# 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. 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 reference[1] unless specified otherwise.

## USES:

***Primary uses:***

Melanoma[4]

*Renal cell cancer

***Other uses:***

Neuroblastoma[5]

*Health Canada approved indication

## SPECIAL PRECAUTIONS:

***Contraindications:***

- history of hypersensitivity reaction to aldesleukin[6]
- significant cardiac, pulmonary, renal, hepatic or central nervous system impairment[6]
- abnormal thallium stress test and/or pulmonary function tests[6]



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- organ allografts[6]
- re-treatment is contraindicated if the following toxicities occurred during an earlier course of therapy[6]:
  - sustained ventricular tachycardia (≥5 beats)
  - uncontrolled cardiac arrhythmias or arrhythmias 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:***
- patients with a ***history of cardiac or pulmonary disease*** but normal thallium stress and pulmonary function tests require extra caution during treatment[6]
- exacerbation of pre-existing or initial presentation of ***autoimmune disease*** and ***inflammatory disorders*** may occur[6]
- treat ***CNS metastases*** prior to aldesleukin treatment as new neurologic signs/symptoms and anatomic lesions have been reported without evidence of metastases[6]
- treat ***pre-existing bacterial infections*** prior to aldesleukin treatment as disseminated infections acquired during treatment are a major contributor to patient morbidity[6]

***Carcinogenicity:*** no information found

***Mutagenicity:*** no information found

***Fertility:*** no information found

***Pregnancy:*** In animal studies, aldesleukin has been shown to have embryolethal effects at doses 27-36 times the human dose. No evidence of teratogenicity was observed.[7]

***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) | arrhythmia (10%) |
| | tachycardia (23%, severe 1%); supraventricular tachycardia (12%, severe 1%) |



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| ORGAN SITE | SIDE EFFECT |
|---|---|
| Clinically important side effects are in ***bold, italics*** | |
| 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[8]: see paragraph following **Side Effects** table |
| | myocardial infarction (1%) |
| coagulation | intravascular coagulopathy (≤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[9] |
| | 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 (≤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%) |



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| ORGAN SITE | SIDE EFFECT |
|---|---|
| Clinically important side effects are in ***bold, italics*** | |
| musculoskeletal | arthralgia[2] |
| | myalgia[2] |
| neurology | see paragraph following **Side Effects** table |
| | anxiety (12%) |
| | ***coma*** (≤10%, severe 2%) |
| | ***confusion*** (34%, severe 1%) |
| | depression |
| | dizziness (11%) |
| | irritability |
| | psychosis (≤10%, severe 1%) |
| | seizures |
| | ***somnolence*** (22%); withhold therapy if moderate to severe as continued administration may result in coma |
| | stupor (≤10%, severe 1%) |
| pain | abdominal pain (11%)[1,2] |
| | back pain[2] |
| | chest pain[2] |
| | pain, not otherwise specified (12%)[1,2] |
| pulmonary | apnea (≤10%, severe 1%) |
| | cough increase (11%) |
| | dyspnea (43%, severe 1%) |
| | lung disorder (24%); physical findings associated with pulmonary congestion, rales, and rhonchi |
| | ***respiratory disorder*** (11%, severe 3%); including ARDS, CXR infiltrates, unspecified pulmonary changes, respiratory failure; may require intubation[2] |
| | rhinitis (10%) |
| renal/genitourinary | acute kidney failure (≤10%, severe 1%) |
| | anuria (≤10%, severe 5%) |
| | ***oliguria*** (63%, severe 6%) |
| syndromes | ***capillary leak syndrome*** (see paragraph following **Side Effects** table) |
| | ***flu-like syndrome***[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%) |

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***Capillary leak syndrome*** 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.[10,11] 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.[1,11]

***Intralesional*** administration is used to achieve high concentrations of drug within the tumour, but with lower systemic exposure and toxicity compared to systemic administration. Intralesional aldesleukin is generally well tolerated and most toxicity is grade 1 and 2 in severity. Intralesional administration has been associated with minor discomfort and pain at the injection site. Almost all patients will experience an inflammatory injection site reaction with local swelling and erythema followed by a selective necrosis of the tumour tissue. The majority of patients will also experience minor flu-like symptoms which usually resolve within 24-48 hours and are readily treated with acetaminophen. Some patients report a longer duration of symptoms following higher doses of aldesleukin.[12-14]

***Neurologic changes*** 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:

***Injection*****:** SteriMax Inc. supplies aldesleukin as 22 million unit (1.3 mg) vials of single-use (preservative free) lyophilized powder. Refrigerate. Protect from light.[6]

***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:***

- preparation in PVC containers is preferred for consistent drug delivery; glass bottles have been used[6]
- reconstitution or dilution with NS or bacteriostatic water for injection may increase aggregation of aldesleukin and should be avoided[6]

***Compatibility:*** consult detailed reference



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## 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[6]*** | ***over 15 minutes;*** do NOT administer using in-line filter |
| 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 |
| ***Intralesional[4,12,13,15,16]*** | ***inject into each target lesion*** |

## 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: | |
|---|---|---|
| **Intravenous:* | **10 weeks[1-3]: | 0.6 million units/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.<br>(total dose per cycle 16.8 million units/kg) |
| | n/a[3]: | 24 million units/$m^2$ IV daily on Days 12-16 and 19-23 of concurrent chemotherapy cycle |
| | 10-18 days[2]: | 18 million units/$m^2$ by continuous IV infusion daily for 5 days |
| **Subcutaneous[3]:* | n/a: | 3-18 million units SC daily for 5 days each week, up to 6 weeks |
| | n/a: | 5 million units/$m^2$ SC three times a week |
| | n/a: | 1.8 million units/$m^2$ SC twice daily 5 days each week, for 6 weeks |



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

Cycle Length:

*Dose reduction is not recommended. Dose modification for toxicity is accomplished by temporary treatment interruption.[6]

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

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

| | |
|---|---|
| *Intralesional:* | the optimal dose per lesion, frequency, and duration of treatment are not known[15]; refer to protocol by which patient is being treated[16] |
| | ***2 weeks***[4,12,14,16]: ***0.5 million units*** (0.3-6 million units) ***injected into each lesion*** (maximum dose per cycle 10 million units [range 10-22 million units]) |
| *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 reduced[1] |
| *Dosage in renal failure:* | no information found; clearance is preserved in patients with rising serum creatinine concentrations[2] |
| *Dosage in hepatic failure:* | no information found |
| *Dosage in dialysis:* | no information found |
| ***Children:*** | safety and effectiveness not established[6]; has been used[5,17] |

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