change (MSC, any grade), and peripheral nervous system (PNS, any grade); increase in age and any event (any grade), MSC (any grade), CNS (any grade), and PNS (any grade); and CNS disease at baseline and any event (grade ≥3), CNS (grade ≥3), and PNS (grade ≥3).

- Serious adverse event/deaths/other significant events

In the adult pivotal phase II studies for patients who received 1500 mg/m2 of nelarabine, serious ADRs that occurred in more than one patient included pyrexia (5%), febrile neutropenia (3%), dehydration (3%), pneumonia (2%), pancytopenia (2%), and ataxia (2%).
In the pivotal paediatric study, serious ADRs were reported in 16% (24/151) of patients across doses. Peripheral sensory neuropathy (n=5, 6%), hypoesthesia (n=3, 4%), convulsion (n=2, 2%), and peripheral motor neuropathy (n=2, 2%). were the most frequently reported serious ADRs in the 650 mg/m2 dose group.

Table 23: Summary of serious ADRs by assigned dose (paediatric patients)

	Number (%) of Subjects			
System Organ Class Preferred Term	**400 mg/m^2** **N=49**	**650 mg/m^2** **N=84**	**900 mg/m^2** **N=18**	**Total** **N=151**
Any AE	**6 (12)**	**13 (15)**	**5 (28)**	**24 (16)**
Gastrointestinal disorders	**0**	**0**	**2 (11)**	**2 (1)**
Pancreatitis	0	0	2 (11)	2 (1)
General disorders & administration site conditions	**1 (2)**	**1 (1)**	**0**	**2 (1)**
Asthenia	0	1 (1)	0	1 (1)
Performance status decreased	1 (2)	0	0	1 (1)
Hepatobiliary disorders	**0**	**1 (1)**	**0**	**1 (1)**
Portal hypertension	0	1 (1)	0	1 (1)
Laboratory Investigations	**0**	**1 (1)**	**2 (11)**	**3 (2)**
Blood amylase increased	0	0	2 (11)	2 (1)
Blood bilirubin increased	0	1 (1)	0	1 (1)
Lipase increased	0	0	2 (11)	2 (1)
Metabolism & nutrition disorders	**0**	**0**	**1 (6)**	**1 (1)**
Lactic acidosis	0	0	1 (6)	1 (1)
Musculoskeletal & connective tissue disorders	**1 (2)**	**0**	**0**	**1 (1)**
Myalgia	1 (2)	0	0	1 (1)
Nervous system disorders	**6 (12)**	**12 (14)**	**3 (17)**	**21 (14)**
Ataxia	2 (4)	1 (1)	0	3 (2)
Convulsion	1 (2)	2 (2)	0	3 (2)
Encephalopathy	0	1 (1)	1 (6)	2 (1)
Facial palsy	1 (2)	0	0	1 (1)
Headache	2 (4)	1 (1)	0	3 (2)
Hypoesthesia	0	3 (4)	0	3 (2)
Lethargy	1 (2)	0	0	1 (1)
Myoclonus	0	0	1 (6)	1 (1)
Neuropathy peripheral	0	0	1 (6)[a]	1 (1)
Neurotoxicity	0	0	1 (6)	1 (1)
Paresthesia	0	1 (1)	0	1 (1)
Peripheral motor neuropathy	1 (2)	2 (2)	0	3 (2)
Peripheral sensory neuropathy	1 (2)	5 (6)	1 (6)	7 (5)
Somnolence	3 (6)	0	0	3 (2)
Status epilepticus	0	1 (1)[a]	0	1 (1)
Tremor	0	0	1 (6)	1 (1)
Psychiatric disorders	**2 (4)**	**0**	**1 (6)**	**3 (2)**
Agitation	0	0	1 (6)	1 (1)
Delirium	0	0	1 (6)	1 (1)
Hallucination	2 (4)	0	1 (6)	3 (2)
Respiratory, thoracic & mediastinal disorders	**1 (2)**	**0**	**1 (6)**	**2 (1)**
Acute respiratory distress syndrome	0	0	1 (6)	1 (1)
Capillary leak syndrome	1 (2)	0	1 (6)	2 (1)
Lung infiltration	1 (2)	0	0	1 (1)
Vascular disorders	**0**	**0**	**1 (6)[a]**	**1 (1)**
Hypotension	0	0	1 (6)[a]	1 (1)

a. These events resulted in death

Serious nervous system events were reported for 8% of the adult patients who received the 1500 mg/m^2 dose in the pivotal Phase 2 studies. None of the serious nervous system events occurred in more than 2 patients. In the pivotal study in paediatric patients, at the 650 mg/m^2 dose, the most common serious nervous system events were peripheral sensory neuropathy (6%), convulsion (4%), and hypoesthesia (4%).

