PRESCRIBING INFORMATION

# PrPROLEUKIN* (aldesleukin)

Interleukin-2
22 million IU/vial

Pharmaceutical Standard: Biological Response Modifier

Novartis Pharmaceuticals Canada Inc.
385 Bouchard Blvd.
Dorval, Quebec
H9S 1A9

Date of Approval: July 6th, 2006

Date of Revision: March 21, 2011

## ACTIONS, CLINICAL PHARMACOLOGY

PROLEUKIN* (aldesleukin) an analogue of human interleukin-2 produced by recombinant DNA technology, has been shown to possess the biological activities of human native interleukin-2.[1,2] PROLEUKIN* exhibits antitumour activity; the exact mechanism by which PROLEUKIN* mediates its antitumor activity in animals and humans is unknown. *In vitro* studies performed on human cell lines demonstrate the immunoregulatory properties of PROLEUKIN*, including: a) enhancement of lymphocyte mitogenesis and stimulation of long-term growth of human interleukin-2 dependent cell lines; b) enhancement of lymphocyte cytotoxicity; c) induction of killer cell (lymphokine-activated (LAK) and natural (NK)) activity; and d) induction of interferon-gamma production.

The *in vivo* administration of PROLEUKIN* in animals and humans produces multiple immunological effects in a dose dependent manner. These effects include activation of cellular immunity with profound lymphocytosis, eosinophilia, and thrombocytopenia, and the production of cytokines including tumor necrosis factor, IL-1 and gamma interferon.[3] *In vivo* experiments in murine tumor models have shown inhibition of tumor growth.[4]

**Pharmacokinetics**: PROLEUKIN* exists as biologically active, non-covalently bound microaggregates with an average size of 27 recombinant interleukin-2 molecules. The solubilizing agent, sodium dodecyl sulfate, may have an effect on the kinetic properties of this product. The pharmacokinetic profile of PROLEUKIN* is characterized by high plasma concentrations following a short intravenous (IV) infusion, rapid distribution into the extravascular space and elimination from the body by metabolism in the kidneys with little or no bioactive protein excreted in the urine.

Studies of IV PROLEUKIN* in sheep and humans indicated that upon completion of infusion approximately 30% of the administered dose is detectable in plasma. This finding is consistent with studies in rats using radiolabeled PROLEUKIN*, which demonstrate a rapid (<1 minute) uptake of the majority of the label into the lungs, liver, kidney, and spleen.

The serum half-life (T 1/2) curves of PROLEUKIN* remaining in the plasma are derived from studies done in 52 cancer patients following a 5-minute IV infusion. These patients were shown to have a distribution and elimination T 1/2 of 13 and 85 minutes, respectively.

The relatively rapid clearance rate of PROLEUKIN* has led to dosage schedules characterized by frequent, short infusions. Observed serum levels are proportional to the dose of PROLEUKIN*.

Following the initial rapid organ distribution, the primary route of clearance of circulating PROLEUKIN* is the kidney. In humans and animals, PROLEUKIN* is cleared from the circulation by both glomerular filtration and peritubular extraction in the kidney.[5-8] This dual mechanism for delivery of PROLEUKIN* to the proximal tubule may account for the preservation of clearance in patients with rising serum creatinine values. Greater than 80% of the amount of PROLEUKIN* distributed to plasma, cleared from the circulation and presented to the kidney is metabolized to amino acids in the cells lining the proximal convoluted tubules. In humans, the mean clearance rate in cancer patients is 268 mL/min.

## INDICATIONS AND CLINICAL USE

PROLEUKIN* (aldesleukin) is indicated for the treatment of adults (≥18 years of age) with metastatic renal cell carcinoma (metastatic RCC). PROLEUKIN* is indicated for the treatment of adults (≥18 years of age) with metastatic malignant melanoma.

In the renal cell cancer studies (n=255), objective response was seen in 37 (15%) patients, with 17 (7%) complete and 20 (8%) partial responders. In the metastatic malignant melanoma studies (n=270), objective response was seen in 43 (16%) patients, with 17 (6%) complete and 26 (10%) partial responders. Prior to enrollment into the studies, patients had progression of disease after prior therapies. A majority (96%) of patients had previous surgical resection of their primary lesions, lymph node dissections, or area of relapse.

Careful patient selection is mandatory prior to the administration of PROLEUKIN*. See **"CONTRAINDICATIONS", "WARNINGS"** and **"PRECAUTIONS"** sections regarding patient screening, including recommended cardiac and pulmonary function tests and laboratory tests.

Evaluation of clinical studies to date reveals that patients with more favorable ECOG performance status (ECOG PS 0) at treatment initiation respond better to PROLEUKIN*, with a higher response rate and lower toxicity (See "**ADVERSE REACTION**" section). Therefore, selection of patients for treatment should include assessment of performance status. Experience in patients with ECOG PS >1 is limited.

**TABLE I: PROLEUKIN* CLINICAL RESPONSE BY ECOG PERFORMANCE STATUS (PS)**

| Pretreatment | METASTATIC RCC | | METASTATIC MALIGNANT MELANOMA | |
|---|---|---|---|---|
| ECOG PS | CR | PR | CR | PR |
| 0 | 14/166 (8%) | 16/166 (10%) | 14/191 (7%) | 22/191 (12%) |
| >1 | 3/89 (3%) | 4/89 (4%) | 3/79 (4%) | 4/79 (5%) |

## CONTRAINDICATIONS

PROLEUKIN* (aldesleukin) is contraindicated in patients with a known history of hypersensitivity to interleukin-2 or any component of the PROLEUKIN* formulation.

PROLEUKIN* is contraindicated in patients with an abnormal thallium stress test or abnormal pulmonary function tests and those with organ allografts. Retreatment with PROLEUKIN* is contraindicated in patients who experienced the following drug related toxicities while receiving an earlier course of therapy:

- Sustained ventricular tachycardia (≥5 beats)
- Cardiac arrhythmias not controlled or unresponsive to management
- Chest pain with electrocardiogram (ECG) changes, consistent with angina or myocardial infarction
- Cardiac tamponade
- Intubation required >72 hours

- Renal failure requiring dialysis >72 hours
- Coma or toxic psychosis lasting >48 hours
- Repetitive or difficult to control seizures
- Bowel ischemia/perforation
- GI bleeding requiring surgery

**WARNINGS**

PROLEUKIN* (aldesleukin) should be administered only to well informed patients in a hospital setting under the supervision of a qualified physician experienced in the use of anti-cancer agents. An intensive care facility and specialists skilled in cardiopulmonary or intensive care medicine must be available.

PROLEUKIN* administration has been associated with capillary leak syndrome (CLS) which is characterized by a loss of vascular tone and extravasation of plasma proteins and fluid into the extravascular space. CLS results in hypotension and reduced organ perfusion which may be severe and can result in death. CLS 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.

Because of the severe adverse events which generally accompany PROLEUKIN* therapy at the recommended dosages, thorough clinical evaluation should be performed to identify patients with significant cardiac, pulmonary, renal, hepatic, or central nervous system (CNS) impairment; PROLEUKIN* is contraindicated in these patients.

Therapy with PROLEUKIN* should be restricted to patients with normal cardiac and pulmonary functions as defined by thallium stress testing and formal pulmonary function testing. Extreme caution should be used in patients with normal thallium stress tests and pulmonary function tests who have a history of prior cardiac or pulmonary disease.

