DRUG NAME: Nelarabine

SYNONYM(S): 506U78 [1], GW 506U78 [1]

COMMON TRADE NAME(S): ATRIANCE®

CLASSIFICATION: antimetabolite

Special pediatric considerations are noted when applicable, otherwise adult provisions apply.

MECHANISM OF ACTION:

Nelarabine, a prodrug of 9-β-*D*-arabinofuranosylguanine (ara-G), is a purine nucleoside antimetabolite. Nelarabine is rapidly demethylated to ara-G by adenosine deaminase and then subsequently phosphorylated to its 5'-monophosphate by deoxyguanosine kinase and deoxycytidine kinase. The monophosphate is converted intracellularly to the active triphosphate form (ara-GTP) which accumulates in leukemic cells and leads to inhibition of DNA synthesis and cell death. Other mechanisms may contribute to the cytotoxic effects of nelarabine. *In vitro*, T cells have shown more sensitivity to the cytotoxic effects of nelabarine than B cells.

PHARMACOKINETICS:

Absorption	rapid and extensive conversion of nelarabine to ara-G; ara-GTP appears intracellularly within 3-25 h on day 1	
Distribution	nelarabine and ara-G are extensively distributed throughout the body; voume of distribution influenced by body surface area	
	cross blood brain barrier?	yes [2]
	volume of distribution	nelarabine: 115 L/m^2 ara-G: 44.8 L/m^2
	plasma protein binding	nelarabine and ara-G: <25%
Metabolism	main route of metabolism is O-demethylation by adenosine deaminase	
	active metabolite(s)	ara-GTP
	inactive metabolite(s)	guanine, methylguanine, xanthine, uric acid
Excretion	nelarabine is rapidly eliminated from plasma; intracellular ara-GTP accumulates with repeated administration of nelarabine	
	urine	nelarabine: 5.3% ara-G: 23.2%
	feces	no information found
	terminal half life	nelarabine: 18-30 min ara-G: 3.2 h
	clearance	nelarabine: 138 L/h/m^2 ara-G: 9.5 L/h/m^2
Children	clearance: nelarabine clearance is ~30% higher in pediatric patients compared to adult patients; no clinically significant difference in ara-G clearance half-life: ara-G half-life is shorter in pediatric patients compared to adult patients (2 h vs 3.2 h); clinical significance is unknown	
Sex	2-3 fold increase in intracellular AUC in average female patients compared to average male patients; no clinically significant difference in overall safety or efficacy	

Adapted from standard reference [3,4] unless specified otherwise.

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USES:

Primary uses:

*Leukemia, acute lymphoblastic

*Lymphoma, non-Hodgkin

Other uses:

*Health Canada approved indication

SPECIAL PRECAUTIONS:

Caution:

- risk of ***severe neurologic events*** may be increased in patients with pre-exisiting CNS disease, previous or concurrent treatment with intrathecal chemotherapy, or previous craniospinal radiation [3,4]
- ***tumour lysis syndrome*** has been reported; consider hydration and prophylaxis in patients at risk for hyperuricemia [3,4]
- patients receiving nelarabine are at risk of somnolence, dizziness, and other neurological disorders which may affect ability to ***drive/operate machinery*** [3,4]
- ***live virus vaccines*** should be avoided during treatment with nelarabine [3,4]
- all lymphoma patients should be screened for Hepatitis B reactivation; for recommended HBV screening and prophylaxis, see BC Cancer Protocol SCHBV ***Hepatitis B Virus Reactivation Prophylaxis***

Special populations: patients ***aged 65 years and older*** may experience increased incidence of neurologic adverse events. [3,4]

Carcinogenicity: No studies have been conducted. [3]

Mutagenicity: Nelarabine is mutagenic in mammalian *in vitro* mutation test. [3,4]

Fertility: Fertility studies have not been conducted. However, in animal toxicology studies, no adverse effects were seen in the testes or ovaries at exposures approximately 32% of those seen following human clinical exposure. [3] The number of corpora lutea, implantation sites, live fetuses, dead fetuses, and pre-implantation losses were unaffected by the administration of nelarabine. Effect on human fertility is unknown. [3]

Pregnancy: In animal studies, the incidence of fetal malformations and abnormalities was increased in study animals. Effects such as cleft palate, absent pollices, gall bladder, or accessory lung lobes, fused or extra sternebrae, and delayed ossification were observed at doses ranging from 0.25 to 2 times those seen following human clinical exposure. Pregnancy tests are recommended prior to treatment for females of childbearing potential. Contraception is recommended during treatment for females of childbearing potential. For male patients with female partners or childbearing potential, contraception is recommended during treatment and for three months after the last dose. [3,4]