Deaths

Ten adult patients (10%) who received the 1500 mg/m2 dose died within 30 days of administration of the last dose in the pivotal phase II studies. Relapse or progression of CLL was the only cause of death in more than 1 patient. All deaths due to relapse or progression of CLL (n=3) occurred in the PGAA2003 study. In study PGAA2002, deaths that were not related to the disease or treatment were to be recorded as "other" and then specified by the investigator, whereas in study PGAA2003, choices of cause of death on the death record were relapse/progression and "other."

Deaths of children in the pivotal study were reported for 28% of patients at the 900 mg/m^2 dose, 10% of patients ects at the 650 mg/m^2 dose, and 16% of patients at the 400 mg/m^2 dose either during treatment or within 30 days of administration of the last dose of nelarabine. The cause of death across doses is summarized in the table 24.

Table 24: Summary of cause of death from first dose to 30 days after last dose by assigned dose (paediatric patients)

	Number (%) of patients			
	400 mg/m^2 N=49	**650 mg/m^2 N=84**	**900 mg/m^2 N=18**	**Total N=151**
Status				
Alive	41 (84)	76 (90)	13 (72)	130 (86)
Died	8 (16)	8 (10)	5 (28)	21 (14)
Cause of Death				
Protocol Treatment Related	0	0	0	0
Tumour	6 (12)	6 (7)	2 (11)	14 (9)
Tumour and drug	0	0	1 (6)	1 (1)
Tumour and infection	1 (2)	0	1 (6)	2 (1)
Infection	0	0	1 (6)	1 (1)
Haemorrhage	1 (2)	0	0	1 (1)
Other	0	1 (1)	0	1 (1)
Unknown	0	1 (1)	0	1 (1)

- Laboratory findings

Grade 3 and 4 clinical chemistry values were observed in 8% to 15% of adult patients. The most common clinical chemistry abnormalities reported were hypokalemia, hyperglycemia, hypocalcemia, hyponatremia, and elevated aspartate transaminase (AST). A similar pattern was observed for paediatric patients, with the exception of hypokalemia, which was reported in 18/40 (45%) subjects.
These adverse events were generally not considered dose-limiting by the investigators. Multiple factors such as concurrent drug therapy, underlying disease processes, and concurrent illness may have contributed to the alterations in clinical chemistry values. The safety of nelarabine in the paediatric population was characterized by expected haematological ADRs. The most reported non-haematological AEs reported at the 650 mg/m2 dose were headache (17%) and increased transaminase levels (12%).

Case findings

Case reports containing grade 2 or higher neurological AEs were reviewed to gain additional insight from patients who experienced neurological events. Imaging (MRI), Computed Tomography (CT), lumbar puncture, electroencephalogram (EEG), electromyogram (EMG)/Nerve Conduction Velocity (NCV). A total of 70 subject case reports that contained objective neurological test results were analysed.
The reports demonstrated that multiple neurological events can be observed in an individual and span the peripheral nervous system, the central nervous system, and include mental status changes. These

events were not always reversible and could be fatal. Several cases, clinically reported as PNS events, were found to involve some central demyelisation. When the peripheral nervous system is involved, there can be both axonal and demyelinative features. Some reports describe a severe demyelinative picture that resembles Guillain-Barré Syndrome. There was also evidence of central demyelisation, primarily involving the cervical and thoracic cord. In one case, this demyelisation pathologically involved the white matter tracts in a pattern like that seen in reports of vitamin B12 deficiency. The spinal MRI scan descriptions were also consistent with the involvement expected with vitamin B12 deficiency.

