ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

▼This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions. See section 4.8 for how to report adverse reactions.

1. NAME OF THE MEDICINAL PRODUCT

Atriance 5 mg/ml solution for infusion

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each ml of solution contains 5 mg of nelarabine.

Each vial contains 250 mg of nelarabine.

Excipient with known effect

Each ml of solution contains 1.770 mg (77 micromols) of sodium.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for infusion.

Clear, colourless solution.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Nelarabine is indicated for the treatment of patients with T-cell acute lymphoblastic leukaemia (T-ALL) and T-cell lymphoblastic lymphoma (T-LBL) whose disease has not responded to or has relapsed following treatment with at least two chemotherapy regimens.
Due to the small patient populations in these disease settings, the information to support these indications is based on limited data.

4.2 Posology and method of administration

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

Posology

Complete blood counts including platelets must be monitored regularly (see sections 4.4 and 4.8).

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

Children and adolescents (aged 21 years and younger)
The recommended dose of nelarabine for children and adolescents (aged 21 years and younger) is 650 mg/m^2 administered intravenously over one hour daily for 5 consecutive days, repeated every

21 days.

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

Limited clinical pharmacology data are available for patients below the age of 4 years (see section 5.2).

Dose modification
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.

Special populations
Elderly
Insufficient numbers of patients aged 65 years of age and older have been treated with nelarabine to determine whether they respond differently than younger patients (see sections 4.4 and 5.2).

Renal impairment
Nelarabine has not been studied in individuals with renal impairment. Nelarabine and 9-β-D-arabinofuranosylguanine (ara-G) are partially renally excreted (see section 5.2). There are insufficient data to support a dose adjustment recommendation for patients with a renal clearance of creatinine Cl_{cr} less than 50 ml/min. Patients with renal impairment must be closely monitored for toxicities when treated with nelarabine.

Hepatic impairment
Nelarabine has not been studied in patients with hepatic impairment. These patients should be treated with caution.

Method of administration

Nelarabine is for intravenous use only and must not be diluted prior to administration. The appropriate dose of nelarabine must be transferred into polyvinylchloride (PVC) or ethyl vinyl acetate (EVA) infusion bags or glass containers and administered intravenously as a two-hour infusion in adult patients and as a one-hour infusion in paediatric patients.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use

NEUROLOGICAL ADVERSE REACTIONS
Severe neurological reactions have been reported with the use of nelarabine. These reactions have included altered mental states including severe somnolence, confusion and coma, central nervous system effects including convulsions, ataxia and status epilepticus, and peripheral neuropathy including hypoesthesia ranging from numbness and paresthesias to motor weakness and paralysis. There have also been reports of reactions associated with demyelination, and ascending peripheral neuropathies similar in appearance to Guillain-Barré Syndrome. (see section 4.8).
Neurotoxicity is the dose-limiting toxicity of nelarabine. Full recovery from these reactions has not always occurred with cessation of nelarabine. Therefore, close monitoring for neurological reactions is strongly recommended, and nelarabine must be discontinued at the first sign of neurological reactions of NCI CTCAE Grade 2 or greater.

Patients treated previously or concurrently with intrathecal chemotherapy or previously with craniospinal irradiation are potentially at increased risk for neurological adverse events (see

section 4.2 - dose modification) and therefore concomitant intrathecal therapy and/or craniospinal irradiation is not recommended.

Immunisation using a live organism vaccine has the potential to cause infection in immunocompromised hosts. Therefore, immunisations with live organism vaccines are not recommended.

Leukopenia, thrombocytopenia, anaemia, and neutropenia, (including febrile neutropenia) have been associated with nelarabine therapy. Complete blood counts including platelets must be monitored regularly (see sections 4.2 and 4.8).

Patients receiving nelarabine are recommended to receive intravenous hydration according to standard medical practice for the management of hyperuricaemia in patients at risk of tumour lysis syndrome. For patients at risk of hyperuricaemia, the use of allopurinol should be considered.

Elderly

Clinical studies of nelarabine did not include sufficient numbers of patients aged 65 and over to determine whether they respond differently from younger patients. In an exploratory analysis, increasing age, especially age 65 years and older, appeared to be associated with increased rates of neurological adverse events.

Carcinogenicity and mutagenicity

Carcinogenicity testing of nelarabine has not been performed. Nelarabine however, is known to be genotoxic to mammalian cells (see section 5.3).

Sodium warning

This medicinal product contains 88.51 mg (3.85 mmol) sodium per vial (50 ml), equivalent to 4.4% of the WHO recommended maximum daily intake of 2 g sodium for an adult.

4.5 Interaction with other medicinal products and other forms of interaction

Nelarabine and ara-G did not significantly inhibit the activities of the major hepatic cytochrome P450 (CYP) isoenzymes CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, or CYP3A4 *in vitro*.

Concomitant administration of nelarabine in combination with adenosine deaminase inhibitors such as pentostatin is not recommended. Concomitant administration may reduce the efficacy of nelarabine and/or change the adverse event profile of either active substance.