Breastfeeding is not recommended due to the potential secretion into breast milk. Because of the potential for serious adverse reactions such as severe neurological reactions in the breastfed infant, women should be advised not to breastfeed during treatment. [3,4]

SIDE EFFECTS:

The table includes adverse events that presented during drug treatment but may not necessarily have a causal relationship with the drug. Because clinical trials are conducted under very specific conditions, the adverse event rates observed may not reflect the rates observed in clinical practice. Adverse events are generally included if they were reported in more than 1% of patients in the product monograph or pivotal trials, and/or determined to be clinically important [5,6].

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Revised: 1 February 2025

ORGAN SITE	SIDE EFFECT
Clinically important side effects are in ***bold, italics***	
blood and lymphatic system/ febrile neutropenia	***anemia*** (95-99%, severe 34%)
	febrile neutropenia (severe 10-12%)
	neutropenia (81%, severe 63%)
	thrombocytopenia (86-88%, severe 59%)
cardiac	sinus tachycardia (8%, severe 1%)
eye	***blindness, unilateral*** (1%)
	blurred vision (4%)
	reduced visual acuity (2%)
	visual disturbance (1%)
gastrointestinal	*emetogenic potential:* low [7,8]
	abdominal distention (6%)
	abdominal pain (9%, severe 1%)
	constipation (21%, severe 1%)
	diarrhea (22%, severe 1%)
	nausea (41%)
	stomatitis (8%, severe 1%)
	vomiting (22%, severe 1%)
general disorders and administration site conditions	*extravasation hazard:* none [9]
	abnormal gait (6%)
	asthenia (17%, severe 1%)
	chest pain (5%)
	edema, including ***peripheral edema*** (26%)
	fatigue (50%, severe 12%)
	non-cardiac chest pain (5%, severe 1%)
	pain (11%, severe 3%)
	pyrexia (23%, severe 5%)
	rigors (8%)
hepatobiliary	acute hepatic failure (including fatal toxic hepatitis)
infections and infestations	***infection***, including sepsis, bacteremia, fungal infection (9%, severe 3%)
	opportunistic infection; fatal events reported
	pneumonia (8%, severe 5%)
investigations	***ALT increase*** (severe 1%); fatal events reported
	AST increase (6%, severe 2%)
	blood bilirubin increase (3%, severe 2%)

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ORGAN SITE	SIDE EFFECT
Clinically important side effects are in ***bold, italics***	
	creatinine phosphokinase increase
metabolism and nutrition	anorexia (9%)
	dehydration (7%, severe 4%)
	hyperglycemia (6%, severe 1%)
	tumour lysis syndrome
musculoskeletal and connective tissue	arthralgia (9%, severe 1%)
	back pain (8%)
	muscular weakness (8%, severe 5%)
	myalgia (13%, severe1%)
	pain in extremity (7%, severe 1%)
	rhabdomyolysis
nervous system (see paragraph following **Side Effects** table)	abnormal coordination (1%)
	amnesia (3%)
	aphasia (severe 1%)
	ataxia (9%, severe 2%)
	balance disorder (2%)
	burning sensation (1%)
	cerebral hemorrhage (severe 1%); fatal events reported
	coma (severe 1%)
	convulsion (severe 1%)
	depressed level of consciousness (6%, severe 1%)
	disturbance in attention (1%)
	dizziness (21%)
	dysarthria (1%)
	dysgeusia (3%)
	headache (15-17%, severe 1%)
	hemiparesis (severe 1%)
	hypoesthesia (17%, severe 2%)
	hyporeflexia (1%)
	intracranial hemorrhage (severe 1%)
	leukoencephalopathy (severe 1%)
	loss of consciousness (severe 1%)
	metabolic encephalopathy (severe 1%)
	myasthenia (8%)

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Revised: 1 February 2025

ORGAN SITE	SIDE EFFECT
Clinically important side effects are in ***bold, italics***	
	neuropathy, including ***peripheral, motor,*** and ***sensory*** (29%, severe 2%)
	neuropathic pain (1%)
	nystagmus (1%)
	paresthesia (15%)
	peripheral neurological disorder (21%, severe 2%)
	peroneal nerve palsy (1%)
	progressive multifocal leukoencephalopathy
	sciatica (1%)
	seizure (severe 1%)
	sensory disturbance (1%)
	sensory loss (2%)
	sinus headache (1%)
	somnolence (23%)
	speech disorder (1%)
	spinal cord disorders (including myelopathy, ischemia, myelitis, paraplegia [10])
	tremor (5%)
psychiatric	confusional state (8%, severe 2%)
	depression (6%, severe 1%)
	hallucination (1%)
	insomnia (7%)
respiratory, thoracic and mediastinal	cough (25%)
	dyspnea (20%, severe 6%)
	dyspnea, extertional (7%)
	epistaxis (8%)
	pleural effusion (10%, severe 6%)
	wheezing (5%)
vascular	hypotension (8%, severe 2%)
	petechiae (12%, severe 2%)

Adapted from standard reference [1,3,4] unless specified otherwise.

