Drug Monograph

A - Drug Name

nelarabine

COMMON TRADE NAME(S): Atriance®

back to top

B - Mechanism of Action and Pharmacokinetics

Nelarabine is a pro-drug of the deoxyguanosine analogue ara-G that is demethylated by adenosine deaminase to ara-G, then phosphorylated to the active moiety ara-GTP, which is incorporated into the DNA of leukemic cells resulting in cytotoxic effects. T-cells are more sensitive than B-cells to nelarabine's cytotoxic effects.

Absorption	Nelarabine is rapidly and extensively converted to ara-G.	
	Peak plasma levels	C_{max} 3-25 hours following 1500 mg/m^2 infused over 2 hours
Distribution	Nelarabine and ara-G are extensively distributed.	
	PPB	< 25%
	Cross blood brain barrier?	yes
Metabolism	Main enzymes involved	O-demethylation by adenosine deaminase to ara-G, followed by hydrolysis to guanine.
	Active metabolites	yes
	Inactive metabolites	yes

Elimination	Mean clearance of nelarabine is 30% higher in pediatric compared to adult patients; clearance of ara-G is similar for both.	
	Half-life	nelarabine: 30 minutes; ara-G: 2-3 hours
	Urine	mean urinary excretion: nelarabine, 5%; ara-G: 23% of administered dose

back to top

C - Indications and Status

Health Canada Approvals:

- T-cell acute lymphoblastic leukemia (T-ALL)
- T-cell lymphoblastic lymphoma (T-LBL)

Refer to the product monograph for a full list and details of approved indications.

back to top

D - Adverse Effects

Emetogenic Potential: Minimal

Extravasation Potential: None

The following adverse effects were reported mainly in adult patients receiving nelarabine monotherapy for T-cell acute lymphoblastic leukemia, lymphoblastic lymphoma, or chronic lymphocytic leukemia in phase I or II clinical trials. Other severe or life-threatening adverse effects may also be included.

ORGAN SITE	SIDE EFFECT* (%)	ONSET**
Cardiovascular	Hypotension (8%)	E
	Tachycardia (8%)	E
Gastrointestinal	Abdominal pain (9%)	E
	Anorexia (9%)	E
	Constipation (21%)	E
	Diarrhea (22%)	E
	Mucositis (8%)	E
	Nausea, vomiting (41%) (severe - 1%)	I E
General	Edema (15%)	E
	Fatigue (50%) (12% severe)	E
Hematological	Myelosuppression ± infection, bleeding (86%) (63% severe neutropenia, including opportunistic infections and PML)	E
Hepatobiliary	↑ LFTs (6%) (2% severe)	E
Metabolic / Endocrine	Hyperglycemia (6%)	E
	Tumor lysis syndrome (rare)	I E
Musculoskeletal	Musculoskeletal pain (13%)	E
	Rhabdomyolysis (also increased CPK; rare)	E
Nervous System	Ataxia (9%)	E
	Confusion (8%)	E
	Dizziness (21%)	E
	Hallucinations (1%)	E
	Headache (15%)	E
	Insomnia (7%)	E
	Leukoencephalopathy (rare)	E

	Myelitis (transverse - rare)	E
	Neuropathy (21%) (may be severe, including cranial - rare)	E
	Seizure (rare)	E
	Somnolence (23%)	E
Ophthalmic	Blurred vision (4%) (also reduced vision; blindness - rare)	E
Respiratory	Cough, dyspnea (25%)	E
	Pleural effusion (10%)	E

* "*Incidence*" may refer to an absolute value or the higher value from a reported range.
"*Rare*" may refer to events with < 1% incidence, reported in post-marketing, phase 1 studies, isolated data or anecdotal reports.

** I = *immediate* (onset in hours to days) E = *early* (days to weeks)
D = *delayed* (weeks to months) L = *late* (months to years)

The most common side effects in adults include myelosuppression ± infection, bleeding, fatigue, nausea, vomiting, cough, dyspnea, somnolence, diarrhea, constipation, dizziness, neuropathy and edema.

The most common side effects in pediatric patients were myelosuppression +/- infection, bleeding, headache, increased transaminase and bilirubin, decreased serum potassium and albumin and vomiting. Severe neurological events, including seizures, were also reported in pediatric patients.

Patients at risk of **tumour lysis syndrome** (i.e. high tumour burden) should have appropriate prophylaxis and be monitored closely.

