PRODUCT MONOGRAPH

PrATRIANCE®

Nelarabine Injection

5 mg/mL

Antineoplastic Agent

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PrATRIANCE®

Nelarabine Injection

PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	Clinically Relevant Nonmedicinal Ingredients
Intravenous infusion	Injection 5 mg/mL	Not applicable. *For a complete listing see Dosage Forms, Composition and Packaging section.*

INDICATIONS AND CLINICAL USE

ATRIANCE® (nelarabine) is indicated for the treatment of patients with T-cell acute lymphoblastic leukemia and T-cell lymphoblastic lymphoma whose disease has not responded to or has relapsed following treatment with at least two chemotherapy regimens.

CONTRAINDICATIONS

ATRIANCE (nelarabine) is contraindicated in patients who have a history of hypersensitivity to nelarabine or any other component of ATRIANCE.

WARNINGS AND PRECAUTIONS

Serious Warnings and Precautions

ATRIANCE (nelarabine) Injection should be administered under the supervision of a physician experienced in the use of cancer chemotherapeutic agents. This product is for intravenous use only.

Severe Neurologic Events:
These events included:

- Altered mental states including severe somnolence
- Central nervous system effects including convulsions and spinal cord necrosis. Patients with pre-existing CNS disease or patients treated previously or concurrently with intrathecal chemotherapy (including methotrexate) or previously with craniospinal irradiation may be at increased risk of more severe (≥ Grade 3) neurologic events (see WARNINGS AND PRECAUTIONS, DOSAGE and ADMINISTRATION, and DRUG INTERACTIONS).
- Peripheral neuropathy including numbness, paresthesias, motor weakness, paralysis, craniospinal demyelination, and ascending peripheral neuropathies similar to Guillain-Barré syndrome

Some of these neurologic adverse events are irreversible and fatal.

ATRIANCE should be discontinued at the first sign of neurologic events of NCI Common Toxicity Criteria grade 2 or greater (See WARNINGS and PRECAUTIONS, Neurologic, ADVERSE REACTIONS, DOSAGE and ADMINISTRATION, Recommended Dose and Dosage Adjustment).

Close monitoring for neurological events is strongly recommended.

General

Patients receiving ATRIANCE should receive intravenous hydration according to standard medical practice for the management of hyperuricemia in patients at risk for tumour lysis syndrome. Consideration should be given to the use of allopurinol in patients at risk of hyperuricemia (See Dosage and Administration section).

Administration of live vaccines to immunocompromised patients should be avoided.

Cardiovascular

The effect of nelarabine on QT interval prolongation has not been investigated.

Carcinogenesis and Mutagenesis

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

Hematologic

Leukopenia, thrombocytopenia, anemia (including Grade 3 and 4), and neutropenia, including febrile neutropenia (Grade 3 or 4) have been associated with nelarabine therapy. Complete blood counts including platelets should be monitored regularly (see ADVERSE REACTIONS, and DOSAGE AND ADMINISTRATION).

Hepatobiliary

In clinical trials, Grade 3 and 4 elevations in transaminases and bilirubin have occurred. In the post-marketing setting, cases of acute hepatic failure (including fatal toxic hepatitis) have been reported although causality has not been established.

Musculoskeletal

Nelarabine is associated with cases of rhabdomyolysis and creatine phosphokinase increased. Discontinuation of nelarabine therapy should be considered if rhabdomyolysis and creatine phosphokinase increased is suspected to be associated with the use of nelarabine.

Neurologic

Neurotoxicity is the dose-limiting toxicity of nelarabine. Patients undergoing therapy with ATRIANCE should be closely observed for signs and symptoms of neurologic toxicity.

Some of these neurologic adverse events are irreversible and fatal.

ATRIANCE should be discontinued at the first sign of neurologic events of NCI Common Toxicity Criteria grade 2 or greater. (See SERIOUS WARNINGS AND PRECAUTIONS, ADVERSE REACTIONS, DOSAGE and ADMINISTRATION, Recommended Dose and Dosage Adjustment).

Close monitoring for neurological events is strongly recommended.

Patients treated previously or concurrently with intrathecal chemotherapy or previously with craniospinal irradiation may be at increased risk for neurologic adverse events (see DOSAGE AND ADMINISTRATION). Case reports describing fatal neurologic outcomes following concurrent intrathecal chemotherapy and intravenous nelarabine have been received (see DRUG INTERACTIONS). The optimal schedule of concurrently administered nelarabine with intrathecal therapy and/or craniospinal irradiation has not been studied and is therefore not recommended. Patients with CNS disease at baseline may have an increased risk of experiencing more severe (grade ≥ 3) neurological events.

Common signs and symptoms of nelarabine-related neurotoxicity include somnolence, confusion, altered level of consciousness, convulsions, ataxia, paraesthesias and hypoesthesia. Severe neurologic toxicity can manifest as coma, status epilepticus, myelopathy, craniospinal demyelination, or ascending neuropathy similar in presentation to Guillain-Barré syndrome (see ADVERSE REACTIONS).

No studies on the effects of nelarabine on the ability to drive and operate machines have been performed. Patients experiencing somnolence, dizziness, neurologic disorders, or any other undesirable effects with a potential impact on the ability to safely drive or use machines should refrain from these activities as long as these undesirable effects persist (see ADVERSE REACTIONS, DRUG INTERACTIONS, Drug-Lifestyle Interactions).

Sexual Function/Reproduction

The effects of nelarabine on human fertility are not known (see Part II, TOXICOLOGY).

Special Populations

Pregnant Women: ATRIANCE may cause fetal harm when administered to a pregnant woman. There are no studies of ATRIANCE in pregnant women. Animal studies have reported increased incidences of fetal malformations and abnormalities following administration of nelarabine during pregnancy compared to controls (see Part II, TOXICOLOGY). One case of pregnancy was reported in a clinical trial with the outcome of fetal death. Causality could not be established due to the fact that the patient received multiple other chemotherapeutic drugs which can contribute to this outcome.

If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be warned of the potential hazard to the fetus.

Females of Childbearing Potential:

Females of childbearing potential (i.e. females who are menstruating or who are physiologically capable of becoming pregnant) should be advised to avoid becoming pregnant during treatment with ATRIANCE.

Females of childbearing potential must be advised to use highly effective contraception while receiving ATRIANCE. Highly effective contraception is a method of birth control which, when used alone or in combination, results in a low failure rate (i.e. less than 1% per year) when used consistently and correctly.

There are no clinical data on drug-drug interaction between ATRIANCE and hormonal contraceptives. The effect of ATRIANCE on hormonal contraceptives in humans is not known.

Male Patients:

Sexually active male patients must use highly effective contraception during treatment with ATRIANCE.

Male patients with partners who are pregnant, possibly pregnant, or who could become pregnant should use condoms during sexual intercourse while receiving ATRIANCE and for 3 months following completion of therapy.

Male patients must be advised to inform their female sexual partners that they are taking ATRIANCE. Male patients must also advise their female partners of the potential serious risks to a developing fetus should pregnancy occur during her partner's treatment with ATRIANCE (See TOXICOLOGY).

Nursing Women: Nelarabine is a pro-drug of the deoxyguanosine analogue 9-β-*D*-arabinofuranosylguanine (ara-G) (see ACTION AND CLINICAL PHARMACOLOGY). It is not known whether nelarabine or ara-G is excreted in human milk. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from ATRIANCE, it is recommended that nursing be discontinued in women who are receiving therapy with ATRIANCE.

Pediatrics: In a phase III study including 685 patients aged < 16 with newly diagnosed T-ALL or T-LBL, the safety profile was consistent with that seen in the Phase I and Phase II studies. See Part II, CLINICAL TRIALS.

Nelarabine pharmacology has not been studied in children under four years of age.