Patients with normal cardiovascular, pulmonary, hepatic, and CNS function may experience serious, life threatening or fatal adverse events. Adverse events are frequent, often serious, and sometimes fatal.

Should adverse events, which require dose modification occur, dosage should be withheld rather than reduced (See "**DOSAGE AND ADMINISTRATION**" section, "**Dose Modifications**" subsection).

PROLEUKIN* has been associated with exacerbation of pre-existing or initial presentation of autoimmune disease and inflammatory disorders. Exacerbation of Crohn's disease, scleroderma, thyroiditis, inflammatory arthritis, diabetes mellitus, oculo-bulbar myasthenia gravis, crescentic IgA glomerulonephritis, cholecystitis, cerebral vasculitis, Stevens-Johnson syndrome and bullous pemphigoid, has been reported following treatment with IL-2.

All patients should have thorough evaluation and treatment of CNS metastases and have a negative scan prior to receiving PROLEUKIN* therapy. New neurologic signs, symptoms, and anatomic lesions following PROLEUKIN* therapy have been reported in patients without evidence of CNS

metastases. Clinical manifestations included changes in mental status, speech difficulties, cortical blindness, limb or gait ataxia, hallucinations, agitation, obtundation, and coma. Radiological findings included multiple and, less commonly, single cortical lesions on MRI and evidence of demyelination. Neurologic signs and symptoms associated with PROLEUKIN* therapy usually improve after discontinuation of PROLEUKIN* therapy; however, there are reports of permanent neurologic defects. One case of possible cerebral vasculitis, responsive to dexamethasone, has been reported. In patients with known seizure disorders, extreme caution should be exercised as PROLEUKIN* may cause seizures.

PROLEUKIN* administration should be held in patients developing moderate to severe lethargy or somnolence; continued administration may result in coma.

PROLEUKIN* treatment is associated with impaired neutrophil function (reduced chemotaxis) and with an increased risk of disseminated infection, including sepsis and bacterial endocarditis. Consequently, pre-existing bacterial infections should be adequately treated prior to initiation of PROLEUKIN* therapy. Patients with indwelling central lines are particularly at risk for infection with gram positive microorganisms. Antibiotic prophylaxis with oxacillin, nafcillin, ciprofloxacin, or vancomycin has been associated with a reduced incidence of staphylococcal infections. Disseminated infections acquired in the course of PROLEUKIN* treatment are a major contributor to treatment morbidity and use of antibiotic prophylaxis and aggressive treatment of suspected and documented infections may reduce the morbidity of PROLEUKIN* treatment. **NOTE: Prior to the use of any product mentioned in this paragraph, the physician should refer to the Product Monograph for the respective product.**

## PRECAUTIONS

**General**: Patients should have normal cardiac, pulmonary, hepatic, and CNS function at the start of therapy. Metastatic renal cell carcinoma patients who have had a nephrectomy are eligible for treatment if they have serum creatinine levels $\leq$ 1.5 mg/dL.

Patients with normal cardiovascular, pulmonary, hepatic, and CNS function may experience serious life threatening or fatal adverse events. Adverse events are frequent, often serious, and sometimes fatal.

Capillary leak syndrome (CLS) begins immediately after PROLEUKIN* (aldesleukin) treatment starts and is marked by increased capillary permeability to protein and fluids and reduced vascular tone. In most patients, this results in a concomitant drop in mean arterial blood pressure within 2 to 12 hours after the start of treatment. With continued therapy, clinically significant hypotension (defined as systolic blood pressure below 90 mm Hg or a 20 mm Hg drop from baseline systolic pressure) and hypoperfusion will occur. In addition, extravasation of protein and fluids into the extravascular space will lead to the formation of edema and creation of new effusions.

Medical management of CLS begins with careful monitoring of the patient's fluid and organ perfusion status. This is achieved by frequent determination of blood pressure and pulse, and by monitoring organ function, which includes assessment of mental status and urine output. Hypovolemia is assessed by catheterization and central pressure monitoring.

Flexibility in fluid and pressor management is essential for maintaining organ perfusion and blood pressure. Consequently, extreme caution should be used in treating patients with fixed requirements for large volumes of fluid (e.g., patients with hypercalcemia).

Administration of IV fluids, either colloids or crystalloids is recommended for treatment of hypovolemia. IV fluids are usually given when the central venous pressure (CVP) is below 3 to 4 mm $H_2O$. Correction of hypovolemia may require large volumes of IV fluids but caution is required because unrestrained fluid administration may exacerbate problems associated with edema formation or effusions.

With extravascular fluid accumulation, edema is common and ascites, pleural or pericardial effusions may develop. Management of these events depends on a careful balancing of the effects of fluid shifts so that neither the consequences of hypovolemia (e.g., impaired organ perfusion) nor the consequences of fluid accumulations (e.g., pulmonary edema) exceed the patient's tolerance.

Clinical experience has shown that early administration of dopamine (1 to 5 μg/kg/min) to patients manifesting capillary leak syndrome, before the onset of hypotension, can help to maintain organ perfusion particularly to the kidney and thus preserve urine output. Weight and urine output should be carefully monitored. If organ perfusion and blood pressure are not sustained by dopamine therapy, clinical investigators have increased the dose of dopamine to 6 to 10 μg/kg/min or have added phenylephrine hydrochloride (1 to 5 μg/kg/min) to low dose dopamine. Prolonged use of pressors, either in combination or as individual agents, at relatively high doses, may be associated with cardiac rhythm disturbances. If there has been excessive weight gain or edema formation, particularly if associated with shortness of breath from pulmonary congestion, use of diuretics, once blood pressure has normalized, has been shown to hasten recovery. **NOTE: Prior to the use of any product mentioned, the physician should refer to the Product Monograph for the respective product**.

PROLEUKIN* treatment should be withheld for failure to maintain organ perfusion, as demonstrated by altered mental status, reduced urine output, a fall in the systolic blood pressure below 90 mm Hg or onset of cardiac arrhythmias (See **"DOSAGE AND ADMINISTRATION"** section, **"Dose Modification"** subsection). Recovery from CLS begins soon after cessation of PROLEUKIN* therapy. Usually, within a few hours, the blood pressure rises, organ perfusion is restored and reabsorption of extravasated fluid and protein begins.

Oxygen is given to the patient if pulmonary function monitoring confirms that $PaO_2$ is decreased.

PROLEUKIN* administration may cause anemia and/or thrombocytopenia. Packed red blood cell transfusions have been given both for relief of anemia and to insure maximal oxygen carrying capacity. Platelet transfusions have been given to resolve absolute thrombocytopenia and to reduce the risk of GI bleeding. In addition, leukopenia and neutropenia are observed.

PROLEUKIN* administration results in fever, chills, rigors, pruritus, and gastrointestinal side effects in most patients treated at recommended doses. These side effects have been aggressively managed as described in the "**ADVERSE REACTIONS**" section.

Kidney and liver function are impaired during PROLEUKIN* treatment. Use of concomitant nephrotoxic or hepatotoxic medications may further increase toxicity to the kidney or liver.

Mental status changes including irritability, confusion, or depression which occur while receiving PROLEUKIN* may be indicators of bacteremia or early bacterial sepsis, hypoperfusion, occult CNS malignancy, or direct PROLEUKIN*-induced CNS toxicity. Alterations in mental status due solely to PROLEUKIN* may progress for several days before recovery begins. Rarely, patients have sustained permanent neurologic deficits (See "**ADVERSE REACTIONS**" section).

