DRUG NAME: Cladribine

SYNONYM(S): CdA,[1] 2-CdA,[1] 2-chloro-2'-deoxyadenosine[2]

COMMON TRADE NAME(S): LEUSTATIN®

CLASSIFICATION: antimetabolite

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

MECHANISM OF ACTION:

Like fludarabine, cladribine is a synthetic purine nucleoside prodrug that is resistant to deamination by adenosine deaminase which permits intracellular accumulation.[1] Cladribine is phosphorylated via deoxycytidine kinase to the active triphosphate derivative (CdATP) which inhibits ribonucleotide reductase.[3] In cells such as lymphocytes with high levels of deoxycytidine kinase and low levels of deoxynucleotidase, CdATP also prevents elongation of DNA strands via direct incorporation into DNA as a false nucleotide.[1,3] Depletion of adenine dinucleotide and adenosine triphosphate (ATP) also occurs.[1,3] Unlike other drugs that affect purine metabolism, cladribine has cytotoxic effects on actively dividing and resting cells.[3] Cladribine is an immunosuppressive agent.[3]

PHARMACOKINETICS:

Oral Absorption	oral solution: 37-55%[4,5]; investigational	
Distribution	extensive[2]	
	cross blood brain barrier?	yes; ~25% of plasma concentration
	volume of distribution (V_D)	4.52 ± 2.82 L/kg
	plasma protein binding	20%
Metabolism	phosphorylated to CdATP	
	active metabolite(s)	CdATP
	inactive metabolite(s) [4]	chloroadenine
Excretion	biphasic	
	urine[3,5]	18-44%
	feces	no information found
	terminal half life	5.4 h
	clearance	664 ml/h/kg 29.5 ± 8.3 L/h/m^2
Children[6,7]	V_D=305-357 L/m^2; clearance=39 L/h/m^2; longer terminal half life than adults	

Adapted from standard reference[3] unless specified otherwise.

USES:

Primary uses:

*Leukemia, hairy cell

Other uses:

Leukemia, chronic lymphocytic[1,5]
Leukemia, chronic myelogenous[5]
Lymphoma, cutaneous T-cell[1]
Lymphoma, non-Hodgkin[1,5]

*Health Canada approved indication

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SPECIAL PRECAUTIONS:

Caution:

- cladribine produces ***severe myelosuppression***; monitor hematologic function regularly especially during the first 4-8 weeks after therapy[3]
- ***high doses*** as preparation for BMT (e.g., 4-9 times the recommended dose for hairy cell leukemia) have been associated with:
  - serious neurotoxicity including irreversible paraparesis and quadriparesis (35-45%)[1,3]
  - acute nephrotoxicity (19-45%)[1,3]
  - severe bone marrow suppression[3]
- all lymphoma patients should be screened for ***Hepatitis B (HBV) reactivation***[8,9]; for recommended HBV screening and prophylaxis, see BC Cancer Protocol SCHBV ***Hepatitis B Virus Reactivation Prophylaxis***[10]

Carcinogenicity: Due to the known genotoxicity of cladribine and immunosuppression associated with the use of nucleoside analogues, the risk of malignancies may be increased in patients treated with cladribine. In clinical trials, malignancies were observed more frequently in cladribine-treated patients compared to placebo-treated patients. In animal studies, the only treatment related neoplastic finding was mainly benign Harderian gland tumours in mice which are not considered to represent a risk to humans (i.e., species specific toxicity).[11]

Mutagenicity: Not mutagenic in Ames test and mammalian *in vitro* mutation test.[3] Cladribine is clastogenic in mammalian *in vitro* and *in vivo* chromosome tests.[3]

Fertility: In animal studies, no effects on fertility or reproductive function were noted. However, testicular effects were noted in treated males, including testicular degeneration, reduced testes weight, degeneration of seminiferous tubules, atrophy of germinal epithelium, and non-motile sperm. Considering cladribine genotoxicity, male-mediated effects on the potential genetic alteration of differentiating sperm cells cannot be excluded. The effect on human fertility is not known.[11]

Pregnancy: In animal studies, cladribine was embryo-lethal in pregnant mice and teratogenic in mice and rabbits (e.g., caused skeletal malformations and variations in fetal growth/development). These effects are consistent with drugs which inhibit DNA synthesis. Contraception is recommended in women and men of reproductive potential during treatment with cladribine and for 6 months after treatment has ended.[11]

Breastfeeding is not recommended due to the potential secretion into breast milk.[3]

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.[8]

At recommended doses, most nonhematologic adverse effects are typically mild to moderate in severity.[1]