4.6 Fertility, pregnancy and lactation

Contraception in males and females

Both sexually active men and women should use effective methods of contraception during treatment with nelarabine. Men with partners who are pregnant or could become pregnant should use condoms during treatment with nelarabine and for at least three months following cessation of treatment.

Pregnancy

There are no or limited amount of data from the use of nelarabine in pregnant women.

Studies in animals have shown reproductive toxicity (see section 5.3). The potential risk in humans is unknown, however, exposure during pregnancy will likely lead to anomalies and malformations of the foetus.

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.

Breast-feeding

It is unknown whether nelarabine or its metabolites are excreted in human breast milk. A risk to the newborn/infant cannot be excluded. Breast-feeding should be discontinued during treatment with Atriance.

Fertility

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.

4.7 Effects on ability to drive and use machines

Atriance has major influence on the ability to drive and use machines.

Patients treated with nelarabine are potentially at risk of suffering from somnolence during and for several days after treatment. Patients must be cautioned that somnolence can affect performance of skilled tasks, such as driving.

4.8 Undesirable effects

Summary of the safety profile

The safety profile from pivotal clinical studies at the recommended doses of nelarabine in adults (1,500 mg/m^2) and children (650 mg/m^2) is based on data from 103 adults and 84 paediatric patients respectively. The most frequently occurring adverse events were fatigue; gastrointestinal disorders; haematological disorders; respiratory disorders; nervous system disorders (somnolence, peripheral neurological disorders [sensory and motor], dizziness, hypoaesthesia, paraesthesia, headache); and pyrexia. Neurotoxicity is the dose-limiting toxicity associated with nelarabine therapy (see section 4.4).

Tabulated list of adverse reactions

The following convention has been utilised for the classification of frequency: very common (≥ 1/10), common (≥ 1/100 to < 1/10), uncommon (≥ 1/1,000 to < 1/100), rare (≥ 1/10,000 to < 1/1,000), very rare (< 1/10,000), and not known (cannot be estimated from the available data).

Adverse reactions	**Adults (1,500 mg/m^2) N=103**	**Children (650 mg/m^2) N=84**
Infections and infestations		
Infection (including but not limited to; sepsis, bacteraemia, pneumonia, fungal infection)	Very common: 40 (39%)	Very common: 13 (15%)
Neoplasms benign, malignant and unspecified (including cysts and polyps)		
Tumour lysis syndrome (see also data from compassionate use programme and non-pivotal studies)	Common: 1 (1%)	N/A

Blood and lymphatic system disorders		
Febrile neutropenia	Very common: 12 (12%)	Common: 1 (1%)
Neutropenia	Very common: 83 (81%)	Very common: 79 (94%)
Leukopenia	Common: 3 (3%)	Very common: 32 (38%)
Thrombocytopenia	Very common: 89 (86%)	Very common: 74 (88%)
Anaemia	Very common: 102 (99%)	Very common: 80 (95%)
Metabolism and nutrition disorders		
Hypoglycaemia	N/A	Common: 5 (6%)
Hypocalcaemia	Common: 3 (3%)	Common: 7 (8%)
Hypomagnesaemia	Common: 4 (4%)	Common: 5 (6%)
Hypokalaemia	Common: 4 (4%)	Very common: 9 (11%)
Anorexia	Common: 9 (9%)	N/A
Psychiatric disorders		
Confusional state	Common: 8 (8%)	Common: 2 (2%)
Nervous system disorders		
Seizures (including convulsions, grand mal convulsions, status epilepticus)	Common: 1 (1%)	Common: 5 (6%)
Amnesia	Common: 3 (3%)	N/A
Somnolence	Very common: 24 (23%)	Common: 6 (7%)
Peripheral neurological disorders (sensory and motor)	Very common: 22 (21%)	Very common: 10 (12%)
Hypoesthesia	Very common: 18 (17%)	Common: 5 (6%)
Paraesthesia	Very common: 15 (15%)	Common: 3 (4%)
Ataxia	Common: 9 (9%)	Common: 2 (2%)
Balance disorder	Common: 2 (2%)	N/A
Tremor	Common: 5 (5%)	Common: 3 (4%)
Dizziness	Very common: 22 (21%)	N/A
Headache	Very common: 15 (15%)	Very common: 14 (17%)
Dysgeusia	Common: 3 (3%)	N/A
Eye disorders		
Blurred vision	Common: 4(4%)	N/A
Vascular disorders		
Hypotension	Common: 8 (8%)	N/A
Respiratory, thoracic and mediastinal disorders		
Pleural effusion	Common: 10 (10%)	N/A
Wheezing	Common: 5 (5%)	N/A
Dyspnoea	Very common: 21 (20%)	N/A
Cough	Very common: 26 (25%)	N/A

