Drug Monograph

A - Drug Name

aldesleukin

SYNONYM(S): interleukin-2; IL-2; lymphocyte mitogenic factor; T-cell growth factor; thymocyte stimulating factor

COMMON TRADE NAME(S): Proleukin® (interleukin-2)

back to top

B - Mechanism of Action and Pharmacokinetics

Aldesleukin, a recombinant interleukin-2, has multiple immunologic effects, including activation of cellular immunity with lymphocytosis, eosinophilia, thrombocytopenia and production of lymphokines including TNF, IL-1 and gamma-interferon. Tumour growth inhibition has been reported in *in vivo* studies. Objective responses are seen in ± 16% of patients but no overall survival benefit in controlled studies has been demonstrated.

Absorption	Oral: no	
Distribution	Pharmacokinetics appear to be dose proportional. Uptake into lung, liver, spleen and kidney is rapid.	
	Cross blood brain barrier?	No information found
	PPB	No information found
Metabolism	Aldesleukin is rapidly metabolized to its composite amino acids in the proximal tubules of the kidney.	
	Active metabolites	Trace
	Inactive metabolites	Yes (to its composite amino acids)

Elimination	2- compartmental disposition, cleared as inactive metabolites by glomerular filtration and peritubular extraction	
	Clearance	268mL/minute
	Half-life	13-85 minutes
	Urine	80% via renal tubular and glomerular filtration

back to top

C - Indications and Status

Health Canada Approvals:

- Carefully selected adults with metastatic renal cell carcinoma
- Carefully selected adults with metastatic malignant melanoma

back to top

D - Adverse Effects

Emetogenic Potential: Minimal (Intralesional)
Low (IV doses ≤ 12 MU/m2)
Moderate (IV doses >12-15 MU/m2)

Extravasation Potential: None

ORGAN SITE	SIDE EFFECT* (%)	ONSET**
Cardiovascular	Arterial thromboembolism (rare)	E
	Cardiotoxicity (<1%)	E
	Venous thromboembolism (rare)	E
	Ventricular arrhythmia (12%) (supraventricular)	I
Dermatological	Other (persistent vitiligo; rare)	E
	Rash (42%) (may be exfoliative)	I E
Gastrointestinal	Abdominal pain (11%)	E
	Anorexia (20%)	E

	Diarrhea (67%)	E
	GI perforation (or obstruction, +/- bleeding; rare)	E
	Mucositis (22%)	E
	Nausea, vomiting (50%)	I E
General	Fatigue (27%)	E
	Flu-like symptoms (52%)	I
	Hyperthermia (1%) (malignant hyper or hypothermia)	E
Hematological	Disseminated intravascular coagulation (1%)	I
	Myelosuppression ± infection, bleeding (37%) (severe 1%)	E
Hepatobiliary	↑ LFTs (40%) (may be severe)	E
	Pancreatitis (rare)	E
Hypersensitivity	Drug reaction (rare)	E
Immune	Other (risk of rejection in allograft recipients, exacerbation of autoimmune diseases)	E D
Infection	Infection (13%) (may be severe, including atypical)	E
Metabolic / Endocrine	Abnormal electrolyte(s) (12%) (decreased Ca, Mg)	E
	Acidosis (12%)	I E
Musculoskeletal	Rhabdomyolysis (especially with interferon; rare)	E
Nervous System	Confusion (34%) (includes somnolence)	E
	Depression (4%) (may be severe)	E D
	Dizziness (11%)	E
	Leukoencephalopathy (rare)	E
	Neuropathy (6%; optic neuritis, demyelination-rare)	E
	Seizure (<1%)	E
Ophthalmic	Conjunctivitis (2%)	E
	Eye disorders (1%)	E
Renal	Creatinine increased (33%) (may be severe)	E
	Tumor lysis syndrome (with chemotherapy)	E
Respiratory	Acute respiratory distress syndrome (ARDS) (3%)	E
	Dyspnea (43%)	E
Vascular	Capillary leak syndrome (71%)	I E
	Vasculitis (cutaneous; cerebral- 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)

Most adverse reactions usually reverse or improve within 2-3 days of discontinuing therapy, due to aldesleukin's short half-life, but drug-related deaths occur in 2-4% of patients treated with aldesleukin.