Neurotoxicity is dose-limiting and may be irreversible and fatal. The risk of severe neurotoxicity (including fatalities) is higher with intrathecal chemotherapy or craniospinal irradiation. Signs and symptoms include somnolence, confusion, altered level of consciousness, seizures, ataxia, paresthesias and hypoesthesia. Severe effects may include coma, status epilepticus, myelopathy, craniospinal demyelination or ascending neuropathy resembling Guillain-Barre syndrome.

Acute **hepatic failure**, including fatalities, has been reported.

back to top

E - Dosing

Refer to protocol by which patient is being treated.

Prophylaxis for tumour lysis syndrome is recommended.

Consider antiviral and other prophylaxis for infection based on institutional guidelines.

Adults:

Single Agent (T-ALL/T-LBL):

Intravenous: 1500 mg/m² Days 1, 3 and 5 every 3 weeks

In Combination with Chemotherapy (T-ALL):*

Intravenous: 650 mg/m² daily for 5 days

*NDFP funded dosing, not from Health Canada. Refer to NDFP form and Dunsmore et al for details.

Dosage with Toxicity:

Refer to the protocol by which the patient is being treated for dose modification guidelines. The following are suggested modifications.

Toxicity / Grade	Action
Platelets < 100 x 10^9/L and/or ANC < 1.5 x 10^9/L OR Febrile neutropenia	Hold until recovery
Grade 3 non-hematologic toxicity (NOT including neurotoxicity)	Hold until recovery
Grade 4 non-hematologic toxicity OR Grade 2 or greater neurotoxicity OR rhabdomyolysis, drug-related increases in CPK	Discontinue

Dosage with Hepatic Impairment:

Nelarabine has not been studied in hepatic impairment. Patients with hepatic impairment should be monitored closely for toxicities.

Dosage with Renal Impairment:

Nelarabine has not been studied in renal impairment.

Nelarabine and ara-G are partially renally excreted. No dosage adjustment is recommended for CrCl ≥ 50 ml/min. No dosing data available for CrCl < 50 ml/min; monitor these patients closely as there may be an increased risk of adverse effects.

Dosage in the elderly:

No dosage adjustment is recommended in the elderly; however, these patients may have reduced renal function (see dosage with renal impairment). Patients over age 65 had increased rates of neurologic adverse effects.

Dosage based on gender:

A pharmacokinetic study found that AUC was 2-3 fold greater in average adult females compared to average adult males. No safety or efficacy differences were observed in clinical trials.

Dosage based on ethnicity:

The effect of race on pharmacokinetics has not been evaluated.

Children:

Refer to local protocols for details on dosing schedule.

back to top

F - Administration Guidelines

- Should not be diluted prior to administration
- Compatible with PVC infusion bags and glass containers.
- Infuse IV over 1 hour (650 mg/m^2) or 2 hours (1500 mg/m^2).
- Visually inspect for particulates and discolouration prior to administration.
- Store unopened vials at 25^{o}C with excursions permitted between 15-30^{o}C

back to top

G - Special Precautions

Contraindications:

- Patients who have a hypersensitivity to this drug or any of its components
- Concurrent intrathecal chemotherapy or craniospinal radiation

Other Warnings/Precautions:

- Patients who have had prior craniospinal irradiation, pre-existing CNS disease, or prior intrathecal therapy may be at increased risk of severe neurologic adverse effects
- Use caution with driving or using machinery as drowsiness, dizziness, or other neurologic effects may occur with treatment
- Avoid live vaccines, since they may result in serious or fatal infections in immunocompromised patients

Other Drug Properties:

- Carcinogenicity: Unknown

Pregnancy and Lactation:

- Mutagenicity: Yes
- Genotoxicity: Yes
- Teratogenicity: Yes
- Fetotoxicity: Yes
  Nelarabine is not recommended for use in pregnancy.
  - Adequate contraception should be used by patients who can become pregnant and their partners during treatment, and for at least **6 months** after the last dose (general recommendation).
  - Adequate contraception should be used by patients who produce sperm and their partners during treatment, and for **3 months** after the last dose.
- Excretion into breast milk: Unknown
  Breastfeeding is not recommended.
- Fertility effects: Unknown

back to top

H - Interactions

No formal drug interaction studies have been performed. Nelarabine does not appear to significantly inhibit CYP-P450 isoenzymes.