Gastrointestinal disorders		
Diarrhoea	Very common: 23 (22%)	Common: 2 (2%)
Stomatitis	Common: 8 (8%)	Common: 1 (1%)
Vomiting	Very common: 23 (22%)	Common: 8 (10%)
Abdominal pain	Common: 9 (9%)	N/A
Constipation	Very common: 22 (21%)	Common: 1 (1%)
Nausea	Very common: 42 (41%)	Common: 2 (2%)
Hepatobiliary disorders		
Hyperbilirubinaemia	Common: 3 (3%)	Common: 8 (10%)
Transaminases increased	N/A	Very common: 10(12%)
Aspartate aminotransferase increased	Common: 6 (6%)	N/A
Musculoskeletal and connective tissue disorders		
Muscle weakness	Common: 8 (8%)	N/A
Myalgia	Very common: 13 (13%)	N/A
Arthralgia	Common: 9 (9%)	Common: 1 (1%)
Back pain	Common: 8 (8%)	N/A
Pain in extremity	Common: 7 (7%)	Common: 2 (2%)
Rhabdomyolysis, blood creatine phosphokinase increased (see "Post – marketing data")	Rare: N/A	Rare: N/A
Renal and urinary disorders		
Blood creatinine increased	Common: 2 (2%)	Common: 5 (6%)
General disorders and administration site conditions		
Oedema	Very common: 11 (11%)	N/A
Gait abnormal	Common: 6 (6%)	N/A
Oedema peripheral	Very common: 15 (15%)	N/A
Pyrexia	Very common: 24 (23%)	Common: 2 (2%)
Pain	Very common: 11 (11%)	N/A
Fatigue	Very common: 51 (50%)	Common: 1 (1%)
Asthenia	Very common: 18 (17%)	Common: 5 (6%)

Description of selected adverse reactions

Infection and infestations
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.

Nervous system disorders
There have been reports of events associated with demyelination and ascending peripheral neuropathies similar in appearance to Guillain-Barré syndrome.
Two paediatric patients had fatal neurological events.

Data from NCI studies/compassionate use programme and phase I studies

In addition to the adverse reactions seen in the pivotal clinical studies, there are also data from 875 patients from NCI studies/compassionate use programme (694 patients) and Phase I (181 patients)

studies of nelarabine. The following additional adverse reactions were seen:

Neoplasms benign and malignant (including cysts and polyps)
Tumour lysis syndrome – 7 cases (see sections 4.2 and 4.4)

Post–marketing data

Rhabdomyolysis and increased blood creatine phosphokinase have been identified during post-approval use of nelarabine. This includes spontaneous case reports as well as serious adverse events from ongoing studies.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

4.9 Overdose

No case of overdose has been reported.

Nelarabine has been administered in clinical studies up to a dose of 75 mg/kg (approximately 2,250 mg/m^2) daily for 5 days to a paediatric patient, up to a dose of 60 mg/kg (approximately 2,400 mg/m^2) daily for 5 days to 5 adult patients and up to 2,900 mg/m^2 in a further 2 adults on days 1, 3 and 5.

Symptoms and signs

It is likely that nelarabine overdose would result in severe neurotoxicity (possibly including paralysis, coma), myelosuppression and potentially death. At a dose of 2200 mg/m^2 given on days 1, 3 and 5 every 21 days, 2 patients developed a significant grade 3 ascending sensory neuropathy. MRI evaluations of the 2 patients demonstrated findings consistent with a demyelinating process in the cervical spine.

Treatment

There is no known antidote for nelarabine overdose. Supportive care consistent with good clinical practice should be provided.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antineoplastic agents, antimetabolites, purine analogues, ATC code: L01B B 07

Nelarabine is a pro-drug of the deoxyguanosine analogue ara-G. Nelarabine is rapidly demethylated by adenosine deaminase (ADA) to ara-G and then phosphorylated intracellularly by deoxyguanosine kinase and deoxycytidine kinase to its 5'-monophosphate metabolite. The monophosphate metabolite is subsequently converted to the active 5'-triphosphate form, ara-GTP. Accumulation of ara-GTP in leukaemic blasts allows for preferential incorporation of ara-GTP into deoxyribonucleic acid (DNA) leading to inhibition of DNA synthesis. This results in cell death. Other mechanisms may contribute to the cytotoxic effects of nelarabine. *In vitro*, T-cells are more sensitive than B-cells to the cytotoxic effects of nelarabine.

Clinical efficacy and data

Adult clinical study in relapsed or refractory T-ALL and T-LBL
In an open-label study carried out by the Cancer and Leukaemia Group B and the Southwest Oncology Group, the safety and efficacy of nelarabine were evaluated in 39 adults with T-cell acute lymphoblastic leukaemia (T-ALL) or lymphoblastic lymphoma (T-LBL). Twenty–eight of the 39 adults had relapsed or were refractory to at least two prior induction regimens and aged between 16 to 65 years of age (mean 34 years). Nelarabine at a dose of 1500 mg/m^2/day was administered intravenously over two hours on days 1, 3 and 5 of a 21 day cycle. Five of the 28 patients (18 %) [95 % CI: 6 %—37 %] treated with nelarabine achieved a complete response (bone marrow blast counts ≤ 5 %, no other evidence of disease, and full recovery of peripheral blood counts). A total of 6 patients (21 %) [95 % CI: 8 %–41 %] achieved a complete response with or without haematological recovery. Time to complete response in both classifications of response ranged from 2.9 to 11.7 weeks. Duration of response (in both classifications of response (n=5) ranged between 15 and 195+ weeks. Median overall survival was 20.6 weeks [95 % CI: 10.4–36.4]. Survival at one year was 29 % [95 % CI: 12 %–45 %].

