

DRUG NAME: Aldesleukin**SYNONYM(S)¹:** Interleukin-2, IL-2**COMMON TRADE NAME(S):** PROLEUKIN®**CLASSIFICATION:** biological response modifier*Special pediatric considerations are noted when applicable, otherwise adult provisions apply.***MECHANISM OF ACTION:**

Aldesleukin is a biosynthetic analogue of the human cytokine interleukin-2.^{1,2} While the exact mechanism is unknown, it has been shown to inhibit tumour growth and have immunomodulating activity.^{1,2} Its immunomodulating effects include enhancement of lymphocyte mitogenesis, enhancement of lymphocyte cytotoxicity, activation of cellular immunity (with profound lymphocytosis, eosinophilia, and thrombocytopenia), and induction of tumor necrosis factor, IL-1, and interferon-gamma production.¹ Aldesleukin is an immunosuppressive agent.¹

PHARMACOKINETICS:

Oral Absorption	no information found	
Distribution	rapid; primarily to lungs, liver, kidney and spleen; 30% of dose detectable in plasma following IV infusion ²	
	cross blood brain barrier?	no information found
	volume of distribution ³	4-7 L
	plasma protein binding	no information found
Metabolism	primarily renal	
	active metabolite(s)	no
	inactive metabolite(s)	amino acids
Excretion	minimal	
	urine	trace or none ^{1,2}
	feces	no information found
	terminal half life ^{1,3}	80-120 min
	clearance	268 mL/min

Adapted from standard reference¹ unless specified otherwise.**USES:****Primary uses:**

- *Melanoma
- *Renal cell cancer

*Health Canada approved indication

Other uses:Neuroblastoma⁴

SPECIAL PRECAUTIONS:**Contraindications:**

- history of hypersensitivity reaction to aldesleukin¹
- abnormal thallium stress test and/or pulmonary function tests¹
- organ allografts¹
- significant cardiac, pulmonary, renal, hepatic or central nervous system impairment¹
- re-treatment is contraindicated if the following toxicities occurred during an earlier course of therapy¹:
 - sustained ventricular tachycardia (≥ 5 beats)
 - cardiac arrhythmias not controlled or unresponsive to management
 - chest pain with ECG changes, consistent with angina or myocardial infarction
 - cardiac tamponade
 - intubation required >72 h
 - renal failure requiring dialysis >72 h
 - coma or toxic psychosis lasting >48 h
 - repetitive or difficult to control seizures
 - bowel ischemia/perforation
 - GI bleeding requiring surgery

Caution:

- administer only in a **hospital setting with an intensive care facility** and specialists skilled in cardiopulmonary or intensive care medicine available¹
- extreme caution in those with normal thallium stress test and normal pulmonary function tests but who have a history of prior cardiac or pulmonary disease¹
- exacerbation of pre-existing or initial presentation of autoimmune disease and inflammatory disorders may occur¹

Carcinogenicity: no information found

Mutagenicity: no information found

Fertility: no information found

Pregnancy: FDA Pregnancy Category C.³ Animal studies have shown fetal risks and there are no controlled studies in women. Drugs should be given only if the potential benefit justifies the potential risk to the fetus. Do not administer to fertile persons of either gender not practicing effective contraception.¹

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.

ORGAN SITE	SIDE EFFECT
Clinically important side effects are in bold, italics	
blood/bone marrow/ febrile neutropenia	anemia (29%)
	leukopenia (16%)
	neutropenia
	thrombocytopenia (37%, severe 1%)
cardiovascular	arrhythmia (10%)

