Atriance 5 mg/ml solution for infusion

Summary of Product Characteristics Updated 20-May-2015 | Novartis Pharmaceuticals UK Ltd

▼ 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 1.725 mg (75 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 is for intravenous use only and must only be administered under the supervision of a physician experienced in the use of cytotoxic agents.

Posology

Patients receiving nelarabine are recommended to receive intravenous hydration according to standard medical practice for the management of hyperuricaemia in patients at risk for tumour lysis syndrome. For patients at risk of hyperuricaemia, the use of allopurinol should be considered (see section 4.4).

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 is 1,500 mg/m^2 administered intravenously over two hours on days 1, 3 and 5 and repeated every 21 days.

Paediatric population

Children and adolescents (aged 21 years and younger)

The recommended dose of nelarabine for children and adolescents 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.

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 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, central nervous system effects including convulsions, and peripheral neuropathy 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.

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.

Neurotoxicity is the dose-limiting toxicity of nelarabine. It is advised that patients undergoing therapy with nelarabine be closely observed for signs and symptoms of neurological toxicity.

Common signs and symptoms of nelarabine-related neurotoxicity include somnolence, confusion, convulsions, ataxia, paraesthesias, and hypoesthesia. Severe neurological toxicity can manifest as coma, status epilepticus, demyelination, or ascending neuropathy similar in appearance to Guillain-Barré syndrome (see section 4.8).

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 aged 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 1.725 mg/ml (75 micromols) of sodium. To be taken into consideration by patients on a controlled sodium diet.

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 and for at least three months following cessation of treatment.

Pregnancy

There are no adequate data from the use of nelarabine in pregnant women.

Studies in animals have shown reproductive toxicity including malformations (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.

Breastfeeding

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.

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

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. 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 trials 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; 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) and Very rare (< 1/10,000), not known (cannot be estimated from the available data)

Adverse events(s)	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 and malignant (including cysts and polyps)		
Tumour lysis syndrome (see also	Common: 1 (1)	N/A

Data from compassionate use programme and non-pivotal studies)		
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)
Paresthesia	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 administrative 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.

One subject in the paediatric group had a fatal neurological event of status epilepticus.

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

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. 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

The following adverse reactions have been identified during post-approval use of nelarabine. This includes spontaneous case reports as well as serious adverse events from ongoing studies.

Musculoskeletal and connective tissue disorders

Rare Rhabdomyolysis, blood creatine phosphokinase increased

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 Yellow Card Scheme at: www.mhra.gov.uk/yellowcard.

4.9 Overdose

No case of overdose has been reported.

Nelarabine has been administered in clinical trials 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 studies

Adult studies

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 studies

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 ef ect 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 treatment with nelarabine daily during 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

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

Clear glass (Type I) vials with a bromobutyl rubber stopper, sealed with an aluminium cap.

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

6.6 Special precautions for disposal and other handling

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.

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

7. Marketing authorisation holder

Novartis Europharm Limited

Frimley Business Park

Camberley GU16 7SR

United Kingdom

8. Marketing authorisation number(s)

EU/1/07/403/001

9. Date of first authorisation/renewal of the authorisation

Date of first authorisation: 22 August 2007

Date of latest renewal: 18 June 2012

10. Date of revision of the text

24 April 2015

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

Legal category:

POM

Company Contact Details

Novartis Pharmaceuticals UK Ltd

Address
Frimley Business Park, Frimley, Camberley, Surrey, GU16 7SR

Fax
+44 (0)1276 698 449

Medical Information e-mail
medinfo.uk@novartis.com

Telephone
+44 (0)1276 692 255

Medical Information Direct Line
+44 (0)1276 698 370

Customer Care direct line
+44 (0)845 741 9442