Paediatric clinical study in relapsed or refractory T-ALL and T-LBL
In an open-label, multicenter study carried out by Childrens Oncology Group, nelarabine was administered intravenously over 1 hour for 5 days to 151 patients ≤ 21 years of age, 149 of whom had relapsed or refractory T-cell acute lymphoblastic leukaemia (T-ALL) or T-cell lymphoblastic lymphoma (T-LBL). Eighty-four (84) patients, 39 of whom had received two or more prior induction regimens and 31 whom had received one prior induction regimen, were treated with 650 mg/m^2/day of nelarabine administered intravenously over 1 hour daily for 5 consecutive days repeated every 21 days.

Of the 39 patients who had received two or more prior induction regimens, 5 (13 %) [95 % CI: 4 %–27 %] achieved a complete response (bone marrow blast counts ≤ 5 %, no other evidence of disease, and full recovery of peripheral blood counts) and 9 (23 %) [95 % CI: 11 %–39 %] achieved complete responses with or without full haematological recovery. Duration of response in both classifications of response ranged between 4.7 and 36.4 weeks and median overall survival was 13.1 weeks [95 % CI: 8.7–17.4] and survival at one year was 14 % [95 % CI: 3 %–26 %].

Thirteen (42 %) of the 31 patients treated with one prior induction regimen achieved a complete response overall. Nine of these 31 patients failed to respond to prior induction (refractory patients). Four (44 %) of the nine refractory patients experienced a complete response to nelarabine.

This medicinal product has been authorised under “exceptional circumstances”. This means that due to the rarity of the disease it has not been possible to obtain complete information on this medicinal product.

The European Medicines Agency will review any new information which may become available every year and this SmPC will be updated as necessary.

5.2 Pharmacokinetic properties

Nelarabine is a pro-drug of the deoxyguanosine analogue ara-G. Nelarabine is rapidly demethylated by adenosine deaminase (ADA) to ara-G and then phosphorylated intracellularly by deoxyguanosine kinase and deoxycytidine kinase to its 5’-monophosphate metabolite. The monophosphate metabolite is subsequently converted to the active 5’-triphosphate from, ara-GTP. Accumulation of ara-GTP in leukaemic blasts allows for preferential incorporation of ara-GTP into deoxyribonucleic acid (DNA) leading to inhibition of DNA synthesis. This results in cell death. Other mechanisms may contribute to the cytotoxic effects of nelarabine. *In vitro*, T-cells are more sensitive than B-cells to the cytotoxic effects of nelarabine.

In a cross-study analysis using data from four Phase I studies, the pharmacokinetics of nelarabine and ara-G were characterized in patients aged less than 18 years and adult patients with refractory

leukaemia or lymphoma.

Absorption

Adults
Plasma ara-G C_{max} values generally occurred at the end of the nelarabine infusion and were generally higher than nelarabine C_{max} values, suggesting rapid and extensive conversion of nelarabine to ara-G. After infusion of 1,500 mg/m^2 nelarabine over two hours in adult patients, mean (%CV) 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.

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.

Distribution

Nelarabine and ara-G are extensively distributed throughout the body based on combined Phase I pharmacokinetic data at nelarabine doses of 104 to 2,900 mg/m^2. Specifically, 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.

Nelarabine and ara-G are not substantially bound to human plasma proteins (less than 25 %) *in vitro*, and binding is independent of nelarabine or ara-G concentrations up to 600 µM.

No accumulation of nelarabine or ara-G was observed in plasma after nelarabine administration on either a daily or a day 1, 3, 5 schedule.

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.

Biotransformation

The principal route of metabolism for nelarabine is O-demethylation by adenosine deaminase to form ara-G, which undergoes 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.

Elimination

Nelarabine and ara-G are rapidly eliminated from plasma with a half-life of approximately 30 minutes and 3 hours, respectively. These findings were demonstrated in patients with refractory leukaemia or lymphoma given a dose of 1,500 mg/m^2 nelarabine (adults) or a 650 mg/m^2 (paediatrics).

Combined Phase 1 pharmacokinetic data at nelarabine doses of 104 to 2,900 mg/m^2 indicate that mean (%CV) clearance (Cl) values for nelarabine are 138 l/h/m^2 (104 %) and 125 l/h/m^2 (214 %) in adult and paediatric patients, respectively, on day 1 (n = 65 adults, n = 21 paediatric patients). The apparent clearance of ara-G (Cl/F) is comparable between the two groups [9.5 l/h/m^2 (35 %) in adult patients and 10.8 l/h/m^2 (36 %) in paediatric patients] on day 1.