- Safety in special populations

Subgroup analyses for intrinsic factors did not show any particular safety concerns regarding ethnic group or gender. Subgroup analyses for extrinsic (environmental) factors were not performed. Nelarabine has not been studied in patients with renal or hepatic impaired function. Nelarabine was administered to a limited number of patients aged ≥ 65 years old. In an exploratory analysis, increasing age, especially aged 65 years and older, appeared to be associated with increased rates of neurological adverse events.
No cases of overdose with nelarabine were reported. There is no evidence of any potential for abuse or dependence. In clinical trials, nelarabine was administered up to 75 mg/kg (approximately 2250 mg/m^2) daily for 5 days to 1 paediatric patient, up to 60 mg/kg (approximately 2400 mg/m2) daily for 5 days to 5 adult patients and up to 2900 mg/m^2 on days 1, 3, 5 to two adult patients. At a dose of 2200 mg/m2 given on days 1, 3, and 5 every 21 days, 2 patients developed a grade 3 ascending sensory neuropathy. MRI evaluations of the two patients demonstrated findings consistent with a demyelisation process in the cervical spine.

- Safety related to drug-drug interactions and other interactions

The results of a combination study with nelarabine and fludarabine showed that fludarabine administration before nelarabine administration on day 3 did not affect the intracellular accumulation of ara-GTP. The safety profile of nelarabine combined with fludarabine (nelarabine on days 1, 3, and 5 and fludarabine on days 3 and 5) was similar that of the two drugs administered individually.

- Discontinuation due to adverse events

In study PGAA2002, three patients were withdrawn from the study due to AEs, including nephrotic range proteinuria (n=1) unrelated to nelarabine, and grade 2 peripheral sensory neuropathy (n=2) considered to be related to nelarabine (study PGAA2002). In study PGAA2003, 28 patients were withdrawn due to one or more AEs. Nervous system AEs were the most frequent class of AEs that led to discontinuation of study drug. These included hypo-aesthesia and peripheral neuropathy, each reported for 6% of patients who received the 1500 mg/m2 starting dose. In the pivotal paediatric study PGAA2001, 14 patients had neurological AEs that led to withdrawal from the study. Peripheral (sensory) neuropathy (n=5), hypo-aesthesia (n=3), ataxia (n=3), and asthenia (n=3) were most commonly reported AEs as either the primary or secondary reasons for withdrawal from the study.

- Post marketing experience

At the time of the assessment by the CHMP, nelarabine had been authorised in the United States, and no regulatory actions for safety reasons had had to been taken since its authorisation on the US market. No data was received that would indicate a different safety profile as the one stated in the SPC.

- Discussion on clinical safety

The safety evaluation of nelarabine was based on 459 adult and paediatric patients who received nelarabine within four phases I studies and three pivotal phase II studies. The most common drug-related adverse events were haematological and gastrointestinal adverse effects. The most concerning (dose-limiting) toxicity of nelarabine was neurologic adverse drug reactions.

In adult patients receiving nelarabine 1500 mg/m2, the safety profile in terms of haematological and gastrointestinal effects was comparable to the other cytotoxic agents. Leukopenia, thrombocytopenia, anaemia, and neutropenia, (including febrile neutropenia) were associated with nelarabine therapy. The SPC recommends that complete blood counts including platelets are monitored regularly (see SPC sections 4.2, 4.4 and 4.8). Neurological adverse events were reported in 8% of the adult patients involved in the two pivotal studies PGAA2002 and PGAA2003. Grade 3 events (ataxia: N=2; convulsion: N=1; hemiparesis: (N=1); hypoesthesia: N=2; loss of consciousness: N=1; peripheral neuropathy: N=1) were reported in 7% of the patients and grade 4 events (cerebral haemorrhage: N=1; coma: N=1), depressed level of consciousness: N=1; intracranial haemorrhage: N=1; leukencephalopathy: N=1) were reported in 2% of the patients.

In paediatric patients receiving nelarbine 650 mg/m^2 (n=84), haematological toxicities (i.e. adverse events and/or abnormal laboratory values) were observed in 99% of patients. Eight (6%) patients died within 30 days after initiation of nelarabine treatment. No deaths were considered due to nelarabine alone. However, 4/151 (3%) patients (including 1 patient in the 400 mg/m^2 group, 1 in the 650 mg/m^2 group, and 2 in the 900 mg/m^2 group) had an outcome of death considered to be at least possibly related to nelarabine. The other deaths were related to tumour. More neurological events were observed in paediatric patients (20% of patients in the 650 mg/m^2 group) than in adults. The most common severe neurological events were peripheral sensory neuropathy (6%), convulsion (4%), and hypo-aesthesia (4%). Ascending peripheral neuropathy could be severe, resulting in diminished motor control; 6% of patients had seizure or related term serious adverse events. One patient experienced status epilepticus possibly related to treatment with nelarabine and died due to multiple causes.