Geriatrics (65 years or older): Clinical studies of ATRIANCE did not include sufficient numbers of patients aged 65 and over to determine whether they respond differently than younger patients. In an exploratory analysis, increasing age, especially aged 65 years and older, appeared to be associated with increased rates of neurologic adverse events.

Renally Impaired Patients: Nelarabine has not been studied in individuals with renal impairment. Nelarabine and ara-G are partially renally excreted. Because the risk of adverse reactions to this drug may be greater in patients with decreased renal function (CrCl <50 mL/min), these patients should be closely monitored for toxicities when treated with ATRIANCE (see DOSAGE AND ADMINISTRATION).

Hepatically Impaired Patients: The influence of hepatic impairment on the pharmacokinetics of nelarabine has not been evaluated. Because the risk of adverse reactions to this drug may be greater in patients with severe hepatic impairment, these patients should be closely monitored for toxicities when treated with ATRIANCE.

ADVERSE REACTIONS

Clinical Trial Adverse Drug Reactions

Relapsed or Refractory T-ALL and T-LBL

Adults: ATRIANCE (nelarabine) was studied in 459 patients in Phase I and Phase II clinical trials. The safety profile for the recommended dosages of ATRIANCE is based on data from 103 adult patients enrolled and treated in the CALGB19801 Study and an adult chronic lymphocytic leukemia study (PGAA2003) who were treated with the recommended dose and schedule.

Pediatrics: The safety profile for children is based on data from 84 pediatric patients enrolled and treated in the COGP9673 study who were treated with the recommended dose and schedule. The most common adverse events in pediatric patients, regardless of causality, were hematologic disorders (anemia, leukopenia, neutropenia and thrombocytopenia). Of the non-hematologic adverse events in pediatric patients, the most frequent events reported were headache, increased transaminase levels, decreased blood potassium, decreased blood albumin, increased blood bilirubin and vomiting.

The most common adverse events in adults, regardless of causality, were fatigue; gastrointestinal (GI) disorders (nausea, diarrhea, vomiting, and constipation); hematologic disorders (severe anemia, leukopenia, neutropenia and thrombocytopenia); respiratory disorders (cough and dyspnea); nervous system disorders (somnolence and dizziness); and pyrexia.

The most common adverse events by System Organ Class, regardless of causality, including severe or life threatening events (NCI Common Toxicity Criteria grade 3 or grade 4) and fatal events (grade 5) are shown in Table 1 for pediatric patients and Table 2 for adult patients.

Table 1 Most Commonly Reported (≥5% Overall) Adverse Events Regardless of Causality in PEDIATRIC Patients Treated with 650 mg/m^2 of ATRIANCE Administered Intravenously Over 1 Hour Daily for 5 Consecutive Days Repeated Every 21 Days

	Percentage of Patients: 650 mg/m^2; N = 84		
	Toxicity Grade		
System Organ Class Preferred Term	Grade 3 %	Grade 4+ %	All Grades %
Blood and Lymphatic System Disorders			
Anemia	45	10	95
Neutropenia	17	62	94
Thrombocytopenia	27	32	88
Leukopenia	14	7	38
Hepatobiliary Disorders			
Transaminases increased	4	0	12
Blood albumin decreased	5	1	10
Blood bilirubin increased	7	2	10
Metabolic/Laboratory			
Blood potassium decreased	4	2	11
Blood calcium decreased	1	1	8
Blood creatinine increased	0	0	6
Blood glucose decreased	4	0	6
Blood magnesium decreased	2	0	6
Nervous System Disorders (see Table 3)			
Gastrointestinal Disorders			
Vomiting	0	0	10
General Disorders & Administration Site Conditions			
Asthenia	1	0	6
Infections & Infestations			
Infection	2	1	5

Grade 4+ = Grade 4 and Grade 5

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 ATRIANCE. All other fatal events were unrelated to treatment with ATRIANCE.

Table 2 Most Commonly Reported (≥5% Overall) Adverse Events Regardless of Causality in ADULT Patients Treated with 1,500 mg/m^2 of ATRIANCE Administered Intravenously Over 2 Hours on Days 1, 3, and 5 Repeated Every 21 Days

	Percentage of Patients; N = 103		
	Toxicity Grade		
System Organ Class **Preferred Term**	**Grade 3** **%**	**Grade 4+** **%**	**All Grades** **%**
Blood and Lymphatic System Disorders			
Anemia	20	14	99
Thrombocytopenia	37	22	86
Neutropenia	14	49	81
Febrile neutropenia	9	1	12
Cardiac Disorders			
Sinus tachycardia	1	0	8
Gastrointestinal Disorders			
Nausea	0	0	41
Diarrhea	1	0	22
Vomiting	1	0	22
Constipation	1	0	21
Abdominal pain	1	0	9
Stomatitis	1	0	8
Abdominal distension	0	0	6
General Disorders and Administration Site Conditions			
Fatigue	10	2	50
Pyrexia	5	0	23
Asthenia	0	1	17
Edema, peripheral	0	0	15
Edema	0	0	11
Pain	3	0	11
Rigors	0	0	8
Gait, abnormal	0	0	6
Chest pain	0	0	5
Non-cardiac chest pain	0	1	5
Infections			

System Organ Class Preferred Term	Percentage of Patients; N = 103 Toxicity Grade Grade 3 %	Grade 4+ %	All Grades %
Infection	2	1	9
Pneumonia	4	1	8
Hepatobiliary Disorders			
AST increased	1	1	6
Blood bilirubin increased	2	0	3
Metabolism and Nutrition Disorders			
Anorexia	0	0	9
Dehydration	3	1	7
Hyperglycemia	1	0	6
Musculoskeletal and Connective Tissue Disorders			
Myalgia	1	0	13
Arthralgia	1	0	9
Back pain	0	0	8
Muscular weakness	5	0	8
Pain in extremity	1	0	7
Nervous System Disorders (see Table 4)			
Psychiatric Disorders			
Confusional state	2	0	8
Insomnia	0	0	7
Depression	1	0	6
Respiratory, Thoracic, and Mediastinal Disorders			
Cough	0	0	25
Dyspnea	4	2	20
Pleural effusion	5	1	10
Epistaxis	0	0	8
Dyspnea, exertional	0	0	7
Wheezing	0	0	5
Vascular Disorders			
Petechiae	2	0	12
Hypotension	1	1	8

Grade 4+ = Grade 4 and Grade 5

Five (5) patients had a fatal event. Fatal events included hypotension (n = 1), respiratory arrest (n = 1), pleural effusion/pneumothorax (n = 1), pneumonia (n = 1), and cerebral hemorrhage/coma/ leukoencephalopathy (n = 1). The cerebral hemorrhage/coma/leukoencephalopathy was thought to be related to treatment with ATRIANCE. All other fatal events were unrelated to treatment with ATRIANCE.

Other Adverse Events: Blurred vision was also reported in 4% of adult patients. There was a single report of biopsy confirmed progressive multifocal leukoencephalopathy in the adult patient population. Blindness unilateral was reported in 1% of adult patients. Reduced visual acuity was reported in 2% of adult patients and visual disturbance was reported in 1% of adult patients. Grade 3, Grade 4 and Grade 5 ALT increases have been reported in 1% of adults. Hallucination was reported in 1% of adult patients. In addition to the safety data from the pivotal clinical trials, tumour lysis syndrome has been observed (see WARNINGS and PRECAUTIONS, General). Infection (including but not limited to; sepsis, bacteremia, pneumonia, fungal infection) were reported in adult patients and pediatric patients in clinical trials. There have been reports of sometimes fatal opportunistic infections in patients receiving nelarabine therapy.

Neurologic Adverse Events: Nervous system events, regardless of drug relationship, were reported for 64% of patients across the Phase I and Phase II studies.