Exacerbation of preexisting autoimmune disease or initial presentation of autoimmune and inflammatory disorders has been reported following PROLEUKIN* alone or in combination with interferon (See "**ADVERSE REACTIONS**" section). Impairment of thyroid function, sometimes preceded by hyperthyroidism, has been reported following PROLEUKIN* treatment. Some of these patients required thyroid replacement therapy. Changes in thyroid function may be a manifestation of autoimmunity. Onset of symptomatic hyperglycemia and/or diabetes mellitus has been reported during PROLEUKIN* therapy.

PROLEUKIN* enhancement of cellular immune function may increase the risk of allograft rejection in transplant patients.

**Laboratory Tests:** The following clinical evaluations are recommended for all patients, prior to beginning treatment and then daily during drug administration.

- Standard hematologic tests - including complete blood count (CBC), differential and platelet counts
- Blood chemistries - including electrolytes, renal and hepatic function tests
- Chest x-rays

Serum creatinine should be $\leq$1.5 mg/dL prior to initiation of PROLEUKIN* treatment.

All patients should have baseline pulmonary function tests with arterial blood gases. Adequate pulmonary function should be documented ($FEV_1 > 2$ litres or $\geq$ 75% of predicted for height and age) prior to initiating therapy. All patients should be screened with a stress thallium study. Normal ejection fraction and unimpaired wall motion should be documented. If a thallium stress test suggests minor wall motion abnormalities further testing is suggested to exclude significant coronary artery disease.

Daily monitoring during therapy with PROLEUKIN* should include vital signs (temperature, pulse, blood pressure, and respiration rate), weight, and fluid intake and output. In a patient with a decreased systolic blood pressure, especially less than 90 mm Hg, constant cardiac rhythm monitoring should be conducted. If an abnormal complex or rhythm is seen, an ECG should be performed. Vital signs in these hypotensive patients should be taken hourly.

During treatment, pulmonary function should be monitored on a regular basis by clinical examination, assessment of vital signs and pulse oximetry. Patients with dyspnea or clinical signs of respiratory impairment (tachypnea or rales) should be further assessed with arterial blood gas determination. These tests are to be repeated as often as clinically indicated.

Cardiac function should be assessed daily by clinical examination and assessment of vital signs. Patients with signs or symptoms of chest pain, murmurs, gallops, irregular rhythm or palpitations

should be further assessed with an ECG examination and cardiac enzyme evaluation. Evidence of myocardial injury, including findings compatible with myocardial infarction or myocarditis, has been reported. Ventricular hypokinesia due to myocarditis may be persistent for several months. If there is evidence of cardiac ischemia or congestive heart failure, PROLEUKIN* therapy should be held, and a repeat thallium study should be done.

**Drug Interactions:** PROLEUKIN* may affect central nervous function. Therefore, interactions could occur following concomitant administration of psychotropic drugs (e.g., narcotics, analgesics, antiemetics, sedatives, and tranquilizers).

Concurrent administration of drugs possessing nephrotoxic (e.g., aminoglycosides, indomethacin), myelotoxic (e.g., cytotoxic chemotherapy), cardiotoxic (e.g., doxorubicin) or hepatotoxic (e.g., methotrexate, asparaginase) effects with PROLEUKIN* may increase toxicity in these organ systems. The safety and efficacy of PROLEUKIN* in combination with any antineoplastics have not been established.

In addition, reduced kidney and liver function secondary to PROLEUKIN* treatment may delay elimination of concomitant medications and increase the risk of adverse events from those drugs.

Hypersensitivity reactions have been reported in patients receiving combination regimens containing sequential high dose PROLEUKIN* and antineoplastic agents, specifically, dacarbazine, cis-platinum, tamoxifen and interferon-alfa. These reactions consisted of erythema, pruritus, and hypotension and occurred within hours of administration of chemotherapy. These events required medical intervention in some patients. Myocardial injury, including myocardial infarction, myocarditis, ventricular hypokinesia, and severe rhabdomyolysis appear to be increased in patients receiving PROLEUKIN* and interferon-alfa concurrently.

Exacerbation or the initial presentation of a number of autoimmune and inflammatory disorders has been observed following concurrent use of interferon-alfa and PROLEUKIN*, including crescentic IgA glomerulonephritis, oculo-bulbar myasthenia gravis, inflammatory arthritis, thyroiditis, bullous pemphigoid, and Stevens-Johnson syndrome.

Although glucocorticoids have been shown to reduce PROLEUKIN*-induced side effects including fever, renal insufficiency, hyperbilirubinemia, confusion, and dyspnea,[11] concomitant administration of these agents with PROLEUKIN* may reduce the antitumor effectiveness of PROLEUKIN* and thus should be avoided.

Beta-blockers and other antihypertensives may potentiate the hypotension seen with PROLEUKIN*.

Delayed adverse reactions to iodinated contrast media: A review of the literature revealed that 12.6% (range 11-28%) of 501 patients treated with various interleukin-2 containing regimens who were then subsequently administered radiographic iodinated contrast media experienced acute, atypical adverse reactions. The onset of symptoms usually occurred within hours (most commonly 1 to 4 hours) following the administration of contrast media. These reactions include fever, chills, nausea, vomiting, pruritus, rash, diarrhea, hypotension, edema, and oliguria. Some clinicians have noted that these reactions resemble the immediate side effects caused by interleukin-2 administration, however the cause of contrast reactions after interleukin-2 therapy is unknown.

Most events were reported to occur when contrast media was given within 4 weeks after the last dose of interleukin-2. These events were also reported to occur when contrast media was given several months after interleukin-2 treatment[13].

**Carcinogenesis, Mutagenesis, Impairment of Fertility:** There have been no studies conducted assessing the carcinogenic or mutagenic potential of PROLEUKIN*.

There have been no studies conducted assessing the effect of PROLEUKIN* on fertility. It is recommended that this drug not be administered to fertile persons of either gender not practicing effective contraception.

**Use in Pregnancy:** PROLEUKIN* has been shown to have embryolethal effects in rats when given in doses at 27 to 36 times the human dose (scaled by body weight). Significant maternal toxicities were observed in pregnant rats administered PROLEUKIN* by IV injection at doses 2.1 to 36 times higher than the human dose during critical period of organogenesis. No evidence of teratogenicity was observed other than that attributed to maternal toxicity. There are no adequate well-controlled studies of PROLEUKIN* in pregnant women. PROLEUKIN* should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

**Nursing Mothers:** It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from PROLEUKIN*, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

**Use in Children:** Safety and effectiveness in children under 18 years of age have not been established.

## ADVERSE REACTIONS

The rate of drug-related deaths in the 255 metastatic RCC patients who received single-agent PROLEUKIN* (aldesleukin) was 4% (11/255); the rate of drug-related deaths in the 270 metastatic malignant melanoma patients who received single-agent PROLEUKIN* was 2% (6/270).

The following data on common adverse events (reported in greater than 10% of patients, any grade), presented by body system, decreasing frequency and by preferred term (COSTART) are based on 525 patients (255 with renal cell cancer and 270 with metastatic malignant melanoma) treated with the recommended infusion dosing regimen.