Overall, nervous system serious ADRs were reported in 14% of patients across studies. Among the 459 patients in the safety database, 13% experienced a grade 3 neurological adverse event and 7% a grade 4 neurological adverse event. The mechanism of action of nelarabine-induced neurological toxicity could not be explained. The effect of nelarabine to neuronal cells is the clinical spectrum of chemotherapy-induced neurotoxicity and could be characterised as central, peripheral or both. It may involve astrocyte dysfunction in maintaining a supportive environment for neuronal homeostasis.
A Guillain-Barré like syndrome was observed in phase I study PGAA1001 (dosing for 5 consecutive days) in 5 of 93 patients. The polyradiculopathy behaved as a chronic demyelating neuropathy and was not reversible. One of the five cases occurred at the 1200 mg/m^2 dose (adult patient). All other cases occurred at doses greater than 1200 mg/m^2. Full recovery from neurotoxic events did not always occurred with cessation of nelarabine. It is advised, in the SPC (see sections 4.2 and 4.4) that patients undergoing therapy with nelarabine be closely observed for signs and symptoms of neurological toxicity. Moreover, it is recommended that nelarabine is discontinued at the first sign of neurological events of National Cancer Institute Common Terminology Criteria Adverse Event Grade 2 or greater. Patients treated previously or concurrently with intrathecal chemotherapy or previously with craniospinal irradiation is potentially at increased risk for neurological adverse events (see section 4.2).

Infection (including but not limited to sepsis, bacteraemia, pneumonia, fungal infection) was a very common adverse drug reaction. There was a single additional report of biopsy confirmed progressive multifocal leukoencephalopathy in the adult population. There have been reports of sometimes fatal opportunistic infections in patients receiving nelarabine therapy (see SPC section 4.8).

In addition to the adverse reactions seen in the pivotal clinical trials, there are also data from 875 patients from NCI studies/compassionate use programme (694 patients) and Phase I (181 patients) studies of nelarabine. In these studies, neoplasms benign and malignant (including cysts and polyps) and 7 cases of tumour lysis syndrome were observed. Intravenous hydration according to standard medical practice for the management of hyperuricemia is recommended in patients at risk for tumour lysis syndrome. For patients at risk of hyperuricemia, the use of allopurinol should be considered (see SPC section 4.2 and 4.4).
Clinical studies of nelarabine did not include sufficient numbers of patients aged 65 and over to determine whether they respond differently from younger patients (see SPC section 4.2, 4.4 and 5.2). Nelarabine has not been studied in patients with renal impairment. These patients must be closely monitored for toxicities when treated with nelarabine (see SPC section 4.2 and 5.2). Nelarabine has not been studied in patients with hepatic impairment. These patients should be treated with caution (see SPC section 4.2).

No cases of overdose with nelarabine have been reported. It is likely that nelarabine overdose would result in severe neurotoxicity (possibly including paralysis, coma); myelosuppression and potentially death (see SPC section 4.9). There is no known antidote for nelarabine overdose. Supportive care consistent with good clinical practice should be provided.
No studies on the effects on the ability to drive and use machines have been performed. Patients treated with nelarabine are potentially at risk of suffering from somnolence during and for several days after treatment. A statement has been included in section 4.7 of the SPC to inform patients that somnolence can affect performance of skilled tasks, such as driving.

5. Pharmacovigilance

Detailed description of the Pharmacovigilance system

The CHMP considered that the Pharmacovigilance system as described by the applicant fulfils the legislative requirements.

Risk Management Plan

The MAA submitted a risk management plan.