ORGAN SITE	SIDE EFFECT
Clinically important side effects are in bold, italics	
(arrhythmia)	tachycardia (23%, severe 1%); supraventricular tachycardia (12%, severe 1%)
cardiovascular (general)	cardiovascular disorder (11%, severe 1%); including fluctuations in blood pressure, asymptomatic ECG changes and CHF
	cardiac arrest (1%)
	hypotension (71%, severe 3%) ^{1,2} ; dose limiting, may be fatal ⁵ : see paragraph following Side Effects table
	myocardial infarction (1%)
coagulation	intravascular coagulopathy (\leq 10%, severe 1%)
constitutional symptoms	asthenia (23%) ^{1,2} ; fatigue ² ; malaise (27%) ^{1,2}
	chills (52%) ^{1,2}
	fever (29%, severe 1%) ^{1,2}
	rigors
	weight gain (16%)
dermatology/skin	extravasation hazard: none ^{2,3}
	exfoliative dermatitis (18%)
	pruritis (24%)
	rash (42%)
gastrointestinal	emetogenic potential: low-moderate ⁶
	abdomen enlarged (10%)
	anorexia (20%)
	diarrhea (67%, severe 2%)
	nausea and vomiting (19%)
	nausea without vomiting (35%)
	stomatitis (22%)
	vomiting without nausea (50%, severe 1%)
infection	infection (13%, severe 1%)
	sepsis (\leq 10%, severe 1%)
lymphatics	edema (15%)
	peripheral edema (28%)
metabolic/laboratory	acidosis (12%, severe 1%)
	bilirubinemia (40%, severe 2%)
	hypocalcemia (11%)
	hypomagnesemia (12%)
	increased alkaline phosphatase (10%)
	increased creatinine (33%, severe 1%)
	increased SGOT (23%, severe 1%)
musculoskeletal	arthralgia ²

ORGAN SITE	SIDE EFFECT
Clinically important side effects are in <i>bold, italics</i>	
	myalgia ²
neurology	see paragraph following Side Effects table
	anxiety (12%)
	<i>coma</i> ($\leq 10\%$, severe 2%)
	<i>confusion</i> (34%, severe 1%)
	depression
	dizziness (11%)
	irritability
	psychosis ($\leq 10\%$, severe 1%)
	seizures
	<i>somnolence</i> (22%); withhold therapy if moderate to severe as continued administration may result in coma
stupor ($\leq 10\%$, severe 1%)	
pain	abdominal pain (11%) ^{1,2}
	back pain ²
	chest pain ²
	pain, not otherwise specified (12%) ^{1,2}
pulmonary	apnea ($\leq 10\%$, severe 1%)
	cough increase (11%)
	dyspnea (43%, severe 1%)
	lung disorder (24%); physical findings associated with pulmonary congestion, rales, and rhonchi
	<i>respiratory disorder</i> (11%, severe 3%); including ARDS, CXR infiltrates, unspecified pulmonary changes, respiratory failure; may require intubation ²
	rhinitis (10%)
renal/genitourinary	acute kidney failure ($\leq 10\%$, severe 1%)
	anuria ($\leq 10\%$, severe 5%)
	<i>oliguria</i> (63%, severe 6%)
syndromes	<i>capillary leak syndrome</i> (see paragraph following Side Effects table)
	<i>flu-like syndrome</i> ² ; may be minimized by use of an antipyretic agent or NSAID immediately before the initiation of therapy and continuing for 12 hours after the last dose ²
vascular	vasodilation (13%)

Adapted from standard reference¹ unless specified otherwise.

Capillary leak syndrome¹ typically begins immediately after treatment starts and is characterized by a loss of vascular tone and extravasation of plasma proteins and fluid into the extravascular space. Resulting ***hypotension*** and reduced organ perfusion may be severe and can result in death. Capillary leak syndrome may be associated with cardiac arrhythmias (supraventricular and ventricular), angina, myocardial infarction, respiratory insufficiency requiring intubation, gastrointestinal bleeding or infarction, renal insufficiency, edema, and mental status changes.

Most of the severe toxicities observed during aldesleukin therapy have been associated with capillary leak syndrome.^{7,8} The manufacturer's monograph and additional references should be consulted for further details regarding management strategies which may include invasive monitoring, IV fluids, pressor support, diuretics, oxygen and blood transfusion.^{1,8}

Neurologic changes¹ have also been reported in patients without evidence of CNS metastases. These include changes in mental status, speech difficulties, cortical blindness, limb or gait ataxia, hallucinations, agitation, obtundation, and coma. Radiological findings included cortical lesions and evidence of demyelination. Signs and symptoms usually improved after discontinuation, however, there are reports of permanent neurologic defects.¹

INTERACTIONS:

AGENT	EFFECT	MECHANISM	MANAGEMENT
dexamethasone ¹	reduced therapeutic effect of aldesleukin	unknown	reserve use of dexamethasone for amelioration of life-threatening toxicities

SUPPLY AND STORAGE:

Injection¹: Novartis Pharmaceuticals Canada Inc. supplies vials containing 22 million IU (1.3 mg) aldesleukin. Refrigerate and protect from light.