**TABLE II: ADVERSE EVENTS OCCURRING IN >10% OF PATIENTS(n=525)**

| Body System | % of Patients | Body System | % of Patients |
|---|---|---|---|
| **Body as a Whole** | | **Metabolic and Nutritional Disorders** | |
| Chills | 52 | Bilirubinemia | 40 |
| Fever | 29 | Creatinine increased | 33 |
| Malaise | 27 | Peripheral edema | 28 |
| Asthenia | 23 | SGOT increased | 23 |
| Infection | 13 | Weight gain | 16 |
| Pain | 12 | Edema | 15 |
| Abdominal pain | 11 | Acidosis | 12 |
| Abdomen enlarged | 10 | Hypomagnesemia | 12 |
| **Cardiovascular System** | | Hypocalcemia | 11 |
| Hypotension | 71 | Alkaline phosphatase increased | 10 |
| Tachycardia | 23 | **Nervous System** | |
| Vasodilation | 13 | Confusion | 34 |
| Supraventricular Tachycardia | 12 | Somnolence | 22 |
| Cardiovascular disorder[a] | 11 | Anxiety | 12 |
| Arrhythmia | 10 | Dizziness | 11 |
| **Digestive System** | | Respiratory System | |
| Diarrhea | 67 | Dyspnea | 43 |
| Vomiting | 50 | Lung disorder[b] | 24 |
| Nausea | 35 | Respiratory disorder[c] | 11 |
| Stomatitis | 22 | Cough increase | 11 |
| Anorexia | 20 | Rhinitis | 10 |
| Nausea and vomiting | 19 | **Skin and Appendages** | |
| **Hemic and Lymphatic System** | | Rash | 42 |
| Thrombocytopenia | 37 | Pruritus | 24 |
| Anemia | 29 | Exfoliative dermatitis | 18 |
| Leukopenia | 16 | **Urogenital System** | |
| | | Oliguria | 63 |

[a] Cardiovascular disorder: fluctuations in blood pressure, asymptomatic ECG changes, CHF.
[b] Lung disorder: physical findings associated with pulmonary congestion, rales, and rhonchi.
[c] Respiratory disorder: ARDS, CXR infiltrates, unspecified pulmonary changes.

The following data on life-threatening adverse events (reported in greater than 1% of patients, grade 4), presented by body system, and by preferred term (COSTART) are based on 525 patients (255 with renal cell cancer and 270 with metastatic malignant melanoma) treated with the recommended infusion dosing regimen.

**TABLE III: LIFE-THREATENING (GRADE 4) ADVERSE EVENTS (n= 525)**

| Body System | # (%) of Patients | Body System | # (%) of Patients |
|---|---|---|---|
| **Body as a Whole** | | **Metabolic and Nutritional Disorders** | |
| Fever | 5 (1%) | Bilirubinemia | 13 (2%) |
| Infection | 7 (1%) | Creatinine increased | 5 (1%) |
| Sepsis | 6 (1%) | SGOT increased | 3 (1%) |
| **Cardiovascular** | | Acidosis | 4 (1%) |
| Hypotension | 15 (3%) | **Nervous** | |
| Supraventricular tachycardia | 3 (1%) | Confusion | 5 (1%) |
| Cardiovascular disorder[a] | 7 (1%) | Stupor | 3 (1%) |
| Myocardial infarct | 7 (1%) | Coma | 8 (2%) |
| Ventricular tachycardia | 5 (1%) | Psychosis | 7 (1%) |
| Heart arrest | 4 (1%) | **Respiratory** | |
| **Digestive** | | Dyspnea | 5 (1%) |
| Diarrhea | 10 (2%) | Respiratory disorder[c] | 14 (3%) |
| Vomiting | 7 (1%) | Apnea | 5 (1%) |
| **Hemic and Lymphatic** | | **Urogenital** | |
| Thrombocytopenia | 5 (1%) | Oliguria | 33 (6%) |
| Coagulation disorder[b] | 4 (1%) | Anuria | 25 (5%) |
| | | Acute kidney failure | 3 (1%) |

[a] Cardiovascular disorder: fluctuations in blood pressure.
[b] Coagulation disorder: intravascular coagulopathy.
[c] Respiratory disorder: ARDS, respiratory failure, intubation.

The following life threatening (grade 4) adverse events were reported by <1% of the 525: reaction unevaluable; hypothermia; shock; bradycardia; ventricular extrasystoles; myocardial ischemia; syncope; hemorrhage; atrial arrhythmia; phlebitis; AV block second degree; endocarditis; pericardial effusion; peripheral gangrene; thrombosis; coronary artery disorder; stomatitis; nausea and vomiting; liver function tests abnormal; gastrointestinal hemorrhage; hematemesis; bloody diarrhea; gastrointestinal disorder; intestinal perforation; pancreatitis; anemia; leukopenia; leukocytosis; hypocalcemia, alkaline phosphatase increased; BUN increased; hyperuricemia; NPN increase; respiratory acidosis; somnolence; agitation; neuropathy; paranoid reaction; convulsion; grand mal convulsion; delirium; lung edema; hyperventilation; hypoxia; hemoptysis; hypoventilation; pneumothorax; mydriasis; pupillary disorder; kidney function abnormal; kidney failure; acute tubular necrosis.

In an additional population of greater than 1,800 patients treated with PROLEUKIN*-based regimens using a variety of doses and schedules (e.g., subcutaneous, continuous infusion, administration with LAK cells) the following serious adverse events were reported: duodenal ulceration; bowel necrosis; myocarditis; supraventricular tachycardia; permanent or transient blindness secondary to optic neuritis; transient ischemic attacks; meningitis; cerebral edema; pericarditis; allergic interstitial nephritis; tracheo-esophageal fistula.

In the same clinical population, the following events which were fatal or resulted in death each occurred with a frequency of <1%: liver or renal failure; intestinal perforation; cardiac arrest; myocardial infarction; malignant hyperthermia; pulmonary edema; respiratory arrest; respiratory failure; stroke; pulmonary emboli; severe depression leading to suicide.

**Postmarketing Experience:**

The reactions reported in the post market setting are reported voluntarily from a population of uncertain size, therefore it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

In world-wide post approval experience, the following serious adverse events have been reported in a variety of treatment regimens that include interleukin-2: hypertension; pneumonia (bacterial, fungal, viral); neutropenia; cholecystitis; colitis; gastritis; hepatitis; hepatosplenomegaly; intestinal obstruction; retroperitoneal hemorrhage; cerebral lesions; intracranial/cerebral hemorrhage; encephalopathy; extrapyramidal syndrome; neuralgia; neuritis; neuropathy (demyelination); rhabdomyolysis; myopathy; myositis; hyperthyroidism; anaphylaxis; cellulitis; injection site necrosis; insomnia, neutropenic fever, leukoencephalopathy, cardiac arrest, pericardial effusion, cardiac tamponade, gastrointestinal perforation including necrosis/gangrene, cardiomyopathy, fatal endocarditis, hypothyroidism, urticaria and eosinophilia.

There have been rare reports of leukoencephalopathy associated with interleukin-2 in the literature, mostly in patients treated for HIV infection. The role of interleukin-2 in elucidating this event remains uncertain. However opportunistic infections, co-administration of interferons as well as multiple courses of chemotherapy are other factors that may pre-dispose the treated population to such event. PROLEUKIN* should not be used in the HIV indication.

During treatment most patients experience lymphocytopenia and eosinophilia, with a rebound lymphocytosis within 24 to 48 hours following treatment. These may be related to the mechanism of antitumour activity of PROLEUKIN*. Severe manifestations of eosinophilia involving eosinophilic infiltration of cardiac and pulmonary tissues have been reported. One clinical trial case with Hodgkin's disease involved eosinophilic infiltration of cardiac tissue and had a fatal outcome.