Table 25: Summary of the risk management plan

Safety concerns	Proposed pharmacovigilance activities	Proposed risk minimization activities
Identified risks		
Haematological toxicity	Routine pharmacovigilance	Undesirable effect in section 4.8 of SmPC
Neurotoxicity Increased risk of neurotoxicity due to previous or concurrent intrathecal chemotherapy or previous craniospinal irradiation	Routine pharmacovigilance, Follow-up questionnaire (see Appendix 2), Additional safety information from: - Clinical trial of intensified therapy in children and young adults with newly diagnosed T-ALL (COG study AALL0434) - Post-marketing surveillance study in children with relapsed/refractory T-ALL and T-LBL	Boxed Warning in section 4.4 of SmPC Special Warning and precaution in section 4.4. of SmPC
Interaction with ADA inhibitors	Routine pharmacovigilance	Interaction with other medicinal products and other forms of interaction in section 4.5 of SmPC
Potential risks		
Rhabdomyolysis	Detailed follow-up will be requested for all reports, routine pharmacovigilance	
Risk of overdose	Routine pharmacovigilance	Posology and method of administration in section 4.2 of SmPC: Restricted to physicians experienced in use of cytotoxic drugs
Risk of off label use	Routine pharmacovigilance	Restricted to physicians experienced in use of cytotoxic drugs
Risk with pregnancy	Routine pharmacovigilance	Recommended not for use during pregnancy, see Pregnancy and Lactation in section 4.6 of SmPC

Safety concerns	Proposed pharmacovigilance activities	Proposed risk minimization activities
Risk with concomitant CNS depressants.	Routine pharmacovigilance	
Risks in combination therapy	Routine pharmacovigilance, Additional safety information from COG study AALL0434 (see above).	Posology and method of administration in section 4.2 of SmPC: Restricted to physicians experienced in use of cytotoxic drugs
Risk of resistance to nelarabine	Routine pharmacovigilance	Common medical practice is to treat for two to four cycles. As soon as a clinical response occurs, the patient usually receives a bone marrow transplant.
Gender related risks	Routine pharmacovigilance and reviewed during preparation of each PSUR	
Ethnic groups background	Routine pharmacovigilance	
Elderly (insufficient numbers of patients in this group have received nelarabine)	Routine pharmacovigilance and reviewed during preparation of each PSUR.	Special warnings and precautions for use in section 4.4 of SmPC, and Pharmacokinetic properties in section 5.2 of SmPC
Missing Information		
Patients with hepatic impairment	Routine pharmacovigilance	Restricted to physicians experienced in use of cytotoxic drugs
Patients with renal impairment	Routine pharmacovigilance	Restricted to physicians experienced in use of cytotoxic drugs
Patients with history of seizure disorders	Routine pharmacovigilance	Boxed Warning regarding neurotoxicity in section 4.4 of SmPC
Patients with active infection	Routine pharmacovigilance	Restricted to physicians experienced in use of cytotoxic drugs
Pharmacokinetics in children <4 years	Routine pharmacovigilance	Restricted to physicians experienced in use of cytotoxic drugs
Carcinogenesis	Routine pharmacovigilance	Restricted to physicians experienced in use of cytotoxic drugs

The CHMP, having considered the data submitted in the application, is of the opinion that no additional risk minimisation activities are required beyond those included in the product information.

6. Overall conclusions, risk/benefit assessment and recommendation

Quality

The Quality of this product was considered to be acceptable when used in accordance with the conditions defined in the SPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way. At the time of the CHMP opinion, there was a minor unresolved quality issue having no impact on the benefit/risk ratio of the product. The applicant gave a letter of undertaking and committed to resolve this as follow-up measures after the opinion, within an agreed timeframe.

There were no issues concerning the non-clinical pharmacology or the toxicology of nelarabine that negatively affected the overall benefit-risk assessment.

Efficacy

The application was based on two uncontrolled, open-label, phase II trials, in adult (PGAA2002) and paediatric (PGAA2001) patients with relapsed or refractory T-cell lineage ALL/LBL, receiving nelarabine as single agent.