Nelarabine and ara-G are partially eliminated by the kidneys. In 28 adult patients, 24 hours after nelarabine infusion on day 1, mean urinary excretion of nelarabine and ara-G was 5.3 % and 23.2 % of the administered dose, respectively. Renal clearance averaged 9.0 l/h/m^2 (151 %) for nelarabine and 2.6 l/h/m^2 (83 %) for ara-G in 21 adult patients.

Because the timecourse of intracellular ara-GTP was prolonged, its elimination half-life could not be accurately estimated.

Paediatric population

Limited clinical pharmacology data are available for patients below the age of 4 years.

Combined Phase 1 pharmacokinetic data at nelarabine doses of 104 to 2,900 mg/m^2 indicate that the clearance (Cl) and V_{ss} values for nelarabine and ara-G are comparable between the two groups. Further data with respect to nelarabine and ara-G pharmacokinetics in the paediatric population are provided in other subsections.

Gender

Gender has no effect on nelarabine or ara-G plasma pharmacokinetics. Intracellular ara-GTP C_{max} and $AUC_{(0–t)}$ values at the same dose level were 2– to 3– fold greater on average in adult female than in adult male patients.

Race

The effect of race on nelarabine and ara-G pharmacokinetics has not been specifically studied. In a pharmacokinetic/pharmacodynamic cross study analysis, race had no apparent effect on nelarabine, ara-G, or intracellular ara-GTP pharmacokinetics.

Renal impairment

The pharmacokinetics of nelarabine and ara-G have not been specifically studied in renally impaired or haemodialysed patients. Nelarabine is excreted by the kidney to a small extent (5 to 10 % of the administered dose). Ara-G is excreted by the kidney to a greater extent (20 to 30 % of the administered nelarabine dose). Adults and children in clinical studies were categorized into the three groups according to renal impairment: normal with Cl_{cr} greater than 80 ml/min (n = 56), mild with Cl_{cr} equalling 50 to 80 ml/min (n = 12), and moderate with Cl_{cr} less than 50 ml/min (n = 2). The mean apparent clearance (Cl/F) of ara-G was about 7 % lower in patients with mild renal impairment than in patients with normal renal function (see section 4.2). No data are available to provide a dose advice for patients with Cl_{cr} less than 50 ml/min.

Elderly

Age has no effect on the pharmacokinetics of nelarabine or ara-G. Decreased renal function, which is more common in the elderly, may reduce ara-G clearance (see section 4.2).

5.3 Preclinical safety data

Adverse reactions not observed in clinical studies, but seen in animals at exposure levels similar to clinical exposure levels and with possible relevance to clinical use were as follows: nelarabine caused histopathological changes to the central nervous system (white matter vacuolation and degenerative changes in cerebrum, cerebellum and spinal cord) of monkeys after daily treatment with nelarabine for 23 days, at exposures below the human therapeutic exposure. Nelarabine showed *in vitro* cytotoxicity to monocytes and macrophages.

Carcinogenicity

Carcinogenicity testing of nelarabine has not been performed.

Mutagenicity

Nelarabine was mutagenic to L5178Y/TK mouse lymphoma cells with and without metabolic activation.

Reproduction toxicity

Compared to controls, nelarabine caused increased incidences of foetal malformations, anomalies, and variations in rabbits when given at doses approximately 24 % of the adult human dose on a mg/m^2 basis during the period of organogenesis. Cleft palate was seen in rabbits given a dose approximately 2-fold the adult human dose, absent pollices in rabbits given a dose approximately 79 % of the adult human dose while absent gall bladder, accessory lung lobes, fused or extra sternebrae and delayed ossification was seen at all doses. Maternal body weight gain and foetal body weights were reduced in rabbits given a dose approximately 2-fold the adult human dose.

Fertility

No studies have been conducted in animals to assess the effects of nelarabine on fertility. However, 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 a mg/m^2 basis for 30 consecutive days.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium chloride
Water for injections
Hydrochloric acid (to adjust the pH)
Sodium hydroxide (to adjust the pH)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years.

Atriance is stable for up to 8 hours at up to 30°C once the vial is opened.

6.4 Special precautions for storage

For storage conditions after first opening of the medicinal product, see section 6.3.

6.5 Nature and contents of container

Clear glass (Type I) vial with a bromobutyl rubber stopper, and an aluminium seal with a red snap-off cap.

Each vial contains 50 ml of solution. Atriance is supplied in packs of 1 vial or 6 vials.

6.6 Special precautions for disposal and other handling

The normal procedures for proper handling and disposal of cytotoxic anti-tumour medicinal products should be adopted, namely:

- Staff should be trained in how to handle and transfer the medicinal product.
- Pregnant staff should be excluded from working with this medicinal product.
- Personnel handling this medicinal product during handling/transfer should wear protective clothing including mask, goggles and gloves.
- All items for administration or cleaning, including gloves, should be placed in high-risk, waste disposal bags for high-temperature incineration. Any liquid waste from the preparation of the nelarabine solution for infusion may be flushed with large amounts of water.
- Accidental contact with the skin or eyes should be treated immediately with copious amounts of water.