Exacerbation or initial presentations of a number of autoimmune and inflammatory disorders have been reported (See "**WARNINGS**" section). Persistent but non-progressive vitiligo has been observed in metastatic malignant melanoma patients treated with interleukin-2. Synergistic, additive and novel toxicities have been reported with PROLEUKIN* used in combination with other drugs. Novel toxicities include delayed adverse reactions to iodinated contrast media and hypersensitivity reactions to antineoplastic agents (See "**PRECAUTIONS**" section).

Experience has shown the following concomitant medications to be useful in the management of patients on PROLEUKIN* therapy: a) standard antipyretic therapy, including non-steroidal anti-inflammatories (NSAIDs), started immediately prior to PROLEUKIN* to reduce fever. Renal function should be monitored as some NSAIDs may cause synergistic nephrotoxicity; b) meperidine used to control the rigors associated with fever; c) $H_2$ antagonists given for prophylaxis of gastrointestinal irritation and bleeding; d) antiemetics and antidiarrheals used as needed to treat other gastrointestinal side effects. Generally these medications were discontinued 12 hours after the last dose of PROLEUKIN*.

Patients with in-dwelling central lines have a higher risk of infection with gram positive organisms.[9-

[11] A reduced incidence of staphylococcal infections in PROLEUKIN* studies has been associated with the use of antibiotic prophylaxis which includes the use of oxacillin, nafcillin, ciprofloxacin, or vancomycin. Hydroxyzine or diphenhydramine have been used to control symptoms from pruritic rashes and continued until resolution of pruritus. Topical creams and ointments should be applied as needed for skin manifestations. Preparations containing a steroid (e.g., hydrocortisone) should be avoided. **NOTE: Prior to the use of any product mentioned, the physician should refer to the Product Monograph for the respective product.**

**Immunogenicity:** Fifty-seven of 77 (74%) metastatic renal cell carcinoma patients treated with an every 8-hour PROLEUKIN* regimen and 33 of 50 (66%) metastatic malignant melanoma patients treated with a variety of IV regimens developed low titers of non-neutralizing anti-PROLEUKIN* antibodies. Neutralizing antibodies were not detected in this group of patients, but have been detected in 1/106 (<1%) patients treated with IV PROLEUKIN* using a wide variety of schedules and doses. The clinical significance of anti-PROLEUKIN* antibodies is unknown.

## SYMPTOMS AND TREATMENT OF OVERDOSAGE

Side effects following the use of PROLEUKIN* (aldesleukin) appear to be dose-related. Exceeding the recommended dose has been associated with a more rapid onset of expected dose-limiting toxicities. Symptoms which persist after cessation of PROLEUKIN* should be monitored and treated supportively. Life-threatening toxicities may be ameliorated by the intravenous administration of dexamethasone,[12] which may result in loss of the therapeutic effects of PROLEUKIN*. **NOTE: Prior to the use of dexamethasone, the physician should refer to the Product Monograph for this product**.

## DOSAGE AND ADMINISTRATION

The recommended PROLEUKIN* (aldesleukin) treatment regimen is administered by a 15-minute IV infusion every 8 hours. Before initiating treatment, carefully review the **"INDICATIONS AND CLINICAL USE", "CONTRAINDICATIONS", "WARNINGS", "PRECAUTIONS",** and **"ADVERSE REACTIONS"** sections, particularly regarding patient selection, possible serious adverse events, patient monitoring and withholding dosage.

The following schedule has been used to treat adult patients with metastatic renal cell carcinoma (metastatic RCC) or metastatic malignant melanoma. Each course of treatment consists of two 5-day treatment cycles separated by a rest period.

600,000 IU/kg (0.037 mg/kg) dose administered every 8 hours by a 15-minute IV infusion for a maximum of 14 doses. Following 9 days of rest, the schedule is repeated for another 14 doses, for a maximum of 28 doses per course, as tolerated. During clinical trials, doses were frequently withheld for toxicity (See "**Clinical Experience**" and "**Dose Mo**difications" subsections). Metastatic RCC patients treated with this schedule received a median of 20 of the 28 doses during the first course of therapy. Metastatic malignant melanoma patients received a median of 18 doses during the first course of therapy.

**Retreatment:** Patients should be evaluated for response approximately 4 weeks after completion of a course of therapy and again immediately prior to the scheduled start of the next treatment course. Additional courses of treatment should be given to patients only if there is some tumor shrinkage following the last course and retreatment is not contraindicated (See "**CONTRAINDICATIONS**" section). Each treatment course should be separated by a rest period of at least 7 weeks from the date of hospital discharge.

Dose Modifications: Dose modification for toxicity should be accomplished by withholding or interrupting a dose rather than reducing the dose to be given. Decisions to stop, hold, or restart PROLEUKIN* therapy must be made after a global assessment of the patient. With this in mind, the following guidelines should be used:

**Retreatment with PROLEUKIN* is contraindicated in patients who experience the following toxicities:**

| Body System | |
|---|---|
| Cardiovascular | Sustained ventricular tachycardia (≥ 5 beats) |
| | Cardiac rhythm disturbances not controlled or unresponsive to management |
| | Chest pain with ECG changes, consistent with angina or myocardial infarction |
| | Cardiac tamponade |
| Respiratory | Intubation for > 72 hours |
| Urogenital | Renal failure requiring dialysis > 72 hours |
| Nervous | Coma or toxic psychosis lasting > 48 hours |
| | Repetitive or difficult to control seizures |
| Digestive | Bowel ischemia/perforation |
| | GI bleeding requiring surgery |

**Doses should be held and restarted according to the following**:

| Body System | Hold dose for | Subsequent doses may be given if |
|---|---|---|
| Cardiovascular | Atrial fibrillation, supraventricular tachycardia, or bradycardia that requires treatment or is recurrent or persistent | Patient is asymptomatic with full recovery to normal sinus rhythm |
| | Systolic bp < 90 mm Hg with increasing requirements for pressors | Systolic bp ≥ 90 mm Hg and stable or improving requirements for pressors |
| | Any ECG change consistent with MI, ischemia or myocarditis with or without chest pain; suspicion of cardiac ischemia | Patient is asymptomatic, MI and myocarditis have been ruled out, clinical suspicion of angina is low; there is no evidence of ventricular hypokinesia |
| Respiratory | $O_2$ saturation < 94% on room air or < 90% with 2 liters $O_2$ by nasal prongs | $O_2$ saturation > 94% on room air or > 90% with 2 liters $O_2$ by nasal prongs |
| Nervous | Mental status changes, including moderate confusion or agitation | Mental status changes completely resolved |

| | | |
|---|---|---|
| Body as a Whole | Sepsis syndrome, patient is clinically unstable | Sepsis syndrome has resolved, patient is clinically stable, infection is under treatment |
| Urogenital | Serum creatinine > 4.5 mg/dL or a serum creatinine of ≥4 mg/dL in the presence of severe volume overload, acidosis, or hyperkalemia | Serum creatinine < 4 mg/dL and fluid and electrolyte status is stable |
| | Persistent oliguria, urine output of < 10 mL/hour for 16 to 24 hours with rising serum creatinine | Urine output >10 mL/hour with a decrease of serum creatinine > 1.5 mg/dL or normalization of serum creatinine |
| Digestive | Signs of hepatic failure including encephalopathy, increasing ascites, liver pain, hypoglycemia | All signs of hepatic failure have resolved* |
| | Stool guaiac repeatedly >3-4+ | Stool guaiac negative |
| Skin | Bullous dermatitis or marked worsening of pre-existing skin condition, avoid topical steroid therapy | Resolution of all signs of bullous dermatitis |

*Discontinue all further treatment for that course. A new course of treatment, if warranted, should be initiated no sooner than 7 weeks after cessation of adverse event and hospital discharge.