Most patients in clinical studies with ATRIANCE had no apparent CNS involvement of their disease at the time of therapy initiation with ATRIANCE. However, in an exploratory analysis of 459 nelarabine treated patients across multiple dose levels and regimens, the presence of CNS involvement with malignancy at baseline was associated with an increased risk (odds ratio 3.35 in regression analysis, $p = 0.0002$) of grade ≥ 3 neurologic toxicity during therapy with ATRIANCE.

Pediatric: The most common neurologic adverse events regardless of causality, including all grades (NCI Common Toxicity Criteria) are shown in Table 3 for pediatric patients.

Table 3 **Neurologic Adverse Events (≥1%) Regardless of Causality in PEDIATRIC Patients Treated with 650 mg/m^2 of ATRIANCE Administered Intravenously Over 1 Hour Daily for 5 Consecutive Days Repeated Every 21 Days**

	Percentage of Patients; N = 84				
Nervous System Disorders Preferred Term	**Grade 1 %**	**Grade 2 %**	**Grade 3 %**	**Grade 4+ %**	**All Grades %**
Headache	8	2	4	2	17
Peripheral neurologic disorders, any event	1	4	7	0	12
Peripheral neuropathy	0	4	2	0	6
Peripheral motor neuropathy	1	0	2	0	4
Peripheral sensory neuropathy	0	0	6	0	6
Somnolence	1	4	1	1	7
Hypoesthesia	1	1	4	0	6
Seizures	0	0	0	6	6
Convulsions	0	0	0	3	4
Grand mal convulsions	0	0	0	1	1
Status epilepticus	0	0	0	1	1
Motor dysfunction	1	1	1	0	4
Nervous system disorder	1	2	0	0	4
Paresthesia	0	2	1	0	4

Table 3 **Neurologic Adverse Events (≥1%) Regardless of Causality in PEDIATRIC Patients Treated with 650 mg/m^2 of ATRIANCE Administered Intravenously Over 1 Hour Daily for 5 Consecutive Days Repeated Every 21 Days**

	Percentage of Patients; N = 84				
Nervous System Disorders Preferred Term	**Grade 1 %**	**Grade 2 %**	**Grade 3 %**	**Grade 4+ %**	**All Grades %**
Tremor	1	2	0	0	4
Ataxia	1	0	1	0	2

Grade 4+ = Grade 4 and Grade 5
One (1) patient had a fatal neurologic event, status epilepticus. This event was thought to be related to treatment with ATRIANCE.

The other grade 3 event in pediatric patients, regardless of causality, was hypertonia reported in 1 patient (1%). The additional grade 4+ events, regardless of causality, were 3rd nerve paralysis, and 6th nerve paralysis, each reported in 1 patient (1%).

The other neurologic adverse events, regardless of causality, reported as grade 1, 2, or unknown in pediatric patients were dysarthria, encephalopathy, hydrocephalus, hyporeflexia, lethargy, mental impairment, paralysis, and sensory loss, each reported in 1 patient (1%).

Adults: The most common neurologic adverse events, regardless of causality, including all grades (NCI Common Toxicity Criteria) are shown in Table 4 for adult patients.

Table 4 **Neurologic Adverse Events (≥1%) Regardless of Causality in ADULT Patients Treated with 1,500 mg/m^2 of ATRIANCE Administered Intravenously Over 2 Hours on Days 1, 3, and 5 Repeated Every 21 Days**

	Percentage of Patients; N =103				
System Organ Class Preferred Term	**Grade 1 %**	**Grade 2 %**	**Grade 3 %**	**Grade 4 %**	**All Grades %**
Somnolence	20	3	0	0	23
Dizziness	14	8	0	0	21
Peripheral neurologic disorders, any event	8	12	2	0	21
Neuropathy	0	4	0	0	4
Peripheral neuropathy	2	2	1	0	5
Peripheral motor neuropathy	3	3	1	0	7
Peripheral sensory neuropathy	7	6	0	0	13
Hypoesthesia	5	10	2	0	17
Headache	11	3	1	0	15
Paresthesia	11	4	0	0	15
Ataxia	1	6	2	0	9

Table 4 Neurologic Adverse Events (≥1%) Regardless of Causality in ADULT Patients Treated with 1,500 mg/m^2 of ATRIANCE Administered Intravenously Over 2 Hours on Days 1, 3, and 5 Repeated Every 21 Days

	Percentage of Patients; N =103				
System Organ Class **Preferred Term**	**Grade 1** **%**	**Grade 2** **%**	**Grade 3** **%**	**Grade 4** **%**	**All Grades** **%**
Depressed level of consciousness	4	1	0	1	6
Tremor	2	3	0	0	5
Amnesia	2	1	0	0	3
Dysgeusia	2	1	0	0	3
Balance disorder	1	1	0	0	2
Sensory loss	0	2	0	0	2

One (1) patient had a fatal neurologic event, cerebral hemorrhage/coma/leukoencephalopathy. This event was thought to be related to treatment with ATRIANCE.

Most nervous system events in the adult patients were evaluated as grade 1 or 2. The additional grade 3 events in adult patients, regardless of causality, were aphasia, convulsion, hemiparesis, and loss of consciousness, each reported in 1 patient (1%). The additional grade 4 events, regardless of causality, were cerebral hemorrhage, coma, intracranial hemorrhage, leukoencephalopathy, and metabolic encephalopathy, each reported in one patient (1%).

The other neurologic adverse events, regardless of causality, reported as grade 1, 2, or unknown in adult patients were abnormal coordination, burning sensation, disturbance in attention, dysarthria, hyporeflexia, neuropathic pain, nystagmus, peroneal nerve palsy, sciatica, sensory disturbance, sinus headache, and speech disorder, each reported in one patient (1%).

Other Neurologic Events: There have also been reports of events associated with demyelination and ascending peripheral neuropathies similar in appearance to Guillain-Barré syndrome.

Supportive Data in Newly Diagnosed T-ALL and T-LBL

Adults and pediatrics: ATRIANCE (nelarabine) was studied in newly diagnosed patients with T-ALL and T-LBL in a Phase III clinical trial.

In this Phase III clinical study of patients between 1 and 30 years of age (N=825) with newly diagnosed T-ALL or T-LBL, patients received augmented Berlin-Frankfurt-Münster regimen (aBFM) with or without nelarabine. The safety profile of the treatment groups was consistent with that known for the individual medicinal products. The addition of nelarabine to the aBFM chemotherapy regimen in the T-ALL and T-LBL populations did not significantly alter the safety profile of the aBFM chemotherapy regimen.

Post-Market Adverse Drug Reactions

The following adverse events have been reported from worldwide marketing experience with Nelarabine. Because these events are reported voluntarily from a population of uncertain size, are associated with concomitant diseases and multiple drug therapies, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure. Decisions to include these events in labeling are typically based on one or more of the following factors: (1) seriousness of the event, (2) frequency of the reporting, or (3) strength of causal connection to the drug:

Nervous system: Several cases of serious spinal cord disorders including myelopathy, spinal cord ischaemia and myelitis transverse have been reported. These events presented with symptoms including leg weakness, numbness, quadriplegia, fecal incontinence and urinary incontinence.

Cases of leukoencephalopathy have been reported.

Musculoskeletal: Cases of rhabdomyolysis and creatine phosphokinase increased have been reported.

Hepatobiliary: In clinical trials, Grade 3 and 4 elevations in transaminases and bilirubin have occurred. Cases of acute hepatic failure have been reported (including fatal toxic hepatitis), although causality has not been established.

DRUG INTERACTIONS

Serious Drug Interactions

Fatal neurologic outcomes following concurrent intrathecal chemotherapy and intravenous nelarabine (see SERIOUS WARNINGS AND PRECAUTIONS box, WARNINGS AND PRECAUTIONS, Neurologic).