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

Sandoz Pharmaceuticals d.d.
Verovškova ulica 57
1000 Ljubljana
Slovenia

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/07/403/001-002

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 22 August 2007
Date of latest renewal: 16 June 2017

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu

ANNEX II

A. MANUFACTURER(S) RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

E. SPECIFIC OBLIGATION TO COMPLETE POST-AUTHORISATION MEASURES FOR THE MARKETING AUTHORISATION UNDER EXCEPTIONAL CIRCUMSTANCES

A. MANUFACTURER(S) RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer(s) responsible for batch release

Novartis Farmacéutica S.A.
Gran Via de les Corts Catalanes, 764
08013 Barcelona
Spain

Novartis Pharma GmbH
Roonstraße 25
D-90429 Nuremberg
Germany

EBEWE Pharma Ges.m.b.H. Nfg.KG
Mondseestrasse 11
4866 Unterach am Attersee
Austria

FAREVA Unterach GmbH
Mondseestraße 11
Unterach am Attersee, 4866,
Austria

The printed package leaflet of the medicinal product must state the name and address of the manufacturer responsible for the release of the concerned batch.

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2).

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

- **Periodic safety update reports (PSURs)**

The requirements for submission of PSURs for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

- **Risk management plan (RMP)**

The marketing authorisation holder (MAH) shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:
- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of

an important (pharmacovigilance or risk minimisation) milestone being reached.

E. SPECIFIC OBLIGATION TO COMPLETE POST-AUTHORISATION MEASURES FOR THE MARKETING AUTHORISATION UNDER EXCEPTIONAL CIRCUMSTANCES

This being an approval under exceptional circumstance and pursuant to Article 14(8) of Regulation (EC) No 726/2004, the MAH shall conduct, within the stated timeframe, the following measures:

Description	Due date
The MAH shall provide yearly updates on any new information concerning the efficacy and safety of the product in 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.	Yearly

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTON

1. NAME OF THE MEDICINAL PRODUCT

Atriance 5 mg/ml solution for infusion
nelarabine

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each ml contains 5 mg of nelarabine.

3. LIST OF EXCIPIENTS

Excipients: Sodium chloride, water for injections, hydrochloric acid, sodium hydroxide. See the leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

Solution for infusion

6 x 50 ml vials
250 mg/50 ml
1 x 50 ml vial
250 mg/50 ml

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Intravenous use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

WARNING: Cytotoxic agent, special handling instructions (see package leaflet).

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Stable for up to 8 hours at up to 30ºC once the vial is opened.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Sandoz Pharmaceuticals d.d.
Verovškova ulica 57
1000 Ljubljana
Slovenia

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/07/403/001	6 x 50 ml vials
EU/1/07/403/002	1 x 50 ml vial

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Justification for not including Braille accepted

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

PARTICULARS TO APPEAR ON THE IMMEDIATE PACKAGING

VIAL LABEL

1. NAME OF THE MEDICINAL PRODUCT

Atriance 5 mg/ml solution for infusion
nelarabine

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each ml contains 5 mg of nelarabine.

3. LIST OF EXCIPIENTS

Excipients: Sodium chloride, water for injections, hydrochloric acid, sodium hydroxide.

4. PHARMACEUTICAL FORM AND CONTENTS

Solution for infusion

250 mg/50 ml

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Intravenous use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

Cytotoxic

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Sandoz Pharmaceuticals d.d.

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/07/403/001	6 x 50 ml vials
EU/1/07/403/002	1 x 50 ml vial

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Justification for not including Braille accepted

17. UNIQUE IDENTIFIER – 2D BARCODE

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

B. PACKAGE LEAFLET

Package leaflet: Information for the patient

Atriance 5 mg/ml solution for infusion

nelarabine

▼This medicine is subject to additional monitoring. This will allow quick identification of new safety information. You can help by reporting any side effects you may get. See the end of section 4 for how to report side effects.

Read all of this leaflet carefully before you start using this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet:

1. What Atriance is and what it is used for
2. What you need to know before you are given Atriance
3. How Atriance is given
4. Possible side effects
5. How to store Atriance
6. Contents of the pack and other information

1. What Atriance is and what it is used for

Atriance contains nelarabine which belongs to a group of medicines known as *antineoplastic agents,* used in chemotherapy to kill some types of cancer cells.

Atriance is used to treat patients with:
- a type of leukaemia, called T-cell acute lymphoblastic leukaemia. Leukaemia causes an abnormal increase in the number of white blood cells. The abnormal high number of white blood cells can appear in the blood and other parts of the body. The type of leukaemia relates to the type of white blood cell mainly involved. In this case, its cells are called lymphoblasts.
- a type of lymphoma, called T-cell lymphoblastic lymphoma. This lymphoma is caused by a mass of lymphoblasts, a type of white blood cell.

If you have any questions about your illness, talk to your doctor

2. What you need to know before you are given Atriance

You (or your child, if he/she is being treated) must not receive Atriance
- if you (or your child, if he/she is being treated) are allergic to nelarabine or any of the other ingredients of this medicine (listed in section 6).