## PHARMACEUTICAL INFORMATION

PROLEUKIN* (aldesleukin), a human recombinant interleukin-2 product, is a highly purified protein with a molecular weight of approximately 15,300 daltons. The chemical name is des-alanyl-1, serine-125 human interleukin-2. PROLEUKIN*, a lymphokine, is produced by recombinant DNA technology using a genetically engineered *E. coli* strain containing an analog of the human interleukin-2 gene. Genetic engineering techniques were used to modify the human interleukin-2 gene, and the resulting expression clone encodes a modified human interleukin-2. This recombinant form differs from native interleukin-2 in the following ways: a) PROLEUKIN* is not glycosylated because it is derived from *E. coli*; b) the molecule has no N-terminal alanine; the codon for this amino acid was deleted during the genetic engineering procedure; c) the molecule has serine substituted for cysteine at amino acid position 125; this was accomplished by site specific manipulation during the genetic engineering procedure; and d) the aggregation state of PROLEUKIN* is likely to be different from that of native interleukin-2.

The *in vitro* biological activities of the native non-recombinant molecule have been reproduced with PROLEUKIN*.[1,2]

PROLEUKIN* biological potency is determined by a lymphocyte proliferation bioassay and is expressed in International Units (IU) as established by the World Health Organization 1st International Standard for Interleukin-2 (human). The relationship between potency and protein mass is as follows:

18 million ($18x10^6$) IU PROLEUKIN* = 1.1 mg protein

**Composition:** PROLEUKIN* is supplied as a sterile, white to off-white, lyophilized cake in single-use vials intended for intravenous (IV) administration. When reconstituted with 1.2 mL Sterile Water for Injection, USP, each mL contains 18 million IU (1.1 mg) PROLEUKIN*, 50 mg mannitol, and 0.18 mg sodium dodecyl sulfate, buffered with approximately 0.17 mg monobasic and 0.89 mg dibasic sodium phosphate to a pH of 7.5 (range 7.2 to 7.8). The manufacturing process for PROLEUKIN* involves fermentation in a defined medium containing tetracycline hydrochloride. The presence of the antibiotic is not detectable in the final product. PROLEUKIN* contains no preservatives in the final product.

**Stability and Storage Recommendations:**

Store vials of lyophilized PROLEUKIN* in a refrigerator at 2° to 8°C (36° to 46°F). Avoid exposure to heat and light.

Reconstituted or diluted PROLEUKIN* is stable for up to 48 hours at refrigerated and room temperatures, 2° to 25°C (36° to 77°F). However, since this product contains no preservative, the reconstituted and diluted solutions should be stored in the refrigerator.

Do not use beyond the expiration date printed on the vial. **NOTE:** This product contains no preservative.

**Reconstitution: Reconstitution and dilution procedures other than those recommended may alter the delivery and/or pharmacology of PROLEUKIN* and thus should be avoided.**

1. PROLEUKIN* (aldesleukin) is a sterile, white to off-white, preservative-free, lyophilized powder suitable for IV infusion upon reconstitution and dilution. **EACH VIAL CONTAINS 22 MILLION IU (1.3 MG) OF PROLEUKIN* AND SHOULD BE RECONSTITUTED ASEPTICALLY WITH 1.2 ML OF STERILE WATER FOR INJECTION, USP. WHEN RECONSTITUTED AS DIRECTED, EACH ML CONTAINS 18 MILLION IU (1.1 MG) OF PROLEUKIN***. The resulting solution should be a clear, colorless to slightly yellow liquid. The vial is for single-use only and any unused portion should be discarded.

2. During reconstitution, the Sterile Water for Injection, USP should be directed at the side of the vial and the contents gently swirled to avoid excess foaming. **DO NOT SHAKE**.

3. The dose of PROLEUKIN*, reconstituted with Sterile Water for Injection, USP (without preservative) should be diluted aseptically in 50 mL of 5% Dextrose Injection, USP (D5W) and infused over a 15-minute period.

In cases where the total dose of PROLEUKIN* is 1.5 mg or less (e.g., a patient with a body weight of less than 40 kilograms), the dose of PROLEUKIN* should be diluted in a smaller volume of D5W.

Concentrations of PROLEUKIN* below 30 μg/mL and above 70 μg/mL have shown increased variability in drug delivery. Dilution and delivery of PROLEUKIN* outside of this concentration range should be avoided.

4. Glass bottles and plastic (polyvinyl chloride) bags have been used in clinical trials with comparable results; it is recommended that plastic bags be used as the dilution container since experimental studies suggest that use of plastic containers results in more consistent drug delivery. **In-line filters should not be used when administering PROLEUKIN*.**

5. Before and after reconstitution and dilution, store in a refrigerator at 2° to 8°C (36° to 46°F). Do not freeze. Administer PROLEUKIN* within 48 hours of reconstitution. The solution should be brought to room temperature prior to infusion in the patient.

6. Reconstitution or dilution with Bacteriostatic Water for Injection, USP, or 0.9% Sodium Chloride Injection, USP should be avoided because of increased aggregation PROLEUKIN* should not be co-administered with other drugs in the same container.

7. Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit.

## DOSAGE FORMS

**Availability:** PROLEUKIN* (aldesleukin) is supplied as a sterile, white to off-white, preservative-free lyophilized product in single-use vials containing 22 million IU (1.3 mg) intended for intravenous (IV) administration. When reconstituted with 1.2 mL Sterile Water for Injection, USP, each mL contains 18 million IU (1.1 mg) of PROLEUKIN*. Discard unused portion.

## PHARMACOLOGY

**Preclinical:** Several biological activities of interleukin-2 suggest that it may have potential value as an anti-cancer therapeutic agent: a) it serves as a growth factor for T-lymphocytes; b) it activates lymphoid cells to perform cytolytic functions *in vivo*; c) it can recruit other lymphoid cells to sites of malignancy.[13-17]

Early experiments in animals indicated that low doses of interleukin-2 (up to several thousand Cetus units per day) given intraperitoneally, intravenously or subcutaneously demonstrated little efficacy in mouse tumor models.[16, 18-21] However, when large doses (up to 300,000 Cetus units interleukin-2 per day) were injected into mice with established pulmonary metastases, interleukin-2 had a strong anti-tumor effect.[4] In this model, interleukin-2 treatment was more successful with well-established tumors than with recently implanted tumors.

Various doses and dose schedules were studied in animal models. Evidence indicates that a bolus dosage of interleukin-2 given three times a day or continuous 24 hour infusion provides better efficacy than a maximum tolerated dose given bolus once a day.[22] It was concluded that for slow - growing tumors, continuous infusion of interleukin-2 for long periods of time is more efficacious, whereas with rapidly growing immunogenic tumors, high doses given early after tumor challenge give better efficacy.

There are several factors in addition to immunogenicity of the tumor that impact on the anti-tumor effect of interleukin-2. They include tumor burden, tumor site and metastatic potential.