No formal drug interaction studies have been carried out with nelarabine.

No clinical data on drug interactions between ATRIANCE and chemotherapy are available, however there are reports of fatal neurologic outcomes following nelarabine with intrathecal chemotherapy.

In one pharmacokinetic study, fludarabine administered prior to nelarabine did not affect the plasma pharmacokinetics of nelarabine and ara-G or ara-GTP (see Part II, DETAILED PHARMACOLOGY).

The involvement of cytochrome P450 enzymes in the metabolism of nelarabine has not been investigated.

There is *in vitro* evidence that pentostatin is a strong inhibitor of adenosine deaminase. This may result in a reduction in the conversion of the prodrug nelarabine to its active moiety and consequently in a reduction in efficacy of nelarabine and/or change in the adverse event profile of either drug. Therefore administration of nelarabine in combination with adenosine deaminase inhibitors, such as pentostatin, is not recommended.

There are no clinical data on drug-drug interaction between ATRIANCE and hormonal contraceptives. The effect of ATRIANCE on hormonal contraceptives in humans is not known.

Drug-Lifestyle Interactions

Effects on ability to drive and use machinery
No studies on the effects of nelarabine on the ability to drive and operate machines have been performed. Patients experiencing somnolence, dizziness, neurologic disorders, or any other undesirable effects with a potential impact on the ability to safely drive or use machines should refrain from these activities as long as these undesirable effects persist (see WARNINGS and PRECAUTIONS, ADVERSE REACTIONS).

DOSAGE AND ADMINISTRATION

Dosing Considerations
Appropriate measures (e.g. hydration, urine alkalinization, and prophylaxis with allopurinol) must be taken to prevent hyperuricemia associated with tumour lysis syndrome.

Supportive measures (e.g. antiemetic agents) and medical care (e.g. antibiotics, blood and platelet transfusions) are recommended, as clinically indicated.

Recommended Dose and Dosage Adjustment

Adults: The recommended adult dose of ATRIANCE is 1,500 mg/m²/day administered intravenously over 2 hours on days 1, 3, and 5, repeated every 21 days.

Children (15 years and younger): The recommended pediatric dose of ATRIANCE is 650 mg/m²/day administered intravenously over 1 hour on days 1 to 5, repeated every 21 days.

The optimal dosing regimen for patients between the ages of 16 and 21 years of age has not been determined.

The recommended duration of treatment has not been clearly established. In clinical trials, treatment was generally continued until there was evidence of disease progression, the patient experienced unacceptable toxicity**,** the patient became a candidate for bone marrow transplant**,** or the patient no longer continued to benefit from treatment.

The optimal schedule of concurrently administered nelarabine with intrathecal therapy and/or craniospinal irradiation has not been studied and is therefore not recommended (see

WARNINGS AND PRECAUTIONS, Neurologic; and DRUG INTERACTIONS).

ATRIANCE has not been studied in patients with hepatic or renal dysfunction. No dose adjustment is recommended for CrCl ≥ 50 mL/min. There are insufficient data to support a dose recommendation for CrCl < 50 mL/min (see ACTION AND CLINICAL PHARMACOLOGY, Renal Insufficiency).

ATRIANCE (nelarabine) should be discontinued at the first sign of neurologic events of NCI Common Toxicity Criteria grade 2 or greater. Administration of the next treatment cycle may be delayed for other toxicity including hematologic toxicity (See SERIOUS WARNINGS AND PRECAUTIONS, WARNINGS AND PRECAUTIONS, Neurologic, ADVERSE REACTIONS).

Administration

Nelarabine Injection is intended to be used without further dilution.

Nelarabine Injection is stable in polyvinylchloride (PVC) infusion bags and glass containers for up to 8 hours at up to 30°C.

ATRIANCE solution should be inspected visually before use. Do not use if solution shows haziness, particulate matter, discolouration, or leakage.

OVERDOSAGE

For management of a suspected drug overdose, contact your regional Poison Control Centre.

There is no known antidote for overdoses of ATRIANCE (nelarabine). It is anticipated that overdosage would result in severe neurotoxicity (possibly including paralysis, coma), myelosuppression, and potentially death. In the event of overdose, supportive care consistent with good clinical practice should be provided.

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 1 pediatric subject and up to a dose of 60 mg/kg (approximately 2,400 mg/m^2) daily for 5 days to 5 adult patients.

Nelarabine has been administered in clinical trials up to a dose of 2,900 mg/m^2 on days 1, 3, and 5 to 2 adult patients. At a dose of 2,200 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.

Because strategies for the management of overdose are continually evolving, it is advisable to contact a poison control center to determine the latest recommendations for the management of an overdose of any drug.

ACTION AND CLINICAL PHARMACOLOGY

Mechanism of Action

Nelarabine is a pro-drug of the deoxyguanosine analogue antimetabolite, 9-β-*D*-arabinofuranosylguanine (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. The monophosphate is subsequently converted intracellularly to the active 5'-triphosphate, ara-GTP. Accumulation of ara-GTP in leukemic cells allows for incorporation of ara-GTP into deoxyribonucleic acid (DNA) leading to inhibition of DNA synthesis which 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 leukemia or lymphoma.

Absorption: 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 plasma nelarabine and ara-G C_{max} values were 13.9 µM and 115 µM), respectively. Mean plasma nelarabine and ara-G AUC values were 13.5 µM.h and 571 µM.h, respectively, after infusion of 1500 mg/m^2. Intracellular C_{max} for ara-GTP appeared within 3 to 25 hours on Day 1. Mean intracellular ara-GTP C_{max} and AUC values were 95.6 µM and 2214 µ M.h at this dose. No pharmacokinetic data are available in pediatric patients at the once daily 650 mg/m^2 nelarabine dose.

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 in 135 patients with refractory leukemia or lymphoma in four Phase I studies. Specifically, for nelarabine, V_{ss} values were 115 L/m^2 and 89.4 L/m^2 in adult and pediatric patients, respectively. For ara-G, V_{ss}/F values were 44.8 L/m^2 and 32.1 L/m^2 in adult and pediatric patients, respectively. Nelarabine volume of distribution (V_{ss}) and ara-G V_{ss}/F were influenced by body surface area (BSA), which supports dosing based on BSA.

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.

Metabolism: 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 hydrolyzed 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: Pharmacokinetic studies in adult patients with refractory leukemia or lymphoma have demonstrated that nelarabine is rapidly eliminated from plasma with a half-life of

approximately 30 minutes. Ara-G is eliminated from plasma at a slower rate than nelarabine, with a half-life of 2.0 and 3.2 hours for pediatric and adult patients, respectively.

Combined Phase 1 pharmacokinetic data at nelarabine doses of 104 to 2900 mg/m^2 on Day 1 indicate that geometric mean clearance (CL) values for nelarabine are 138 L/h/m^2 and 125 L/h/m^2 in adult and pediatric patients, respectively, on Day 1 (n = 65 adults, n = 1 pediatric patients). The apparent clearance of ara-G (CL/F) is comparable between the two groups (9.5 L/h/m^2 in adult patients and 10.8 L/h/m^2 in pediatric patients) on Day 1. Ara-G CL/F was influenced by body surface area (BSA), which supports dosing based on BSA.