The major dose-limiting side effect of aldesleukin is **capillary leak syndrome**. Aldesleukin administration induces decreased vascular tone and increased vascular permeability leading to hypotension, reduced organ perfusion and function (renal, cardiac, hepatic, etc.), ascites, effusions, cardiac arrhythmias/ischemia and respiratory insufficiency. The management of capillary leak syndrome involves careful monitoring of fluid and organ perfusion. Administration of intravenous dopamine or phenylephrine to increase blood pressure may help maintain organ perfusion, particularly renal perfusion and thereby preserve urine output. Administration of subsequent doses of aldesleukin should be delayed until recovery of organ perfusion is observed.

Renal dysfunction is reversible and also usually secondary to capillary leak syndrome. It is also correlated with the dose, duration of treatment and the patient's baseline renal function. The administration of indomethacin for flu-like syndrome may potentiate renal dysfunction by decreasing intrarenal prostaglandins.

A **flu-like syndrome (fever, rigors and chills)** develops in most patients receiving aldesleukin. Treatment with acetaminophen or a NSAID (e.g. ibuprofen, indomethacin) may minimize the risk, but renal function should be monitored carefully. In clinical trials, meperidine was administered to control the rigors associated with fever.

The clinical significance of developing **non-neutralizing anti-interleukin-2 antibodies** to aldesleukin is unknown. The incidence of antibodies formation is less than 1%. Exacerbation of autoimmune disorders such as Crohns, myasthenia, vasculitis, hypo or hyperthyroidism and diabetes mellitus may also occur.

Hypersensitivity has been described and may be exacerbated when aldesleukin is administered with other drugs; delayed reactions may occur with contrast media.

CNS toxicity is dose-related and generally reversible, but it may be associated with demyelination and may be irreversible in some patients.

back to top

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.

Patients must be managed as an inpatient in a tertiary care setting with full ICU facilities. Consider the following pre-medications (generally discontinued 12 hours after the last dose of aldesleukin):

- prophylactic antibiotics in patients with indwelling catheters
- Antipyretics
- H_2 antagonists
- Start meperidine and antidiarrheals early at the onset of symptoms.

Note: 1 MU = 1 million units = 1 million IU (international units) = 0.061 mg

Adults:

Optimal dosage and regimen for aldesleukin have not been established, but the following regimen has been approved by Health Canada.

Intravenous: 600,000 IU/kg (by a 15-minute infusion q8h; maximum 14 doses x 2)

Day	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19
Dose	XXX	XXX	XXX	XXX	XX										XXX	XXX	XXX	XXX	XX

(X refers to a single dose)

The course may be repeated 7 weeks after hospital discharge, if tolerable and there is evidence of anti-tumour response.

Dosage with Toxicity:

Aldesleukin should be held for toxicity rather than reducing the dose to be given. Consult the product monograph for detailed management recommendations.

Dose interruption:

Body system		Hold; May Restart after Recovery	Discontinue permanently
Cardiovascular	Atrial fibrillation, SVT, bradycardia	X	
	Hypotension – pressors needed	X	
	EKG ischemia or myocarditis	X	
	Sustained VT, incontrollable arrhythmia		X
	Angina, AMI, tamponade		X
Respiratory	O_2 saturation < 94% on room air or < 90% with 2 liters O_2	X	
	Intubation for > 72hrs		X
CNS	Moderate-severe confusion, agitation, lethargy or somnolence	X	
	Coma, psychosis > 48 hrs		X
	Uncontrollable seizures		X
Infection	Grade 4, unstable	X	
Renal	Serum creatinine > 400 µmol/L Oliguria - < 10 mL/hour for 16-24 hours with ↑ creatinine	X	
	Dialysis required ≥ 72hrs		X
Hepatic	Hepatic failure**	X	
Skin	Bullous dermatitis	X	
GI	Ischemia, perforation		X
	Bleed not requiring surgery	X	
	Bleed requiring surgery		X

**Abandon course. Do not start new course for at least 7 weeks after recovery.

Dosage in myelosuppression: No adjustment required

Dosage with Hepatic Impairment:

Hold until recovery if any signs of hepatic failure are present. See table above.

Dosage with Renal Impairment:

Do not start treatment if creatinine > 130 µmol/L. See table above.

Dosage in the elderly:

Limited data in elderly patients. Monitor renal function closely as the elderly may have decreased renal function.