Warnings and precautions
Severe nervous system side effects have been reported with the use of Atriance. Symptoms may be mental (e.g. tiredness) or physical (e.g. convulsions, feelings of numbness or tingling, weakness and paralysis). **Your doctor will check for these symptoms regularly during treatment (see also section 4, "Possible side effects").**

Your doctor also needs to know the following before you are given this medicine:
- **if you (or your child, if he/she is being treated) have any kidney or liver problems**. Your dose of Atriance may need to be adjusted.
- **if you (or your child, if he/she is being treated) have recently been, or plan to be vaccinated** with a live vaccine (for example polio, varicella, typhoid).
- **if you (or your child, if he/she is being treated) have any blood problems** (for example anaemia).

Blood tests during treatment
Your doctor should perform blood tests regularly during treatment to check for blood problems that have been associated with the use of Atriance.

Elderly
If you are an elderly person, you could be more sensitive to nervous system side effects (see the list above under "Warnings and precautions"). Your doctor will check for these symptoms regularly during treatment.

Tell your doctor if any of these apply to you.

Other medicines and Atriance
Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines**.** This includes any herbal products or medicines you have bought without a prescription

Remember to tell your doctor if you start to take any other medicines while you are on Atriance.

Pregnancy, breast-feeding and fertility
Atriance is not recommended for pregnant women. It may harm a baby if conceived before, during or soon after treatment. Consideration to appropriate birth control is recommended to be discussed with your doctor. Do not try and become pregnant/father a child until your doctor advises you it is safe to do so.

Male patients, who may wish to father a child, should ask their doctor for family planning advice or treatment. If pregnancy occurs during treatment with Atriance, you must tell your doctor immediately.

It is not known whether Atriance is passed on through breast milk. Breast-feeding must be discontinued while you are taking Atriance. Ask your doctor for advice before taking any medicine.

Driving and using machines
Atriance can make people feel drowsy or sleepy, both during and for some days after treatment. If you feel tired or weak, do not drive, and do not use any tools or machines.

Atriance contains sodium
This medicine contains 88.51 mg (3.85 mmol) sodium (main component of cooking/table salt) per vial (50 ml). This is equivalent to 4.4% of the recommended maximum daily dietary intake of sodium for an adult.

3. How Atriance is given

The dose of Atriance you are given will be based on:
- **your/your child's (if he/she is being treated) body surface area** (which will be calculated by your doctor based on your height and weight).
- **the results of blood tests** carried out before treatment

Adults and adolescents (aged 16 years and older)
The usual dose is 1,500 mg/m^2 of body surface area per day.

A doctor or nurse will give you the dose of Atriance as an infusion (a drip). It is usually dripped into your arm over a period of about 2 hours.

You will have an infusion (a drip) once a day on days 1, 3 and 5 of treatment. This pattern of treatment will normally be repeated every three weeks. This treatment may vary, depending on the results of your regular blood tests. Your doctor will decide how many treatment cycles are required.

Children and adolescents (aged 21 years and younger)
The recommended dose is 650 mg/m^2 of body surface area per day.

A doctor or nurse will give you/your child (if he/she is being treated) a suitable dose of Atriance as an infusion (a drip). It is usually dripped into your arm over a period of about 1 hour.

You/your child (if he/she is being treated) will have an infusion (a drip) once a day for 5 days. This pattern of treatment will normally be repeated every three weeks. This treatment may vary, depending on the results of regular blood tests. Your doctor will decide how many treatment cycles are required.

Stopping treatment with Atriance
Your doctor will decide when to stop the treatment.

If you have any further questions on the use of this medicine, ask your doctor or pharmacist.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

The majority of side effects reported with Atriance were seen in adults, children and adolescents. Some of the side effects were reported more often in adult patients. There is no known reason for this.

If you have any concerns, discuss them with your doctor.

Most serious side effects

These may affect **more than 1 in 10 people** treated with Atriance.
- **Signs of infection**. Atriance may reduce the number of white blood cells and lower your resistance to infection (including pneumonia). This can even be life threatening. Signs of an infection include:
  - fever
  - serious deterioration of your general condition
  - local symptoms such as sore throat, sore mouth or urinary problems (for example, a burning sensation when urinating, which may be a urinary infection)

Tell your doctor immediately if you get any of these. A blood test will be taken to check possible reduction of white blood cells.

Other very common side effects
These may affect **more than 1 in 10 people** treated with Atriance
- Changes in the sense of feeling in hands or feet, muscle weakness appearing as difficulty getting up from a chair, or difficulty walking (*peripheral neuropathy*); reduced sensitivity to light touch, or pain; abnormal sensations such as burning and, prickling, a sensation of something crawling on the skin.
- Feeling generally weak and tired (*temporary anaemia*). In some cases you may need a blood transfusion.
- Unusual bruising or bleeding, caused by a decrease in the number of clotting cells in the blood. This can lead to severe bleeding from relatively small injuries such as a small cut. Rarely, it can lead to even more severe bleeding (*haemorrhage*). Talk to your doctor for advice on how to

minimize the risk of bleeding.
- Feeling drowsy and sleepy; headache; dizziness.
- Shortness of breath, difficult or laboured breathing; cough.
- Feeling of an upset stomach (*nausea*); being sick/throwing up (*vomiting*); diarrhoea; constipation
- Muscle pain.
- Swelling of parts of the body due to accumulation of abnormal amounts of fluid (*oedema*).
- High body temperature (*fever*); tiredness; feeling weak/loss of strength.