Nelarabine and ara-G are partially eliminated by the kidneys. Mean urinary excretion of nelarabine and ara-G was 5.3% and 23.2% of the administered dose, respectively, in 28 adult patients over the 24 hours after nelarabine infusion on Day 1. Renal clearance averaged 16.4 L/h for nelarabine and 4.9 L/h for ara-G in 21 adult patients. Ara-G clearance (CL/F) was influenced by baseline calculated creatinine clearance (CLcr).
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 leukemic blasts were quantifiable for a prolonged period after nelarabine administration, and the elimination half-life could not be accurately estimated. 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. There is substantial intersubject variability in nelarabine, ara-G, and intracellular ara-GTP pharmacokinetics. Intracellular ara-GTP AUC and C_{max} values were higher in patients who responded to treatment with nelarabine than in patients who did not respond. Nelarabine and ara-G exposure were not associated with response.

Special Patient Populations

Children (15 years and younger): No pharmacokinetic data are available in pediatric patients at the once daily 650 mg/m^2 nelarabine dosage. Combined Phase 1 pharmacokinetic data at nelarabine doses of 104 to 2,900 mg/m^2 on Day 1 indicate that the geometric mean clearance (CL) values for nelarabine are 138 L/h/m^2 and 125 L/h/m^2 in adult and pediatric patients, respectively, on Day 1 (n = 65 adults, n = 21 pediatric patients). The apparent clearance of ara-G (CL/F) is comparable between the two groups (9.5 L/h/m^2 in adult patients and 10.8 L/h/m^2 in pediatric patients) on Day 1.

Nelarabine and ara-G are extensively distributed throughout the body. Specifically, for nelarabine, V_{ss} values were 115 L/m^2 and 89.4 L/m^2 in adult and pediatric patients, respectively. The volume of distribution of ara-G (V_{ss}/F) is 44.8 L/m^2 and 32.1 L/m^2 in adult and pediatric patients, respectively.

Gender: The effect of gender on nelarabine and ara-G pharmacokinetics has not been specifically studied. In a pharmacokinetic/pharmacodynamic cross-study analysis, nelarabine and ara-G pharmacokinetics were not different between adult male and female patients; however,

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. There was no apparent difference in safety or efficacy parameters were observed by gender in clinical trials.

Race: The effect of race on nelarabine and ara-G pharmacokinetics has not been specifically studied. In a pharmacokinetic/pharmacodynamic cross-study analysis, race (Caucasian/other) 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 hemodialyzed 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). In a pharmacokinetic/pharmacodynamic cross-study analysis with a limited number of renally impaired patients (n = 2 with CLcr <50 mL/min), baseline calculated creatinine clearance (CLcr) was a significant predictor of ara-G apparent clearance (CL/F). The mean apparent clearance (CL/F) of ara-G was about 7% lower in patients with mild renal impairment (CLcr 50 to 80 mL/min) than in patients with normal renal function (>80 mL/min). Because the risk of adverse reactions to this drug may be greater in patients with decreased renal function (CLcr <50 mL/min), these patients should be closely monitored for toxicities when treated with ATRIANCE (see DOSAGE AND ADMINISTRATION).

Hepatic Insufficiency: The influence of hepatic impairment on the pharmacokinetics of nelarabine has not been evaluated.

Elderly (65 years or older): Nelarabine and ara-G pharmacokinetics have not been specifically studied in an elderly population. 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 WARNINGS AND PRECAUTIONS).

STORAGE AND STABILITY

Store between 15° to 30°C.

SPECIAL HANDLING INSTRUCTIONS

Caution should be used during handling, preparation and disposal of nelarabine. Use of gloves and other protective clothing to prevent skin contact is recommended. Proper aseptic technique should be used.

Guidelines on the proper handling and disposal of anticancer drugs should be consulted[1-9].

DOSAGE FORMS, COMPOSITION AND PACKAGING

ATRIANCE (nelarabine) Injection is a clear, colorless solution containing 5 mg nelarabine and 4.5 mg sodium chloride per mL in Water for Injection, USP. Hydrochloric acid and sodium hydroxide may have been used to adjust the pH. The solution pH ranges from 5.0 to 7.0.

ATRIANCE Injection is supplied in Type I, clear glass, single use vials with a gray bromobutyl rubber (latex-free) stopper and a red snap-off aluminum seal containing 250 mg nelarabine in 50 mL Water for Injection, USP.

Available in cartons of 1 single use vial and 6 single use vials.

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

Drug Substance

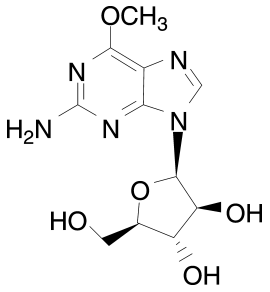
Proper name: nelarabine

Chemical name: 2-amino-9-β-*D*-arabinofuranosyl-6-methoxy-9*H*-purine

Molecular formula: $C_{11}H_{15}N_5O_5$

Molecular mass: 297.27

Structural formula:



Physicochemical properties: Nelarabine is slightly soluble to soluble in water and melts with decomposition between 209° and 217°C.

CLINICAL TRIALS

Study demographics and trial design

The safety and efficacy of ATRIANCE (nelarabine) were evaluated in three open-label, multicentre studies conducted under the sponsorship of the National Cancer Institute of the U.S. National Institutes of Health.

Pediatric clinical study in relapsed or refractory T-ALL and T-LBL

The safety and efficacy of ATRIANCE in pediatric patients were studied in a clinical trial conducted by the Children's Oncology Group (COG). This study included 151 treated patients 21 years of age and younger, 149 of whom had relapsed or refractory T-cell acute lymphoblastic leukemia (T-ALL) or T-cell lymphoblastic lymphoma (T-LBL). Eighty-four (84) patients, 39 of whom had received two or more prior induction regimens, were treated with 650 mg/m^2/day of ATRIANCE administered intravenously over 1 hour daily for 5 consecutive days repeated every 21 days (see Table 5). Patients who experienced signs or symptoms of peripheral neuropathy on therapy were to be evaluated for discontinuation of further therapy with ATRIANCE.[10]

Table 5 Pediatric Clinical Study - Patient Allocation

Patient Population	**N**
Patients treated at 650 mg/m^2/day for 5 days every 21 days	84
Patients with T-ALL or T-LBL with two or more prior inductions treated at 650 mg/m^2/day for 5 days every 21 days	39

Baseline patient and disease characteristics of the 84 patients treated with 650 mg/m^2/day of ATRIANCE were consistent with those generally observed for patients with these diseases. Patients ranged in age from 2.5-21.7 years (overall mean, 11.9 years), 52% were 3 to 12 years of age and most were male (74%) and Caucasian (62%). The majority (77%) of patients had a diagnosis of T-ALL.

Adult clinical study in relapsed or refractory T-ALL and T-LBL

The safety and efficacy of ATRIANCE in adult patients were studied in a clinical trial conducted by the Cancer and Leukemia Group B (CALGB). This study included 39 treated patients, 28 of whom were with T-cell acute lymphoblastic leukemia (T-ALL) or T-cell lymphoblastic lymphoma (T-LBL) that had relapsed following or was refractory to at least two prior induction regimens. ATRIANCE 1,500 mg/m^2 was administered intravenously over 2 hours on days 1, 3 and 5 repeated every 21 day treatment cycle. Seventeen patients had a diagnosis of T-ALL and 11 had a diagnosis of T-LBL. For patients with ≥2 prior inductions, the age range was 16-65 years (mean 34 years) and most patients were male (82%) and Caucasian (61%). Patients with central nervous system (CNS) disease were not eligible. Patients who experienced grade 2 or greater peripheral neuropathy on therapy were typically discontinued from further therapy with ATRIANCE.

Adult and pediatric clinical study in newly diagnosed T-ALL and T-LBL
The efficacy and safety of ATRIANCE, in combination with an aBFM regimen, were assessed in a randomised Phase III study. Newly diagnosed T-ALL or T-LBL patients between 1 and 30 years of age were enrolled. A total of 825 patients were randomised or assigned to treatment arms with or without ATRIANCE based on risk categorisation following induction treatment and type of disease (T ALL or T-LBL). Out of 702 T-ALL patients, 659 patients were randomised to receive an aBFM regimen with ATRIANCE (N=323) or without ATRIANCE (N=336).