Neurotoxicity is the dose-limiting toxicity of nelarabine. A wide array of neurologic adverse events commonly occur, some of which have been severe, irreversible, or fatal. Patients with CNS disease at baseline or patients treated previously or concurrently with intrathecal chemotherapy (e.g., methotrexate) or craniospinal radiation are at increased risk of more severe neurologic events. Common signs and symptoms include somnolence, confusion, altered level of consciousness, convulsions, ataxia, paraesthesia, and hypoesthesia. Severe toxicity can manifest as coma, status epilepticus, myelopathy, craniospinal demyelination, or ascending neuropathy similar in presentation to Guillain-Barré syndrome. Symptom onset is often within 5 to 8 days from start of first infusion (range: 1 to 269 days), with a median duration of 2 to 6 days (range: 1 to 393 days). Monitor closely for early signs and symptoms of

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Revised: 1 February 2025

neurological events throughout treatment. Discontinue nelarabine at the first sign of any grade 2 or higher neurological event. [1,3,4]

INTERACTIONS:

AGENT	EFFECT	MECHANISM	MANAGEMENT
fludarabine [3,4]	no effect on plasma pharmacokinetics of nelarabine and ara-G or the intracellular accumulation of ara-GTP in leukemic blasts		
pentostatin [3,4]	reduction in conversion of prodrug nelarabine to its active moiety	strong inhibition of adenosine deaminase by pentostatin	avoid concurrent use

SUPPLY AND STORAGE:

***Injection*:** Sandoz Canada Inc. supplies nelarabine as 250 mg ready-to-use, single-use (preservative free) vials in a concentration of 5 mg/mL. Store at room temperature. [3]

For basic information on the current brand used at BC Cancer, see Chemotherapy Preparation and Stability Chart in Appendix.

SOLUTION PREPARATION AND COMPATIBILITY:

For basic information on the current brand used at BC Cancer, see Chemotherapy Preparation and Stability Chart in Appendix.

Compatibility: consult detailed reference

PARENTERAL ADMINISTRATION:

BC Cancer administration guideline noted in ***bold***, ***italics***

Subcutaneous	no information found
Intramuscular	no information found
Direct intravenous	no information found
Intermittent infusion [3,4]	over 2 h
	in pediatric patients, doses are given over 1 h
Continuous infusion	no information found
Intraperitoneal	no information found
Intrapleural	no information found
Intrathecal	no information found
Intra-arterial	no information found
Intravesical	no information found

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Revised: 1 February 2025

DOSAGE GUIDELINES:

Refer to protocol by which patient is being treated.

Adults:

BC Cancer usual dose noted in ***bold, italics***

Intravenous [3,4,11]*:*	Cycle Length: 3 weeks:	1500 mg/m^2 IV for one dose on days 1, 3 and 5 (total dose per cycle 4500 mg/m^2)
Concurrent radiation [3]*:*	the optimal schedule of concurrently administered nelarabine with radiation has not been determined	
Dosage in myelosuppression:	modify according to protocol by which patient is being treated	
Dosage in renal failure [3,4]*:*	CrCl ≥50 mL/min: no adjustment required CrCl <50 mL/min: the risk of toxicity may be greater in patients with decreased renal function; monitor for toxicity	
	calculated creatinine clearance = $\frac{N^* \times (140 - Age) \times \text{weight in kg}}{\text{serum creatinine in micromol/L}}$ * For males N=1.23; for females N=1.04	
Dosage in hepatic failure [3,4]*:*	the risk of toxicity may be greater in patients with severe hepatic impairment; monitor for toxicity	
Dosage in dialysis:	no information found	

Children: optimal dosing for patients 16-21 years of age has not been established [3]

Intravenous [3,4]*:*	Cycle Length: 3 weeks:	650 mg/m^2 IV for one dose on days 1 to 5 (total dose per cycle 3250 mg/m^2)

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