Children:

Safety and effectiveness in children under 18 years of age have not been established.

back to top

F - Administration Guidelines

- Each vial (1.3 mg) should be reconstituted with 1.2 mL of SWI.
- During reconstitution, SWI USP should be directed at the side of the vial and the contents gently swirled to avoid excess foaming. Do not shake.
- Addition of BSWI or NS may promote aggregation and these solutions should not be used
- For IV administration, dilute further in 50 mL bag of D5W; infuse over 15 minutes
- Final concentration of drug should be 30 - 70µg/mL
- Drug delivery is more consistent when diluted in PVC container rather than non-PVC container
- In-line filter should not be used when administering aldesleukin
- Keep refrigerated; do not freeze. Avoid exposure to heat and light.

back to top

G - Special Precautions

Contraindications:

- known allergic reaction to aldesleukin, interleukin-2 or any components of the product
- abnormal thallium stress test
- abnormal pulmonary function tests
- organ allografts
- significant cardiac, pulmonary, renal, hepatic or CNS impairment
- concomitant use of cisplatin, vinblastine and dacarbazine as fatal tumour lysis syndrome has been reported

Other Warnings/Precautions:

- use with extreme caution in patients with known cardiac, pulmonary or seizure disorders (even with normal thallium and pulmonary function tests)
- use with extreme caution in patients with large fluid requirements (e.g., hypercalcemia)
- use with caution in patients with inflammatory or autoimmune disorders
- use with caution in combination with antihypertensives and psychotropic drugs as well as hepatotoxic, cardiotoxic or nephrotoxic drugs

Other Drug Properties:

- Carcinogenicity: Unknown

Pregnancy and Lactation:

- Embryotoxicity: Probable
  Aldesleukin 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: Unknown
  Breastfeeding is not recommended.

Other:

Patients should have baseline pulmonary function tests with arterial blood gases, thallium stress tests to exclude the presence of significant coronary artery disease, and brain imaging to exclude metastases. Patients who have had a nephrectomy are still eligible for treatment if they have serum creatinine levels within normal range. Pre-existing infections must be treated prior to starting aldesleukin.

back to top

H - Interactions

AGENT	EFFECT	MECHANISM	MANAGEMENT
Psychotropics (narcotics, sedatives, tranquilizers, antiemetics)	Enhances CNS toxicities	Additive	Caution
Antihypertensives	Potentiate hypotension	Additive	Caution; monitor blood pressure
Radiographic iodinated contrast media	non-anaphylactic hypersensitivity	Unknown	Caution
Glucocorticoids	↓ anti-tumour effect of aldesleukin	Unknown	Avoid, but may be needed to manage side effects
cytotoxics	Potentiate myelosuppression, TLS	Additive	Caution
Nephrotoxic drugs (i.e. aminoglycosides, amphotericin B, methotrexate)	potentiate renal toxicity	Additive (possibly)	Caution
Hepatotoxic agents (e.g., methotrexate, asparaginase)	potentiate hepatotoxicity	Additive (possibly)	Caution
Cardiotoxic agents (e.g., doxorubicin)	Potentiate cardiotoxicity	Additive (possibly)	Caution
DTIC, cisplatin, interferon, tamoxifen	↑ hypersensitivity	Additive	Caution
Interferon	↑ hypersensitivity, cardiotoxicity and rhabdomyolysis, autoimmune disease	Unknown	Caution
Drug excreted via liver or kidney	↓ excretion	↓ renal, liver function	Caution

back to top

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 and frequent
Electrolytes, blood glucose	Baseline and frequent
Liver function tests	Baseline and frequent
Renal function tests, fluid intake and output	Baseline and frequent
Pulmonary function tests with arterial blood gases (FEV_1 > 2L or ≥ 75% of predicted for age)	Baseline
CT scan of brain to exclude CNS metastases	Baseline
Thallium stress tests to exclude significant coronary artery disease	Baseline
Frequent weight, vital signs, EKG etc. during treatment	
Chest x-ray	Baseline and regular
Clinical toxicity assessment for GI, hydration, cardiovascular, CNS, perfusion, autoimmune effects	regular

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

Suggested Clinical Monitoring

Monitor Type	Monitor Frequency
• Repeat thallium testing if suspicion of ischemia or congestive cardiac failure • Constant cardiac rhythm monitoring and hourly vital signs in patients with hypotension, especially bp < 90 mmHg	

back to top

J - Supplementary Public Funding

New Drug Funding Program (NDFP Website)

- Aldesleukin (interleukin-2) - In-Transit Metastases from Melanoma

back to top

K - References

McEvoy GK, editor. AHFS Drug Information 2009. Bethesda: American Society of Health-System Pharmacists, p. 915-24.

Proleukin® (aldesleukin/interleukin-2) [product monograph]. Dorval, Quebec: Novartis Pharmaceuticals Canada Inc.; Sept 20, 2012.

April 2024 Updated pregnancy/breastfeeding section

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.

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back to top