Patients in the ATRIANCE arms received ATRIANCE in 5-day cycles of 650 mg/m^2/day added to an aBFM backbone chemotherapy; two cycles were administered during Consolidation, one cycle during Delayed Intensification, and one cycle in each of the first 3 Maintenance treatment phases.

The study was designed to evaluate the potential clinical benefit in event-free survival (EFS) when ATRIANCE is added to an aBFM regimen to treat T-ALL patients following initial remission after Induction phase treatment. EFS in this trial for T-ALL patients was defined as the time to the EFS events. EFS events include any type of relapse, death in remission or second malignant neoplasm.

The median age of T-ALL patients analysed for EFS was 9 to 10 years of age (range: 1 to 29 years). The majority of patients were: between 3 to 12 years of age (~60%), male (~75%) and Caucasian (~70%).

Study results

Pediatric clinical study in relapsed or refractory T-ALL and T-LBL
Complete response (CR) in the pediatric clinical study was defined as bone marrow blast counts ≤5%, no other evidence of disease, and full recovery of peripheral blood counts. Complete response with or without full hematologic recovery (CR*) was also assessed as a meaningful outcome in this heavily pretreated population. Duration of CR is reported from date of response to date of relapse, and may include subsequent stem cell transplant. Efficacy results, including survival at one year, are presented in Table 6.

Table 6 Efficacy Results in Patients 21 Years of Age and Younger at Diagnosis With ≥2 Prior Inductions Treated with 650 mg/m^2 of ATRIANCE Administered Intravenously Over 1 Hour Daily for 5 Consecutive Days Repeated Every 21 Days

	N = 39
CR n (%) [95% CI]	5 (13%) [4%, 27%]
CR* n (%) [95% CI]	9 (23%) [11%, 39%]
Duration of complete response (range in weeks) **	3.3 to 9.3
Median overall survival (weeks) [95% CI]	13.1 [8.7, 17.4]
Kaplan-Meier Survival estimate at 1 year [95% CI]	14% [3%, 26%]

CR = Complete response
CR* = Complete response with or without hematologic recovery (includes patients who achieved a CR)

** Does not include 5 patients who were transplanted or had subsequent systemic chemotherapy) duration of response in these 5 patients was 4.7 to 42.1 weeks).

The mean number of days on therapy was 46 days (range of 7 to 129 days). Time to complete response ranged from 3.4 to 12 weeks and median time to CR* was 3.4 weeks (95% CI: 3.0, 3.7).

Adult clinical study in relapsed or refractory T-ALL and T-LBL

Complete response (CR) in the adult clinical study was defined as bone marrow blast counts ≤5%, no other evidence of disease, and full recovery of peripheral blood counts. Complete response with or without complete hematologic recovery (CR*) was also assessed as a meaningful outcome in this heavily pretreated population. The results of the study for patients who had received ≥2 prior inductions are shown in Table 7.

Table 7 Efficacy Results in Adult Patients With ≥2 Prior Inductions Treated with 1,500 mg/m^2 of ATRIANCE Administered Intravenously Over 2 Hours on Days 1, 3, and 5 Repeated Every 21 Days

	N = 28
CR n (%) [95% CI]	5 (18%) [6%, 37%]
CR* n (%) [95% CI]	6 (21%) [8%, 41%]
Duration of complete response (range in weeks)**	15 to 195+
Median overall survival (weeks) [95% CI]	20.6 weeks [10.4, 36.4]
Kaplan-Meier Survival estimate at 1 year [95% CI]	29% [12%, 45%]

CR = Complete response
CR* = Complete response with or without hematologic recovery (includes patients who achieved a CR)
** Does not include 1 patient who was transplanted (duration of response was 156+ weeks)

The mean number of days on therapy was 56 days (range of 10 to 136 days). Time to complete response and time to CR* ranged from 2.9 to 11.7 weeks.

Adult and pediatric clinical study in newly diagnosed T-ALL and T-LBL

The addition of ATRIANCE to an aBFM regimen resulted in a 31% reduction in the risk of having an event (i.e. death, secondary malignancy or relapse) in the T-ALL population, with a HR of 0.691 (90% CI: 0.486, 0.981), p=0.081. Median EFS was not reached in either treatment group. The 4-year EFS rate was 88.9% in the ATRIANCE with aBFM treatment group and 83.5% in the aBFM treatment group.

EFS in T-LBL patients was an exploratory objective. The study was not powered to detect a difference in EFS between the ATRIANCE and no-ATRIANCE treatment groups in T-LBL patients. Nine patients (15.0%) in the ATRIANCE treatment group and 10 patients (16.4%) in the no-ATRIANCE treatment group had an EFS event (HR of 0.947, 90% CI: 0.445, 2.016). Median EFS was not reached in either treatment group. The 4-year EFS rate was 86.5% in the ATRIANCE with aBFM treatment group and 86.6% in the aBFM treatment group.

DETAILED PHARMACOLOGY

No pre-clinical safety pharmacology studies were performed to investigate the effects of nelarabine on vital organ systems (cardiovascular, respiratory, central nervous system).

Drug Interactions

In a pharmacokinetic study in 13 adult patients receiving 1,200 mg/m^2 of nelarabine, fludarabine administration at 30 mg/m^2 4 hours prior to nelarabine administration did not affect the plasma pharmacokinetics of nelarabine and ara-G or the intracellular accumulation of ara-GTP in leukemic blasts.

In-vitro studies in human liver microsomes suggest that nelarabine and ara-G did not significantly inhibit the activities of the major hepatic cytochrome P450 (CYP) enzymes CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, or CYP3A4 *in vitro* at concentrations of nelarabine and ara-G up to 100 μM.

TOXICOLOGY

Repeat Dose Toxicity

The potential toxicity of nelarabine was investigated in repeat dose intravenous studies of 5 days duration in mice at doses of 600 to 1800 mg/m^2/day and ketamine-sedated cynomolgus monkeys at doses of 720 to 3600 mg/m^2/day and for 30 days duration in the non-sedated monkey at doses of 120 to 480 mg/m^2/day.

In the mouse, no clinical signs of neurotoxicity were seen. Furthermore, no macroscopic changes were observed at necropsy.

A dose limiting neurotoxicity characterized by seizures, muscle tremor and weakness, incoordination, ataxia, depth perception deficits, and unresponsiveness occurred in male and female cynomolgus monkeys given ≥720 mg/m^2/day for 5 days or at ≥240 mg/m^2/day for up to 30 days. No neurotoxicity occurred in monkeys given 120 mg/m^2/day for 30 days.

The onset of clinical neurotoxicity was dose-dependent, beginning immediately after the dosing period in individual monkeys given 3600 mg/m^2/day for 5 days, as late as post dose day 10 and 13, in monkeys given 720 or 1800 mg/m^2/day, respectively for 5 days, and on Day 19, in monkeys given 240 or 480 mg/m^2/day for 30 days. Clinical neurotoxicity was completely reversible after 5 days of dosing and after 30 days of dosing at 240 mg/m^2/day, but only partially reversible at 480 mg/m^2/day given for 23 days. Within 3 weeks after dosing was stopped, in monkeys given 480 mg/m^2/day for 23 days, muscle tremors lessened and general body condition improved; however, clinical neurotoxicity had not completely resolved by the end of the two month recovery period. No histopathologic lesions were observed in central or peripheral nervous system tissues of monkeys given nelarabine for 5 days. Histopathologic changes evident as 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 two months after dosing was stopped. Neurotoxicity generally correlated with greater systemic exposure to ara-G.