The concept of adoptive immunotherapy has been studied extensively in mouse tumor models. Data were generated by the U.S. National Institutes of Health (NIH) to directly compare lymphokine activated killer (LAK) cell therapy with and without interleukin-2.[23] LAK cells alone did not induce reduction in pulmonary metastases, interleukin-2 alone led to a moderate decrease in the number of metastases, but with interleukin-2 and LAK combined, the decrease in metastases was significant. Similar results were obtained from other studies using a peritoneal tumor model.[24]

Additional studies were done to determine if reducing tumor mass or the number of metastases resulted in significantly extended survival time for the mice. Results indicate that there was a correlation between a good therapeutic effect with interleukin-2 or interleukin-2 and LAK cells and extended survival times.[25]

**Clinical:** The pharmacokinetic profile of PROLEUKIN* (aldesleukin) is characterized by high plasma concentrations following a short intravenous infusion, rapid distribution to extravascular, extracellular space, and elimination from the body by metabolism in the kidneys with little or no bioactive protein excreted in the urine. In humans the half lives for distribution and elimination are 13 and 85 minutes, respectively. A third, slower phase of clearance has been observed in laboratory animals. The relatively rapid clearance rate of interleukin-2 has led to dosage schedules characterized by frequent bolus administrations or infusions.

PROLEUKIN* is cleared from the body primarily (80-90%) by metabolism to amino acids in the cells lining the proximal convoluted tubules of the kidneys. Access of the protein to the tubules is apparently by direct filtration at the glomerular membrane of Bowman's capsule, and by peritubular extraction from the efferent arterioles surrounding the proximal tubules. This dual mechanism for access to the tubules may account for the normal clearance pattern of interleukin-2 in patients experiencing kidney toxicity with serum creatinine values between 1.5 and 3 mg/dL. Limited data suggest that serum creatinine greater than 3 mg/dL may correlate with an extended elimination half life.

In clinical studies, PROLEUKIN* was diluted in 5% Dextrose Injection, USP (D5W), D5W containing 0.1% human serum albumin (HSA), or 5% HSA in normal saline. Pharmacokinetic studies showed that a higher amount of bioactive drug was found in the circulation of animals dosed with solutions containing HSA. Preclinical efficacy studies in a murine tumor model showed no differences when the dose was diluted in either 5% HSA in normal saline or 0.1% HSA in D5W. However, it appeared that no difference in either objective response rate, or on-study mortality were observed in groups of patients receiving PROLEUKIN* diluted in different ways.

Clinical Experience: Two hundred fifty-five patients with metastatic renal cell cancer (metastatic RCC) were treated with single agent PROLEUKIN* in 7 clinical studies conducted at 21 institutions. Two hundred seventy patients with metastatic malignant melanoma were treated with single agent PROLEUKIN* in 8 clinical studies conducted at 22 institutions. Patients enrolled in trials of single agent PROLEUKIN* were required to have an Eastern Cooperative Oncology Group (ECOG) Performance Status (PS) of 0 or 1 and normal organ function as determined by cardiac stress test, pulmonary function tests, and creatinine ≤1.5 mg/dL. Patients with brain metastases,

active infections, organ allografts and diseases requiring steroid treatment were excluded.

PROLEUKIN* was given by 15 min IV infusion every 8 hours for up to 5 days (maximum of 14 doses). No treatment was given on days 6 to 14 and then dosing was repeated for up to 5 days on days 15 to 19 (maximum of 14 doses). These 2 cycles constituted 1 course of therapy. Patients could receive a maximum of 28 doses during a course of therapy. In practice >90% of patients had doses withheld. Metastatic RCC patients received a median of 20 of 28 scheduled doses of PROLEUKIN*. Metastatic malignant melanoma patients received a median of 18 of 28 scheduled doses of PROLEUKIN* during the first course of therapy. Doses were withheld for specific toxicities (See "**DOSAGE AND ADMINISTRATION**" section, "**Dose Modifications**" subsection and "**ADVERSE REACTIONS**" section).

In the renal cell cancer studies (n=255), objective response was seen in 37 (15%) patients, with 17 (7%) complete and 20 (8%) partial responders. The 95% confidence interval for objective response was 11% to 20%. Onset of tumor regression was observed as early as 4 weeks after completion of the first course of treatment, and in some cases, tumor regression continued for up to 12 months after the start of treatment. The median duration of response for all responding patients is 54 months (3 to 131+ months). The median duration for patients with complete responses has not yet been observed and for patients with partial response was 20 months. Twelve patients who achieved a complete response and six patients who achieved a partial response had responses ongoing at the time of last contact. The median progression-free survival for all responding patients was 55 months. Responses were observed in both lung and non-lung sites (e.g., liver, lymph node, renal bed occurrences, and soft tissue). Of the 37 responding patients, 12 patients with individual bulky lesions (largest lesion >25 $cm^2$) and 22 patients with large cumulative tumor burden (total >26 $cm^2$) achieved responses.

In the metastatic malignant melanoma studies (n=270), objective response was seen in 43 (16%) patients, with 17 (6%) complete and 26 (10%) partial responders. The 95% confidence interval for objective response was 12% to 21%. The median duration of response for all responding patients was 9 months (1 to 122+ months); the median duration of objective complete responses has not been observed and the median duration for partial response was 6 months. Ten patients who achieved a complete response and three patients who achieved a partial response had responses ongoing at the time of last contact. The median progression-free survival for the 43 responding patients was 13 months. Responses in metastatic malignant melanoma patients were observed in both visceral and non-visceral sites (e.g., lung, liver, lymph node, soft tissue, adrenal, subcutaneous). Of the 43 responding patients, 14 patients with individual bulky lesions (largest lesion >25 $cm^2$) and 21 patients with large cumulative tumor burden (total >25 $cm^2$) achieved responses.

**TABLE IV: PROLEUKIN* CLINICAL RESPONSE DATA**

| | METASTATIC RCC | | METASTATIC MALIGNANT MELANOMA | |
|---|---|---|---|---|
| | Number of Responding Patients (response rate) | Median Response Duration in Months (range) | Number of Responding Patients (response rate) | Median Response Duration in Months (range) |
| CR=s | 17 (7%) | 80+* (7 to 131+) | 17 (6%) | 59+* (3 to 122+) |

| | | | | |
|---|---|---|---|---|
| PR=s | 20 (8%) | 20 (3 to 126+) | 26 (10%) | 6 (1 to 111+) |
| PR's + CR's | 37 (15%) | 54 (3 to 131+) | 43 (16%) | 9 (1 to 122+) |

(+) sign means ongoing

*Median duration not yet observed; a conservative value is presented which represents the minimum median duration of response.

## TOXICOLOGY

PROLEUKIN* (aldesleukin) has been evaluated in preclinical toxicology studies primarily in the rat, although studies have also been conducted in mice, rabbits, and sheep. In the rat, a series of acute and subacute toxicity studies were conducted to assess the safety of PROLEUKIN*. The sheep was utilized specifically to investigate cardiovascular effects of PROLEUKIN*. Recent investigations have been carried out in the rat to address the effect of diluting PROLEUKIN* in 5% Dextrose Injection USP (D5W) with 0.1% HSA on the toxicological profile, and to assess the toxicity of the pelletable protein component of the product.

