Drug Monograph

A - Drug Name

cladribine

SYNONYM(S): 2-chloro-2'-deoxyadenosine; CdA, 2-CdA; NSC-105014-F

COMMON TRADE NAME(S): Leustatin®

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B - Mechanism of Action and Pharmacokinetics

Cladribine is structurally related to fludarabine and pentostatin but has a different mechanism of action. It is phosphorylated by deoxycytidine kinase to its corresponding nucleotide CdATP, which accumulates and is incorporated into the DNA of cells such as lymphocytes. High levels of CdATP lead to DNA strand breaks, inhibition of DNA synthesis, and cell death. May be selective for cells with high deoxycytidine kinase. Unlike other antimetabolite drugs, cladribine has cytotoxic effects on resting as well as proliferating lymphocytes and monocytes. It causes cells to accumulate at the G_1/S phase junction, suggesting that cytotoxicity is associated with events critical to cell entry into S phase. Cladribine is resistant to deamination by adenosine deaminase.

Absorption	Acid labile Bioavailability	 (oral) 37-55%
Distribution	No information found Cross blood brain barrier? PPB	 25% of plasma levels 20%
Metabolism	Prodrug, activated by intracellular phosphorylation Active metabolites	 CdATP

	Inactive metabolites	Chloroadenine
Elimination	Biphasic	
	Urine	10-30%, within 24 hours
	Half-life	5.4 hours (terminal t½)

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C - Indications and Status

Health Canada Approvals:

- Hairy cell leukemia

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D - Adverse Effects

Emetogenic Potential: Minimal

Extravasation Potential: None

Adverse effects include those with incidences ≥ 5% and those that are less common, but may be severe. Exact incidences are noted where available.

ORGAN SITE	SIDE EFFECT* (%)	ONSET**
Cardiovascular	Tachycardia (≥5%)	E
	Venous thromboembolism (2%) (thrombosis)	E D
Dermatological	Rash (27%) (may be severe)	E
Gastrointestinal	Abdominal pain (≥5%)	E
	Anorexia (≥5%)	I E
	Constipation (≥5%)	E
	Diarrhea (≥5%)	E
	Nausea, vomiting (28%) (mild)	I E

General	Edema (≥5%)	E
	Fatigue (45%)	E
	Fever (69%)	I
Hematological	Hemolysis (rare)	E
	Myelosuppression ± infection, bleeding (70%) (37% severe anemia)	E
Hepatobiliary	↑ LFTs (mild; rare)	E D
Hypersensitivity	Drug reaction (rare)	I
Infection	Infection (28%) (including opportunistic)	E
Injection site	Injection site reaction (19%)	I
Metabolic / Endocrine	Tumour lysis syndrome (rare)	I
Musculoskeletal	Musculoskeletal pain (≥5%)	E
Neoplastic	Secondary malignancy (including MDS; rare)	L
Nervous System	Dizziness (≥5%)	E
	Headache (22%)	I
	Insomnia (≥5%)	E
	Neurotoxicity (rare for standard dose; 45% with high dose)	E D
Ophthalmic	Conjunctivitis	E
Renal	Nephrotoxicity (with high doses; rare)	E
Respiratory	Cough, dyspnea (7%)	E
	Pneumonitis (rare)	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 for cladribine include myelosuppression, fever, fatigue, infection, nausea, vomiting, rash, headache, injection site reaction, cough, dyspnea and abdominal pain.

Patients at risk of tumour lysis syndrome should have appropriate prophylaxis and be monitored closely.

Severe **bone marrow suppression** has been commonly observed, especially at high doses. This appears to be dose-dependent and is usually reversible. Significant and prolonged lymphopenia has been noted. **Cumulative myelotoxicity and prolonged thrombocytopenia** can occur after multiple cycles.

Febrile episodes and infections are common. Cladribine can be **immunosuppressive**, causing a reduction in the number of CD4 (helper) and CD8 (suppressor) T lymphocytes, which can last for years. Cases of opportunistic infections and secondary malignancies have been reported.

High doses (4 to 9 times the recommended dose x 7-14 days) in conjunction with cyclophosphamide and total body radiation as preparation for bone marrow transplantation have been associated with severe, irreversible **neurologic toxicity** (paraparesis, quadriparesis, axonal polyneuropathy, demyelination) and/or **acute renal impairment** (some patients required dialysis). Axonal neuropathy has been reported with high doses of cladribine alone. Neurologic toxicity appears to be dose-related; however, severe neurotoxicity has been reported rarely with standard cladribine dosing regimens (0.09mg/kg/day x 7 days).

Severe rashes, including Steven-Johnson Syndrome and Toxic Epidermal Necrolysis have been reported in patients who were also receiving other medications (e.g. allopurinol, antibiotics).