Among 39 adult patients treated with nelarabine 1500 mg/m2 (days 1, 3, 5, repeated every 21 days), five patients having received more than 2 prior inductions, and two patients having received 1 prior induction, experienced a complete response (CR:18%, 95%CI [6% - 37%] and CR:18%, 95%CI [2%, 52%], respectively). Nine patients (23%) had a complete response with no evidence of disease with or without hematologic recovery (CR*). Among these 9 patients, seven went on to achieve a complete response with full hematologic recovery (CR) and two had a best response of CR*.
Duration of CR was 51 and 212 weeks in two patients having received one prior induction, and ranged from 15.1 to at least 195.4 weeks in five patients having received two or more prior inductions. Duration of CR* ranged from 4.7 to 215 weeks, and 4 to at least 195.4 weeks in patients having received one prior, or at least two prior inductions, respectively. These durations were sufficiently long for a patients to proceed to transplant (4-8 weeks according to most guidelines). The median survival was 20.1 weeks for patients having received 1 prior induction and 20.6 weeks for patients having received more than prior inductions. The one year survival rate for all treated patients was 31% (95% CI: 16% - 45%).

Among the 22 paediatric patients with highly refractory disease that did not respond to the most recent induction regimen, and who received the recommended dose (650 mg/m2, one hour daily for 5 consecutive days, repeated every 21 days), 18% (4/22) of patients achieved a CR with nelarabine and remained in continuous complete remission for 4.7 to 36.4 weeks. Three of these patients received allogeneic bone marrow transplant during the remission period. Survival ranged from 16.6 to 57.4 weeks in the four highly refractory subjects who achieved CR.

Safety

The safety profile of nelarabine was based on the data from the pivotal trials, which involved 103 adults and 84 paediatric patients receiving nelarabine at the recommended doses of 1,500 mg/m ^{2} and 650 mg/m ^{2}, respectively. The most frequent adverse events were fatigue, gastrointestinal disorders, haematological disorders, respiratory disorders, nervous system disorders, and pyrexia.
Neurological toxicity is the dose-limiting toxicity of nelarabine. Despite an extensive phase I program, the dose had to be further decreased in both adults and children early in the phase II program. Children were more sensitive to the neurotoxic effects of nelarabine and although dose-adjustments were made, more than one third of the pediatric population experienced at least one neurological adverse event. These events included altered mental states including severe somnolence, central nervous system effects including convulsions, and peripheral neuropathy ranging from numbness and paresthesias to motor weakness and paralysis. There were also reports of events associated with demyelination, and ascending peripheral neuropathies similar in appearance to Guillain-Barré Syndrome. Full recovery from these events did not always occurred with cessation of nelarabine. Therefore, close monitoring for neurological events is strongly recommended in the SPC, where dose modification and treatment discontinuation guidance are provided. An explorative analysis was performed by the applicant to identify risk factors of neurotoxicity, however, the very limited safety database and the retrospective nature of the data collection necessitates a more stringent post-marketing follow-up than what is expected in routine pharmacovigilance safety reports (see post-marketing specific obligations in the benefit risk section).

In addition to the adverse reactions seen in the pivotal clinical trials, there are also data from 875 patients from NCI studies/compassionate use programme (694 patients) and Phase I (181 patients) studies of nelarabine. In these studies, neoplasms benign and malignant (including cysts and polyps) and 7 cases of tumour lysis syndrome were observed. Cases of rhabdomyolysis and increased CPK values were noted, and these events are being monitored closely.
From the safety database all the adverse reactions reported in clinical trials have been included in the Summary of Product Characteristics.

Having considered the safety concerns in the risk management plan, the CHMP considered that the proposed activities described in section 3.5 adequately addressed these.

- User consultation

The Applicant performed a user consultation testing on the package leaflet. The design of the test formed the basis of an adequate and competent testing of the PIL in regard to finding, diagnosing and amending possible weaknesses. The present readability test was well designed to meet its main objectives. The results showed that the user test met the guideline benchmark with 18 out of 20 people being able to locate each question and 18 out of 20 able to correctly answer. The results of the user testing described in the user testing report support the changes made to the PIL.