For basic information on the current brand used at the BC Cancer Agency, see [Chemotherapy Preparation and Stability Chart](#) in Appendix.

SOLUTION PREPARATION AND COMPATIBILITY:

For basic information on the current brand used at the BC Cancer Agency, see [Chemotherapy Preparation and Stability Chart](#) in Appendix.

Additional information: Dilution preferably in a plastic (PVC) container.²

Compatibility: consult detailed reference

PARENTERAL ADMINISTRATION:

BCCA administration guideline noted in ***bold, italics***

Subcutaneous ²	has been used
Intramuscular	no information found
Direct intravenous	no information found
Intermittent infusion ^{1,2}	over 15 minutes
Continuous infusion ²	has 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.

Adults:

BCCA usual dose noted in ***bold, italics***

	Cycle Length:	
<i>*Intravenous:</i>	**10 weeks ¹⁻³ :	0.6 million IU/kg*** IV every 8 hours to a maximum of 14 doses. Following 9 days of rest, the schedule is repeated for another 14 doses, to a maximum of 28 doses per cycle, as tolerated. (total dose per cycle 16.8 million IU/kg)
	n/a ³ :	24 million IU/m ² IV daily on Days 12-16 and 19-23 of concurrent chemotherapy cycle
	10-18 days ² :	18 million IU/m ² by continuous IV infusion daily for 5 days
<i>*Subcutaneous³:</i>	n/a:	3-18 million IU SC daily for 5 days each week, up to 6 weeks
	n/a:	5 million IU/m ² SC three times a week
	n/a:	1.8 million IU/m ² SC twice daily 5 days each week, for 6 weeks

*In the event of adverse events requiring dose adjustment, dosage should be withheld rather than reduced.¹ See **Contraindications** under **Special Precautions**.

**Each cycle should be separated by a rest period of at least 7 weeks from the date of hospital discharge

*** 18 million IU = 1.1 mg
1 Roche Unit (RU) = 3 IU
1 Cetus Unit (CU) = 6 IU

Concurrent radiation: no information found

Dosage in myelosuppression: modify according to protocol by which patient is being treated; in the event of adverse events requiring dose adjustment, dosage should be withheld rather than reduced¹

Dosage in renal failure: no information found; clearance is preserved in patients with rising serum creatinine concentrations²

Dosage in hepatic failure: no information found

Dosage in dialysis: no information found

Children:

Intravenous & Subcutaneous: safety and effectiveness not established¹; has been used.⁴

REFERENCES:

1. Novartis Pharmaceuticals Canada Inc. PROLEUKIN® product monograph. Dorval, Quebec; 6 July 2006.
2. McEvoy GK, editor. AHFS 2008 Drug Information. Bethesda, Maryland: American Society of Health-System Pharmacists, Inc. p. 917-925.
3. Rose BD editor. Aldesleukin: Drug information. UpToDate 16.1 ed. Waltham, Massachusetts: UpToDate®; 2008.
4. B.C. Children's Hospital. Children's Oncology Group (COG) Protocol ANBL0032. Vancouver, British Columbia: BC Children's Hospital; 16 April 2009.
5. Rose BD editor. Aldesleukin. www.uptodate.com ed. Waltham, Massachusetts: UpToDate 15.1; 2007.
6. BC Cancer Agency. (SCNAUSEA) Guidelines for Prevention and Treatment of Chemotherapy-induced Nausea and Vomiting in Adults. Vancouver, British Columbia: BC Cancer Agency; 1 March 2008.
7. Fyfe G, Fisher R, Rosenberg S, et al. Results of treatment of 255 patients with metastatic renal cell carcinoma who received high-dose recombinant interleukin-2 therapy. *J Clin Oncol* 1995;13(3):688-696.
8. Schwartzenuber DJ. Guidelines for the safe administration of high dose IL-2. *J Immunother* 2001;24(2):287-293.