The clinical neurotoxicity seen in monkeys given nelarabine for 5 or 30 days was qualitatively similar to that seen in humans at therapeutic doses.

The major findings from 5 and 30 day repeat dose studies in monkeys indicate that nelarabine targeted the mitotically active cells in bone marrow, lymphoid organs, and intestinal tract. The incidence and severity of the toxicity was dose-and time-dependent and all effects reversed during recovery.

Decreases in total white blood cell values, chiefly due to a neutropenia and monocytopenia, occurred at all doses in monkeys given nelarabine at ≥720 mg/m^2/day for 5 or ≥120 mg/m^2/day for 30 days. Decreases in red blood cell counts and platelet counts also occurred but at higher doses. No clinically detectable bleeding accompanied the decrease in platelet count. Hypocellular bone marrow was seen only in monkeys given 3600 mg/m^2/day over 5 days. All changes reversed during the recovery period with a rebound leukocytosis seen in individual monkeys.

Thymus weights were reduced at 30 days in females at ≥120 mg/m^2/day and at ≥240 mg/m^2/day in males. This effect was reversible, as thymus weights had returned to normal by the time of the recovery necropsy. Monkeys with low thymus weights had normal peripheral lymphocyte counts.

Histopathologic changes in mitotically active tissues were seen in three (of four) monkeys given 3600 mg/m^2/day for 5 days. Findings included lymphoid depletion of cervical and mesenteric lymph nodes, splenic involution, thymic atrophy, hypocellular bone marrow, and intestinal epithelial cell maturation arrest. Another female monkey dosed at 3600 mg/m^2/day had no histopathologic abnormalities after a 60 day recovery period, indicating these lesions were reversible.

Effects on mitotically active tissues in monkeys, as evidenced by decreased RBC, WBC, neutrophils, and platelets, were qualitatively similar to those observed in humans at therapeutic dose levels.

Genotoxicity

Like other drugs in the nucleoside analogue class, nelarabine was mutagenic in the microtiter version of the L5178Y/TK+/- mouse lymphoma mutagenesis assay in the presence and absence of rat liver S9 metabolic activation. Significant increases in mutant frequency were observed when cells were treated for (i) three hours in the absence of S9 metabolic activation and (ii) three hours in the presence of S9 metabolic activation at concentrations up to 5000 µg/mL nelarabine. Since nelarabine and other nucleoside analogs are known genotoxic agents, administration of nelarabine to patients should be considered on an individual case basis, following a risk-benefit evaluation.

Reproductive and Developmental Toxicity

Compared to controls, nelarabine caused increased incidences of fetal malformations, anomalies, and variations in rabbits when given via 8-hour intravenous infusions at doses ≥354 mg/m^2/day (approximately 24% of the adult dose on a mg/m^2 basis) during days 7 to 19 of gestation. Cleft palate was seen in rabbits given 3,540 mg/m^2/day (approximately 2-fold the adult dose), absent pollices in rabbits given ≥1,180 mg/m^2/day (approximately 79% of the adult dose) while absent gall bladder, absent accessory lung lobes, fused or extra sternebrae and delayed ossification was seen at all doses. Maternal body weight gain and fetal body weights were reduced in rabbits given 3,540 mg/m^2/day (approximately 2-fold the adult dose). The number of corpora lutea, implantation sites, live fetuses, dead fetuses, sex ratio, and pre-implantation losses were unaffected by the administration of nelarabine.

No studies have been conducted in animals to assess effects on fertility. However, no adverse effects were seen in the testes or ovaries of monkeys given nelarabine intravenously at doses up to 480 mg/m^2/day (approximately 32% of the adult dose on a mg/m^2 basis) for 30 consecutive days. The effect on human fertility is unknown.

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PART III: CONSUMER INFORMATION

PrATRIANCE®
(nelarabine)

This leaflet is Part III of a three-part "Product Monograph" published when ATRIANCE® (nelarabine) Injection was approved for sale in Canada and is designed specifically for Consumers. This leaflet is a summary and will not tell you everything about ATRIANCE. Read this information carefully before you or your child start taking ATRIANCE and read the information you get each time before you or your child get more ATRIANCE as there may be new information. This information does not take the place of talking with your or your child's doctor about your/your child's medical condition or treatment. If you have any questions about ATRIANCE, ask your/your child's doctor. Your/your child's doctor can determine if ATRIANCE is right for you or your child.

ABOUT THIS MEDICATION

What the medication is used for:
ATRIANCE is used to treat adults and children who have a certain type of leukemia (T-cell acute lymphoblastic leukemia) or lymphoma (T-cell lymphoblastic lymphoma).

What it does:
ATRIANCE damages cancer cells, causing their death.

When it should not be used:
You, or your child, should not take ATRIANCE if you/your child are allergic to the medicinal ingredient, nelarabine, or to any of the non-medicinal ingredients.

What the medicinal ingredient is:
ATRIANCE Injection contains nelarabine.

What the nonmedicinal ingredients are:
ATRIANCE Injection contains sodium chloride in Water for Injection, USP. Hydrochloric acid and sodium hydroxide may have been used to adjust the pH.

What dosage forms it comes in:
ATRIANCE is available as a sterile solution containing 5 mg of nelarabine per mL.

WARNINGS AND PRECAUTIONS

Serious Warnings and Precautions

ATRIANCE should be given under the supervision of a doctor experienced in the use of anti-cancer drugs.

ATRIANCE should only be given by injection into a vein.

ATRIANCE may **cause brain or nervous system disorders which can be fatal**. **If you have pre-existing brain or nervous system disorders or have had chemotherapy injection into the area around the spinal cord or radiation to your head or spine, you may be at increased risk of more serious side effects.**

Serious side effects include:
- Feel very sleepy or drowsy
- Less feeling. Tingling or numb fingers, hands, toes or feet
- Weak getting up from a chair or doing stairs
- Being confused
- Collapse, go unconscious or lack awareness
- Significant spinal cord damage that may be permanent and disabling
- Hard to speak and understand what people say
- Hard to remember
- Difficult to awaken
- Hard to control your eyes
- Seizures or coma
- Poor balance, unsteady or trips while walking
- Fine motor skills are hard to do such as doing up a button

Contact the doctor right away if any of the above occur.

The above symptoms may not go away, even when ATRIANCE is stopped.

Before you or your child receive treatment with ATRIANCE tell your/your child's doctor:
- about any medical condition you or your child have, including liver or kidney problems, or if you or your child have had chemotherapy injection into the area around the spinal cord or radiation to your head or spine
- if you/your child or any of your close family/friends have recently been, or plan to be vaccinated with a live vaccine such as Polio, Varicella (chickenpox) or Typhoid

Decrease in red blood cells (severe anemia): **ATRIANCE can cause a decrease in red blood cells which can be life-threatening.** Your doctor will monitor you periodically. Signs that certain red cell counts are low may include:
- Severe lack of energy
- Pale skin
- Weakness
- Shortness of breath

Decrease in white blood cells (leukopenia and neutropenia): **ATRIANCE can cause a decrease in white blood cells that may lead to infection which can be life-threatening, or to unexpected bruising or bleeding**. Your doctor will monitor you periodically. Signs that certain white cell counts are low may include:

- Symptoms of infection (fever, chills, sore throat)
- Bruise or bleed easily
- Cold

Muscle or bone problems: **ATRIANCE may cause muscle pain or weakness that does not go away after you stop taking the drug.**

Liver problems: **ATRIANCE can cause problems with your liver which may develop into serious conditions such as hepatitis and liver failure, which may be fatal.** Signs that your liver may not be working properly may include:

- Loss of appetite
- Feeling sick (nausea)
- Being sick (vomiting)
- Pain in your stomach (abdomen)
- Yellowing of your skin or the whites of your eyes (jaundice)
- Dark-colored urine
- Itching of your skin

Pregnancy, Birth Control and Fertility for Men and Women, and Breastfeeding
ATRIANCE may harm or put an unborn baby at serious risk.