Risk-benefit assessment

According to CHMP guidelines, this full application should have been based on data generated by randomised, controlled clinical trials rather than by open-label, non-comparator studies. However the lack of randomized trial in this very heavily treated population is justified in view of the small size of the population of patients in second relapse. Furthermore, even in the absence of adequately controlled trials, nelarabine treatment achieved meaningful response rate and duration of response in a significant proportion of adult and pediatric 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 stem cell transplantation.
The safety profile of nelarabine was not very different from other nucleoside analogues. As expected myelosuppression with neutropenia and thrombocytopenia was the most common toxicity, which is probably unavoidable in the setting of leukaemia treatment.
An important identified risk was the dose-limiting neurotoxicity of nelarabine. Grade 3 and 4 neurotoxicity was frequent in clinical trials (19% of paediatric patients and 13% of adult patients). Adequate information has been provided in the SPC to help treating physicians to minimise the incidence and severity of haematological and neurological toxicity. However, regarding the safety profile of nelarbine there are still uncertainties, especially in terms of long term neurotoxicity in paediatric patients, due to the limited size of the safety database. This is justified in view of the small size of the population of patients in second relapse, but requires for the applicant to introduce specific investigations concerning the safety of the product. A risk management plan was submitted. The CHMP, having considered the data submitted, was of the opinion that pharmacovigilance activities in addition to the use of routine pharmacovigilance were needed to investigate further some of the safety concerns. The CHMP agreed that the following additional data to be provided as specific obligations were required:

- The marketing authorisation holder was required to better define the safety profile of nelarabine incorporated into multiagent regimens including (prophylactic) treatment of CNS disease. To this end, the holder will provide post-marketing, data from an on-going phase III Children's Oncology Group study AALL0434, entitled "intensified methotrexate, nelarabine and augmented BFM therapy for children and young adults with newly diagnosed T-cell actute lymphoblastic leukaemia".
- In order to expand the safety database of nelarabine in children regarding neurological adverse reactions, the marketing authorisation holder will provide data from a post-marketing surveillance study for Atriance in the indicated patient population under 21 years of age receiving the 650mg/m^2 dose of nelarabine.

No additional risk minimisation activities were required beyond those included in the product information.

In conclusion, there is sufficient evidence for the antileukaemic activity of nelarabine in both paediatric and adult patient. The effect of nelarabine, in terms of response is considered clinically relevant and the ultimate goal of the therapy, stem cell transplantation, seems not to be affected adversely by pre-treatment with nelarabine. 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 nelarabine on overall survival. However, it is acknowledged that the indication for which the

medicinal product is intended is encountered so rarely that the applicant cannot reasonably be expected to provide comprehensive data on the clinical efficacy and safety of the medicinal product. Therefore, the marketing authorisation should be granted under exceptional circumstances.

Similarity with authorised orphan medicinal products

The Applicant has provided reports discussing the issue of similarity in the context of Art. 3 of Commission Regulation (EC) No 847/2000 as regard to the orphan medicinal products Evoltra (clofarabine), Sprycel (dasatininb) and Glivec (Imatinib) which have been granted a marketing authorisation for ALL in the EU. The Applicant claimed that Atriance is not similar to any of the authorised Orphan medicinal products for a condition relating to the proposed therapeutic indication.

The CHMP concluded that, having considered the arguments presented by the applicant, the Rapporteurs assessment, and the conclusions of the Quality working Party, there are differences in the mechanism of action of nelarabine and clofarabine. The two active substances are considered not to be similar as regards mechanism of action since they act on different pharmacodynamic targets (DNA polymerases α and β, DNA polymerases α and ribonucleotide reductase, for nelarabine and clofarabine, respectively). However, the CHMP concluded that nelarabine and clofarabine are similar in terms of molecular structural aspects since both molecules share the same principal molecular structural features and the changes in molecular structure are only minor.

The CHMP also concluded that there are substantial differences in the mechanism of action of nelarabine and imatinib or dasatinib. Nelarabine and imatinib or dasatinib are not similar in terms of molecular structural aspects since both molecules do not share the same principal molecular structural features and the changes in molecular structure are not minor.

Therefore, CHMP is of the opinion that Atriance is not similar to any authorised orphan medicinal products within the meaning of Article 3 of Commission Regulation (EC) No. 847/200 (See Appendix 1).

Recommendation

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considered by consensus that the risk-benefit balance of Atriance in 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 was favourable and therefore recommended the granting of the marketing authorisation under exceptional circumstances.

In addition, the CHMP, with reference to Article 8 of Regulation EC No 141/2000, considers Atriance not to be similar (as defined in Article 3 of Commission Regulation EC No. 847/2000) to authorised orphan medicinal products for the same therapeutic indication.