An acute toxicity study in rat showed that a single intravenous dose of 12.5 mg/kg of PROLEUKIN* was not lethal, and not toxic. Repeat dose studies ranging from 5 to 11 days in duration in rat, rabbit and/or sheep, provided findings consistent with those observed in man. Signs of toxicity noted included hepatotoxicity, pulmonary interstitial inflammation, decreased serum albumin, anemia, and thrombocytopenia. The toxicologic findings, which were considered to be extensions of pharmacologic properties, were characterized as leukocytosis, lymphocytosis, eosinophilia, extramedullary hematopoiesis, and hepatosplenomegaly. In the sheep, hypotension due to decreased peripheral resistance, fever, and lymphopenia was observed. These effects were generally reversible after cessation of drug administration.

In the rat, repeat-dose studies indicated that the maximum tolerated dose (MTD) of PROLEUKIN* was approximately 1.0 mg/kg/day ($18 \times 10^6$ IU/kg/day).

There have been no studies conducted assessing the effects of PROLEUKIN* on fertility. The effects of PROLEUKIN* on male or female fertility is unknown; therefore, the use of PROLEUKIN* in fertile persons is not recommended unless the benefits outweigh the potential risks. PROLEUKIN* was administered to pregnant rats by IV injection during organogenesis (days 6 to 15 of gestation) at 0.5 to 2.0 mg/kg. All dose levels produced maternal toxicity; however, no evidence of teratogenicity was observed. No mutagenic or carcinogenic assessments of the product have been made, based on the intended use of the drug to treat metastatic RCC or metastatic malignant melanoma, both life-threatening diseases.

Collectively these data indicate that PROLEUKIN* induces toxicity via extensions of its pharmacologic effects. When drug administration was discontinued, reversal of target organ toxicity was routinely observed.

## REFERENCES

1. Doyle MV, Lee MT, Fong S. Comparison of the biological activities of human recombinant interleukin-$2_{125}$ and native interleukin-2. *J Biol Response Mod* 1985;4:96-109.

2. Ralph P, Nakoinz I, Doyle M, et al. Human B and T lymphocyte stimulating properties of interleukin-2 (IL-2) muteins. In: *Immune Regulation By Characterized Polypeptides*. Alan R. Liss, Inc. 1987:453-62.

3. Winkelhake JL and Gauny SS. Human recombinant interleukin-2 as an experimental therapeutic. *Pharmacol Rev* 1990;42:1-28.

4. Rosenberg SA, Mule JJ, Spiess PJ, et al. Regression of established pulmonary metastases and subcutaneous tumor mediated by the systemic administration of high-dose recombinant interleukin-2. *J Exp Med* 1985;161:1169-88.

5. Konrad MW, Hemstreet G, Hersh EM, et al. Pharmacokinetics of recombinant interleukin-2 in humans. Cancer Res 1990;50:2009-17.

6. Donohue JH and Rosenberg SA. The fate of interleukin-2 after *in vivo* administration. *J Immunol* 1983;130:2203-8.

7. Koths K, Halenbeck R. Pharmacokinetic studies on 35S-labeled recombinant interleukin-2 in mice. In: Sorg C and Schimpl A, eds. *Cellular And Molecular Biology Of Lymphokines*. Academic Press: Orlando, Fl, 1985:779.

8. Gibbons JA, Luo ZP, Hansen ER et al. Quantitation of the renal clearance of interleukin-2 using nephrectomized and ureter ligated rats. *J Pharmacol Exp Ther* 1995;272:119-125

9. Bock SN, Lee RE, Fisher B, et al. A prospective randomized trial evaluating prophylactic antibiotics to prevent triple-lumen catheter-related sepsis in patients treated with Immunotherapy. *J Clin Oncol* 1990;8:161-69.

10. Hartman LC, Urba, WJ, Steis RG, et al. Use of prophylactic antibiotics for prevention of intravascular catheter-related infections in interleukin-2-treated patients. *J Natl Cancer Inst* 1989;81:1190-93.

11. Snydman DR, Sullivan B, Gill M, et al. Nosocomial sepsis associated with interleukin-2. *Ann Intern Med* 1990;112:102-07.

12. Mier JW, Vachino G, Klempner MS, et al. Inhibition of interleukin-2-induced tumor necrosis factor release by dexamethasone: Prevention of an acquired neutrophil chemotaxis defect and differential suppression of interleukin-2-associated side effects. *Blood* 1990;76:1933-40.

13. Choyke PL, Miller DL, Lotze MT, et al. Delayed reactions to contrast media after interleukin-2 immunotherapy. *Radiology* 1992;183:111-114.

14. Wang A, Lu S-D, Mark DF. Site-specific mutagenesis of the human interleukin-2 gene: Structure-function analysis of the cysteine residues. *Science* 1984;224:1431-3.

15. Hefeneider SH, Conlon PJ, Henney CS, et al. *in vivo* interleukin-2 administration augments the generation of alloreactive cytolytic T lymphocytes and resident natural killer cells. *J Immunol* 1983;130:222-7.

16. Handa K, Suzuki R, Matsui H, et al. Natural killer (NK) cells as a responder to interleukin-2 (IL-2). Il. IL-2 induced interferon-gamma production. *J Immunol* 1983;130:988-92.

17. Mule JJ, Shu S, Schwarz SL, et al. Adoptive immunotherapy of established pulmonary metastases with LAK cells and recombinant interleukin-2. *Science* 1984;225:1487-9.

18. Rosenstein M, Yron I, Kaufmann Y, et al. Lymphokine activated killer cells: lysis of fresh syngeneic NK-resistant murine tumor cells by lymphocytes cultured in interleukin-2. *Cancer Res* 1984;44:1946-53.

19. Rosenberg SA, Lotze MT, Muul LM, et al. Observations on the systemic administration of autologous lymphokine-activated killer cells and recombinant interleukin-2 to patients with metastatic cancer. *N Engl J Med* 1985;313:1485-92.

20. Cheever MA, Greenberg PD, Fefer A, et al. Augmentation of the anti-tumor therapeutic efficacy of long-term cultured T-lymphocytes by *in vivo* administration of purified interleukin-2. *J Exp Med* 1982;155:968-80.

21. Forni G, Giovarelli M, Santoni A. Lymphokine-activated tumor inhibition *in vivo*. 1. The local administration of interleukin-2 triggers nonreactive lymphocytes from tumor-bearing mice to inhibit tumor growth. *J Immunol* 1985;134:1305-11.

22. Donohue JH, Rosenstein M, Change AE, et al. The systemic administration of purified interleukin-2 enhances the ability of sensitized murine lymphocytes to cure a disseminated syngeneic lymphoma. *J Immunol* 1984;132:2123-8.

23. Talmadge JE, Phillips H, Schindler J, et al. Systematic preclinical study on the therapeutic properties of recombinant human interleukin-2 for the treatment of metastatic disease. *Cancer Res* 1987;47:5725-32.

24. Mule JJ, Shu S, Rosenberg SA. The anti-tumor efficacy of lymphokine-activated killer cells and recombinant interleukin-2 *in vivo. J Immunol* 1985;135:646-52.

25. Ottow RT, Steller EP, Sugarbaker PH, et al. Immunotherapy of intraperitoneal cancer with interleukin-2 and lymphokine-activated killer cells reduces tumor load and prolongs survival in murine models. *Cell Immunol* 1987;104:366-76.

26. Mule JJ, Ettinghausen SE, Spiess PJ, et al. Antitumor efficacy of lymphokine-activated killer cells and recombinant rlL-2 *in vivo*: survival benefit and mechanisms of tumor escape in mice undergoing immunotherapy. *Cancer Res* 1986;46:676-83.