ORGAN SITE	SIDE EFFECT
Clinically important side effects are in ***bold, italics***	
blood/bone marrow/ febrile neutropenia	anemia (severe 37%) nadir typically occurs during the first 2 weeks with recovery by week 8; hemolytic anemia and aplastic anemia also reported
	bone marrow hypocellularity (34%); prolonged hypocellularity (32 months) has been reported
	erythroid macrocytosis[1]; prolonged, reported in patients who received up to 6 courses of cladribine[1]
	febrile neutropenia (47%; 32% with severe neutropenia)

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ORGAN SITE	SIDE EFFECT
Clinically important side effects are in ***bold, italics***	
	hypereosinophilia; typically occurs in patients receiving multiple courses of cladribine[1]
	lymphopenia; may be significant and prolonged
	myelosuppression; dose-related, most notable during the first month after treatment
	neutropenia (severe 70%); nadir typically occurs during the first 2 weeks with recovery by week 5
	thrombocytopenia (12%); nadir typically occurs during the first 2 weeks with recovery by day 12; recovery may be delayed in patients with severe baseline thrombocytopenia[1]
cardiovascular (arrhythmia)	tachycardia (≤6%)[1,3,5]
constitutional symptoms	chills (≤9%)[1,3,5]
	fatigue (≤45%), asthenia (≤9%)[1,3]
	fever (67-69%, severe 11%); during the first month of therapy; less than a third of febrile events are associated with a documented infection
	insomnia (≤7%)[1,3]
	diaphoresis (≤9%)[1,3,5]
dermatology/skin	*extravasation hazard:* none[12]
	injection site reaction (≤19%); including redness (≤6%),[1,3] swelling, pruritis (≤6%),[1,3] pain (≤6%)[3]
	phlebitis (2%); likely related to the infusion procedure and/or indwelling catheter rather than the treatment
	rash (≤27%); typically mild
	Stevens-Johnson syndrome and toxic epidermal necrolysis (<1%)
	urticaria; typically occurs in patients receiving multiple courses of cladribine[1]
gastrointestinal	*emetogenic potential:* rare[13]
	anorexia (≤17%)[1,3]
	constipation (≤9%)[1,3,5]
	diarrhea (≤10%)[1,3,5]
	nausea (28%); typically mild and not associated with vomiting
	vomiting (≤13%)[1,3,5]
hemorrhage	epistaxis (>5%)[1,3,5]
	purpura (≤10%),[1,3,5] petechiae (≤8%)[1,3,5]
hepatobiliary/pancreas	elevated bilirubin and transaminases; reversible and typically mild; typically occurs in patients receiving multiple courses of therapy[1]
infection	***immunosuppression***; prolonged depression of CD4 counts (CD4 nadir typically during the first 4-6 months, with recovery by 40 months), transient suppression of CD8 counts, and prolonged lymphopenia
	infection (28%); during the first month after treatment; including septicemia, pneumonia (6%), and infections associated with immunosuppression (e.g., opportunistic infections); deaths have occurred
lymphatics	edema (≤6%)[1,3,5]

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ORGAN SITE	SIDE EFFECT
Clinically important side effects are in ***bold, italics***	
metabolic/laboratory	hyperuricemia
musculoskeletal	myalgia (≤7%)[1,3,5]; arthralgia (>5%)[1,3,5]
	weakness (9%)[5]
neurology	dizziness (≤9%)[1,3,5]
	neurotoxicity (severe <1%); with standard-dose
	neurotoxicity (35-45%)[1,3]; with high dose (4-9 times the recommended dose); may be severe and irreversible including peripheral polyneuropathy, paraparesis, and quadriparesis
pain	abdominal pain (≤6%)[1,3,5]
	headache (≤22%)
	trunk pain (≤6%)[1,3]
pulmonary	abnormal breath sounds (≤11%)[1,3,5]
	cough (≤10%)[1,3,5]
	dyspnea (≤7%)[1,3,5]
	pulmonary interstitial infiltrates; typically of infectious etiology
renal/genitourinary	renal insufficiency (19-45%)[1,3]; with high dose (4-9 times the recommended dose); not reported with standard doses
secondary malignancy	myelodysplastic syndrome (0.03%)
syndromes	tumour lysis syndrome (<1%)
vascular	thrombosis (2%); likely related to the infusion procedure and/or indwelling catheter rather than treatment

Adapted from standard reference[3] unless specified otherwise.