AGENT	EFFECT	MECHANISM	MANAGEMENT
adenosine deaminase inhibitors (pentostatin)	↓ nelarabine concentration and/or efficacy	↓ conversion of nelarabine pro-drug to active form (in vitro)	Avoid
Intrathecal chemotherapy (e.g. methotrexate)	reports of fatal neurotoxicity	Additive	Avoid

back to top

I - Recommended Clinical Monitoring

Recommended Clinical Monitoring

Monitor Type	Monitor Frequency
CBC	Baseline and before each cycle
Liver function tests	Baseline and before each cycle
Renal function tests	Baseline and before each cycle
Clinical toxicity assessment for neurotoxicity, infections and bleeding, tumour lysis syndrome, GI, musculoskeletal and respiratory effects	At each visit

Grade toxicity using the current NCI-CTCAE (Common Terminology Criteria for Adverse Events) version

back to top

J - Supplementary Public Funding

New Drug Funding Program (NDFP Website)

- Nelarabine - Newly Diagnosed T-cell Acute Lymphoblastic Leukemia

back to top

K - References

Berg SL, Blaney SM, Devidas M, et al.; Children's Oncology Group. Phase II study of nelarabine (compound 506U78) in children and young adults with refractory T-cell malignancies: a report from the Children's Oncology Group. J Clin Oncol. 2005 May 20;23(15):3376-82.

CADTH reimbursement final recommendation: Nelarabine. October 2023.

DeAngelo DJ, Yu D, Johnson JL, et al. Nelarabine induces complete remissions in adults with relapsed or refractory T-lineage acute lymphoblastic leukemia or lymphoblastic lymphoma: Cancer and Leukemia Group B study 19801. Blood. 2007 Jun 15;109(12):5136-42.

Dunsmore KP, Winter SS, Devidas M, et al. Children's Oncology Group AALL0434: A phase III Randomized clinical trial testing nelarabine in newly diagnosed T-cell acute lymphoblastic leukemia.

J Clin Oncol. 2020 Oct 1;38(28):3282-93.

McEvoy GK, ed in chief. AHFS: Drug Information. Bethesda, MD: American Society of Health-System Pharmacists; 2013: 1136-37.

Product Monograph: Atriance® (nelarabine). Sandoz Canada Inc., November 2022.

Schiff D, Wen PY, van den Bent MJ, et al. Neurological adverse effects caused by cytotoxic and targeted therapies. Nat Rev Clin Oncol 2009 Oct;6(10):596-603.

February 2024 Updated Mechanism of action, Dosing, Warnings/Precautions and Monitoring sections; added NDFP form

back to top

L - Disclaimer

Refer to the New Drug Funding Program or Ontario Public Drug Programs websites for the most up-to-date public funding information.

The information set out in the drug monographs, regimen monographs, appendices and symptom management information (for health professionals) contained in the Drug Formulary (the "Formulary") is intended for healthcare providers and is to be used for informational purposes only. The information is not intended to cover all possible uses, directions, precautions, drug interactions or adverse effects of a particular drug, nor should it be construed to indicate that use of a particular drug is safe, appropriate or effective for a given condition. The information in the Formulary is not intended to constitute or be a substitute for medical advice and should not be relied upon in any such regard. All uses of the Formulary are subject to clinical judgment and actual prescribing patterns may not follow the information provided in the Formulary.

The format and content of the drug monographs, regimen monographs, appendices and symptom management information contained in the Formulary will change as they are reviewed and revised on a periodic basis. The date of last revision will be visible on each page of the monograph and regimen. Since standards of usage are constantly evolving, it is advised that the Formulary not be used as the sole source of information. It is strongly recommended that original references or product monograph be consulted prior to using a chemotherapy regimen for the first time.

Some Formulary documents, such as the medication information sheets, regimen information sheets and symptom management information (for patients), are intended for patients. Patients should always consult with their healthcare provider if they have questions regarding any information set out in the Formulary documents.

While care has been taken in the preparation of the information contained in the Formulary, such information is provided on an "as-is" basis, without any representation, warranty, or condition, whether express, or implied, statutory or otherwise, as to the information's quality, accuracy, currency, completeness, or reliability.

CCO and the Formulary's content providers shall have no liability, whether direct, indirect, consequential, contingent, special, or incidental, related to or arising from the information in the Formulary or its use thereof, whether based on breach of contract or tort (including negligence), and even if advised of the possibility thereof. Anyone using the information in the Formulary does so at his or her own risk, and by using such information, agrees to indemnify CCO and its content providers from any and all liability, loss, damages, costs and expenses (including legal fees and expenses) arising from such person's use of the information in the Formulary.

back to top