- Do not use ATRIANCE during pregnancy
- Do not take ATRIANCE if you are pregnant or plan to become pregnant
- If you get pregnant while you or your male partner are being treated with ATRIANCE, tell your doctor
- Men and women must use a highly effective method of birth control while taking ATRIANCE. Discuss birth control options with your doctor, to be sure pregnancy is avoided
  Women: Prevent pregnancy while taking ATRIANCE.
  Men: Inform female sexual partners that you are taking ATRIANCE. Tell them the serious risk of harm to an unborn baby. Prevent pregnancy in your partner while taking ATRIANCE.
- It is not known whether taking ATRIANCE could affect how well your birth control pills will work. This could result in pregnancy
- ATRIANCE may affect your ability to become pregnant or to father a child
- ATRIANCE may pass through breast milk. Do not breast feed while taking ATRIANCE
- Male patients with partners who are pregnant, possibly pregnant, or who could become pregnant should use condoms during sexual intercourse while receiving ATRIANCE and for 3 months following completion of therapy

BEFORE you use ATRIANCE also talk to your doctor if you:

- Have any past problems with muscles (pain, tenderness)
- Have low white blood cells
- Have low red blood cells
- Have had bleeding problems or blood clots
- Have any liver problems
- Have any kidney problems

Driving and using machines: Before you perform tasks which may require special attention, wait until you know how you respond to ATRIANCE. Some side effects such as sleepiness, dizziness, or **brain and nervous system disorders** can affect your ability to drive or use machines.

INTERACTIONS WITH THIS MEDICATION

Tell your/your child's doctor or pharmacist about any medications you/your child are taking, including prescription and non-prescription medicines, vitamins and natural health products.

It is not known whether taking ATRIANCE could affect how well your birth control pills will work. This could result in pregnancy.

PROPER USE OF THIS MEDICATION

Usual dose:
Adults: The recommended adult dose of ATRIANCE is 1,500 mg/m²/day administered intravenously (into a vein) over 2 hours on days 1, 3, and 5, repeated every 21 days.

Children: The recommended pediatric dose of ATRIANCE is 650 mg/m²/day administered intravenously over 1 hour on days 1 to 5, repeated every 21 days.

Missed dose:
If you or your child miss a scheduled dose of ATRIANCE, contact your/your child's doctor. Your/your child's doctor will advise you on what to do about the next dose.

Overdose:

If you think you (or your child) have been given ATRIANCE more frequently than you should, or at a higher dose, or in case of drug overdose, contact a health care practitioner, hospital emergency department or regional Poison Control Centre immediately, even if there are no symptoms.

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

Most patients taking ATRIANCE will experience side effects, although it is not always possible to tell whether such effects are caused by ATRIANCE, other medications you/your child may be taking, or the cancer itself. The occurrence of side effects has been reported to be different between adults and children. If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your/your child's doctor. Some possible side effects of ATRIANCE are listed below:

Adults:

Very common (may occur in more than 10 out of every 100 people):

- nervous system problems such as difficulty with sense of feeling in hands and/or feet, reduced sensitivity to light touch or pain, or abnormal sensation such as burning, prickling or sensations of something crawling on skin;
- infections (including pneumonia);
- blood problems including decreased blood counts, reduced resistance to infection, temporary anemia (which may make you feel tired or weak), bruising or bleeding;
- feeling sleepy or drowsy, headache, dizziness, build up of fluid around the lungs, shortness of breath, difficult or laboured breathing, cough, nausea (feeling sick), or being sick/throwing up, diarrhea, constipation, muscle pain, swelling due to accumulation of fluid, high body temperature or fever, tiredness, feeling weak/loss of strength.

Common (may occur in 1 to 10 out of every 100 people):

- loss of muscle coordination, convulsions, weight loss and loss of appetite, difficulty with memory/feeling disoriented, blurred vision, increases in blood levels of liver enzymes;
- tremors;
- pain in the joints, back or extremities;
- chest pain;
- stomach pain;
- nausea and vomiting, shortness of breath, irregular heartbeat, clouding of urine, lethargy and/or joint discomfort (tumour lysis syndrome);
- low blood pressure;
- taste disturbance or loss of taste;
- dehydration.

Children:

Very common (may occur in more than 10 out of every 100 people):

- difficulty with sense of feeling in hands and/or feet;
- blood problems including decreased blood counts, reduced resistance to infection, temporary anemia (which may make you feel tired or weak), bruising or bleeding;
- abnormally low levels of potassium in the blood (which may make you feel weak), being sick/throwing up, headache, increases in blood levels of liver enzymes.

Common (may occur in 1 to 10 out of every 100 people):

- infection (including pneumonia);
- convulsions, reduced sensitivity to light touch or pain, abnormal sensation such as burning, prickling or sensations of something crawling on skin;
- loss of muscle coordination or balance;
- tremors;
- feeling drowsy or sleepy;
- abnormally low glucose in the blood (which may cause symptoms like feeling sick, sweating, weakness, faintness, confusion or hallucinations; abnormally low levels of calcium in the blood which may cause symptoms like muscle cramps, abdominal cramps or spasms); abnormally low levels of magnesium in the blood; increase in creatinine (a substance produced by the kidneys) in the blood;
- high body temperature/fever, feeling weak/loss of strength.

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM

Symptom / effect	**Talk with your doctor**		**Stop taking ATRIANCE and call your doctor immediately**
	Only if severe	**In all cases**	
Common/ very common			
Brain or nervous system disorders including headache, sleepiness, tingling or numbness in fingers, hands, toes or feet; collapse or periods of unconsciousness or lack of awareness, or seizures.		✓	
Very common			
Low white blood cells which may give you a greater chance of infection, which may be life threatening. Symptoms of infection may include: fever; serious deterioration of general condition; fever with local symptoms such as sore throat/mouth or urinary problems.		✓	
Low platelets which may give you a greater chance for bleeding. Symptoms may include easy bruising or unusual bleeding while brushing teeth or from other sources.		✓	
Common			
Stroke: Speech difficulty, weak on one side of the body, dizziness, poor balance		✓	
Uncommon			
Blindness		✓	

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM			
Symptom / effect	**Talk with your doctor**		**Stop taking ATRIANCE and call your doctor immediately**
	Only if severe	**In all cases**	
Hallucinations: See or hear things that are not there		✓	
Sudden or very bad headache		✓	
In post marketing experience			
Cases of spinal cord disorders including a block of blood supply to, or inflammation of, the spinal cord have been reported. Symptoms may include leg weakness, numbness, paralysis of arms and legs, fecal and/or urinary incontinence.		✓	
Abnormal breakdown of muscle tissue (rhabdomyolysis). Symptoms may include abnormal urine colour, muscle aching, weakness of affected muscles.		✓	
Cases of acute liver failure have been reported. Symptoms may include yellowing of skin and eyes, stomach pain, nausea and/or vomiting.			✓

This is not a complete list of side effects. For any unexpected effects while taking ATRIANCE, contact your/your child's doctor or pharmacist.

HOW TO STORE IT

Store between 15° to 30°C.

Reporting Side Effects

You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada/adverse-reaction-reporting.html) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

MORE INFORMATION

This leaflet summarizes important information about ATRIANCE. If you have questions or problems, talk with your/your child's doctor or other healthcare provider immediately. You can ask your/your child's doctor or pharmacist for information about ATRIANCE that is written for healthcare providers.

This document plus the full product monograph, prepared for health professionals can be found at:

http://www.novartis.ca or by contacting the sponsor,

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