Hyperuricemia may result from cell lysis by cytotoxic chemotherapy and may lead to electrolyte disturbances or acute renal failure.[14] It is most likely with highly proliferative tumours of massive burden, such as leukemias, high-grade lymphomas, and myeloproliferative diseases. The risk may be increased in patients with preexisting renal dysfunction, especially ureteral obstruction. Suggested prophylactic treatment for high-risk patients[15]:

- aggressive hydration: 3 L/m²/24 hr with target urine output >100 ml/h
- if possible, discontinue drugs that cause hyperuricemia (e.g., thiazide diuretics) or acidic urine (e.g., salicylates)
- monitor electrolytes, calcium, phosphate, renal function, LDH, and uric acid q6h x 24-48 hours
- replace electrolytes as required
- allopurinol 600 mg po initially, then 300 mg po q6h x6 doses, then 300 mg po daily x 5-7 days

Urine should be alkalinized only if the uric acid level is elevated, using sodium bicarbonate IV or PO titrated to maintain urine pH>7. Rasburicase (FASTURTEC®) is a novel uricolytic agent that catalyzes the oxidation of uric acid to a water-soluble metabolite, removing the need for alkalinization of the urine.[16] It may be used for treatment or prophylaxis of hyperuricemia; however, its place in therapy has not yet been established. Aluminum hydroxide (e.g., AMPHOGEL®) may be added orally if phosphate becomes elevated. If aluminum hydroxide has been added, discontinue sodium bicarbonate.[17]

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INTERACTIONS: no documented interactions

SUPPLY AND STORAGE:

Injection: Janssen-Ortho Inc. supplies cladribine as a preservative-free 10 mg/10 mL solution. Store in the refrigerator, protect from light during storage. Freezing does not affect the solution. If freezing occurs, thaw at room temperature, do not refreeze.[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.

Additional information: must be diluted prior to intravenous administration[3]

Compatibility: consult detailed reference

PARENTERAL ADMINISTRATION:

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

Subcutaneous[2,5,9]	***rotate sites on thighs, abdomen, and flank***
Intramuscular	no information found
Direct intravenous[3]	not recommended; must be diluted prior to intravenous administration[3]
Intermittent infusion[3,5]	***over* 1-*2 h***
Continuous infusion[3]	***over 24 h; 7-day infusions have been used***
Intraperitoneal	no information found
Intrapleural	no information found
Intrathecal	no information found
Intra-arterial	no information found
Intravesical	no information found

DOSAGE GUIDELINES:

Refer to protocol by which patient is being treated. Numerous dosing schedules exist and depend on disease, response, and concomitant therapy. Guidelines for dosing also include consideration of absolute neutrophil count (ANC). Dosage may be reduced, delayed or discontinued in patients with bone marrow depression due to cytotoxic/radiation therapy or with other toxicities.

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Adults:

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

Intravenous:

Cycle Length:

n/a[5,9]: ***0.14 mg/kg*** (range 0.028-0.14 mg/kg) ***IV or SC once daily for 5 consecutive days starting on day 1***
(total dose 0.7 mg/kg [range 0.14-0.7 mg/kg])

n/a[1,3,5]: 0.09-0.1 mg/kg IV over 24 hours for 7 consecutive days starting on day 1
(total dose 0.63-0.7 mg/kg)
- may be administered as a continuous 7-day infusion

n/a[2,3]: 3.6 mg/m^2 IV over 24 hours for 7 consecutive days starting on day 1
(total dose 25.2 mg/m^2)
- may be administered as a continuous 7-day infusion

n/a[1,5]: 3.4 mg/m^2 SC once daily for 7 consecutive days starting on day 1
(total dose 23.8 mg/m^2)

Concurrent radiation: no information found

Dosage in myelosuppression: modify according to protocol by which patient is being treated; if no guidelines available, refer to Appendix 6 "Dosage Modification for Myelosuppression"

Dosage in renal failure: use with caution[3]; dosage adjustment recommendations exist[18], including the following [9]:

Creatinine clearance (mL/min)	Dose
>70	100%
30-70	60%
<30	do not use

Calculated creatinine clearance = $\frac{N^* \times (140 - \text{Age}) \times \text{weight in kg}}{\text{Serum Creatinine in micromol/L}}$

* For males N=1.23; for females N=1.04

Dosage in hepatic failure: use with caution[3]

Dosage in dialysis: unknown if removed by dialysis[1]

Children: *safety and effectiveness have not been established[3]; has been used[1,5-7]

*Note: Cladribine IV solutions prepared with bacteriostatic NS (e.g., for a 7-day infusion) contain benzyl alcohol and should NOT be used in neonates[3]

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