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E - Dosing

Refer to protocol by which patient is being treated.

Screen for hepatitis B virus in all cancer patients starting systemic treatment. Refer to the hepatitis B virus screening and management guideline.

Usually given as a continuous infusion. Patients who respond to their first course of cladribine may be retreated, but non-responsive patients rarely gain benefit from additional courses.

Adults:

Intravenous: 0.09 mg/kg/day as continuous infusion for 7 days

Dosage with Toxicity:

Toxicity	Cladribine dose
Myelosuppression	No adjustment required. Consider delay until recovery to baseline counts.
Neurotoxicity	Delay or discontinue, depending on severity
Nephrotoxicity	Delay or discontinue, depending on severity. See dosage with renal impairment table.

Dosage with Hepatic Impairment:

Exercise caution. No data available.

Dosage with Renal Impairment:

10-30% excretion in urine, thus caution should be exercised.

Suggested reductions:

Creatinine clearance (mL/min)	% dose
≥ 50	100%
10-50	75%
≤ 10	50%

Dosage in the elderly:

Use with caution due to possible decreases in hepatic, renal, or cardiac function.

Children:

Safety and efficacy in children have not been established. Fatal dose-limiting toxicity occurred at doses of 10.7mg/m^2/day in a Phase I study. Do not use benzyl alcohol-containing diluents in infants or neonates.

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F - Administration Guidelines

- Continuous infusion; can be given by ambulatory infusion with CADD pump. Bacteriostatic normal saline (containing benzyl alcohol preservative) should be used as diluent. Drug and diluent should be passed through 0.22 µ hydrophilic syringe filter.
- May mix in 500 mL Normal Saline and administer over 2 hours each day.
- Do not mix with dextrose 5% in water (results in increased degradation of cladribine).
- Do not admix with other drugs.
- Vials and infusion solution should be protected from light and refrigerated (2-8°C)
- Refer to the cladribine product monograph for detailed stability information

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G - Special Precautions

Contraindications:

- Patients who have a hypersensitivity to this drug or any of its components

Other Warnings/Precautions:

- Exercise caution in patients with severe bone marrow impairment of any etiology.
- Patients receiving high doses in a clinical trial (prior to bone marrow transplantation) had severe neurotoxicity
- Avoid the use of live vaccines due to the increased risk of infection.

Other Drug Properties:

- Carcinogenicity: Yes

Pregnancy and Lactation:

- Clastogenicity: Yes
- Genotoxicity: Yes
- Fetotoxicity: Documented in animals
- Embryotoxicity: Documented in animals
- Pregnancy:
  Cladribine is not recommended for use in pregnancy. Adequate contraception should be used by patients and their partners during treatment, and for at least **6 months** after the last dose (general recommendation).
- Excretion into breast milk: Yes
  Breastfeeding is not recommended.
- Fertility effects: Probable
  Documented in animal studies with male animals

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H - Interactions

No significant drug interactions reported. Exercise caution when administered in association with other agents known to cause myelosuppression.

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I - Recommended Clinical Monitoring

Treating physicians may decide to monitor more or less frequently for individual patients but should always consider recommendations from the product monograph.

Refer to the hepatitis B virus screening and management guideline for monitoring during and after treatment.

Recommended Clinical Monitoring

Monitor Type	Monitor Frequency
CBC	Baseline, at each visit and as clinically indicated, especially during the first 4 to 8 weeks after treatment
Uric acid	Baseline and as clinically indicated, especially when treatment is initiated and in patients at risk of tumour lysis syndrome
Renal and liver function tests	Baseline, at each visit and as clinically indicated, especially with underlying renal or hepatic impairment
Clinical toxicity assessment for fever, infection, bleeding, rash, neurotoxicity, fatigue and GI toxicity	At each visit

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

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K - References

Cladribine: Drug information. UptoDate LexiDrug. Accessed Oct 23, 2024

Else M, Dearsden CE, Matutes E, et al. Long-term follow-up of 233 patients with hairy cell leukaemia, treated initially with pentostatin or cladribine, at a median of 16 years from diagnosis. BJH 2009; 145; 733–40.

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Morton J, Taylor K, Bunce I, et al. High response rates with short infusional 2-chlorodeoxyadenosine in novo and relapsed low-grade lymphoma. Australian and New Zealand Lymphoma Study Group. Br J Haematol. 1996 Oct; 95(1): 110-5.

Piro LD, Carrera CJ, Carson DA, et al. Lasting remissions in hairy-cell leukemia induced by a single infusion of 2-chlorodeoxyadenosine. NEJM 1990; 322; 1117-21.

Product Monograph: Cladribine for injection. Fresenius Kabi Canada Ltd., March 2015.

November 2024 Updated Pregnancy and Lactation section

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L - Disclaimer

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

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