Tell a doctor if any of these becomes troublesome.

Common side effects

These may affect **up to 1 in 10 people** treated with Atriance:
- Violent, uncontrollable muscular contractions often accompanied by unconsciousness that can be due to an epileptic attack (*seizures*).
- Clumsiness and lack of coordination affecting balance, walking, limb or eye movements, or speech.
- Unintentional rhythmic shaking of one or more limbs (*tremors*).
- Muscle weakness (possibly associated with *peripheral neuropathy* – see above), joint pain, back pain; pains in hands and feet including a sensation of pins and needles sensation and numbness.
- Lowered blood pressure.
- Weight loss and loss of appetite (*anorexia*); stomach pains; sore mouth, mouth ulcers or inflammation.
- Problems with memory, feeling disoriented; blurred vision; altered or loss of sense of taste (*dysgeusia*).
- Build up of fluid around the lungs leading to chest pain and difficulty in breathing (*pleural effusion*); wheezing
- Increased amounts of bilirubin in your blood, which may cause yellowing of the skin and may make you feel lethargic.
- Increases in blood levels of liver enzymes.
- Increases in blood creatinine levels (a sign of kidney problems, which might lead less frequent urination).
- The release of tumour cell contents (*tumour lysis syndrome*), which may put extra stress on your body. Initial symptoms including nausea and vomiting, shortness of breath, an irregular heartbeat, clouding of urine, lethargy and/or joint discomfort. If this does occur, it is most likely to occur at the first dose. Your doctor will take appropriate precautions to minimise the risk of this.
- Low blood levels of some substances:
  - low calcium levels, which may cause muscle cramps, abdominal cramps or spasms
  - low magnesium levels, which may cause muscle weakness, confusion, "jerky" movements, high blood pressure, irregular heart rhythms and decreased reflexes with severely low blood magnesium levels.
  - low potassium levels may cause a feeling of weakness
  - low glucose levels, which may cause nausea, sweating, weakness, faintness, confusion or hallucinations.

Tell a doctor if any of these becomes troublesome.

Rare side effects

These may affect **up to 1 in 1,000 people** treated with Atriance
- Serious disease that destroys skeletal muscle characterized by the presence of myoglobin (a breakdown product of muscle cells) in the urine (*Rhabdomyolysis*), increase in blood creatine phosphokinase.

Tell a doctor if any of these becomes troublesome.

Reporting of side effects
If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects

not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Atriance

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the carton and vial.

This medicine does not require any special storage conditions.

Atriance is stable for up to 8 hours at up to 30°C once the vial is opened.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What Atriance contains
- The active substance is nelarabine. Each ml of Atriance solution for infusion contains 5 mg of nelarabine. Each vial contains 250 mg of nelarabine.
- The other ingredients are sodium chloride, water for injections, hydrochloric acid, sodium hydroxide (see section 2 “Atriance contains sodium”).

What Atriance looks like and contents of the pack
Atriance solution for infusion is a clear, colourless solution. It is provided in clear glass vials with a rubber stopper and sealed with an aluminium cap.

Each vial contains 50 ml.

Atriance is supplied in packs of 1 vial or 6 vials.

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This leaflet was last approved in

This medicine has been authorised under “exceptional circumstances”. This means that because of the rarity of this disease it has been impossible to get complete information on this medicine.
The European Medicines Agency will review any new information on the medicine every year and this leaflet will be updated as necessary.

Detailed information on this medicine is available on the European Medicines Agency web site: http://www.ema.europa.eu. There are also links to other websites about rare diseases and treatments.

The following information is intended for medical or healthcare professionals only:

INSTRUCTIONS ON HOW TO STORE AND DISPOSE OF ATRIANCE

Storage of Atriance solution for infusion

This medicinal product does not require any special storage conditions.

Atriance is stable for up to 8 hours at up to 30ºC once the vial is opened.

Instructions for handling and disposal of Atriance

The normal procedures for proper handling and disposal of anti-tumour medicinal products should be adopted, namely:

- Staff should be trained in how to handle and transfer the medicinal product.
- Pregnant staff should be excluded from working with this medicinal product.
- Personnel handling this medicinal product during handling/transfer should wear protective clothing including mask, goggles and gloves.
- All items for administration or cleaning, including gloves, should be placed in high-risk, waste disposal bags for high-temperature incineration. Any liquid waste from the preparation of the nelarabine solution for infusion may be flushed with large amounts of water.
- Accidental contact with the skin or eyes should be treated immediately with copious amounts of water.