

NEW ZEALAND DATA SHEET

PROLEUKIN®

**Aldesleukin powder for injection 18 million International Units
(1.1mg)**

Description

PROLEUKIN® (Aldesleukin) for injection, 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 analogue of the human interleukin-2 gene. Genetic engineering techniques were used to modify the human IL-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 nonrecombinant molecule have been reproduced with PROLEUKIN.

PROLEUKIN is supplied as a sterile, white to off-white, lyophilised cake in single-use vials intended for intravenous or subcutaneous administration. When the 18 million International Unit (IU) vial is reconstituted with 1.2 mL Water for Injections B.P., each mL contains 18 million IU (1.1 mg) PROLEUKIN, 50 mg mannitol, and 180 mcg sodium lauryl sulfate, buffered with approximately, 170 mcg sodium phosphate dibasic monohydrate and 890 mcg sodium phosphate monobasic to a pH of 7.5 (range 7.2 to 7.8).

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

18 million IU PROLEUKIN = 1.1 mg protein

Pharmacology

PROLEUKIN® (Aldesleukin) has been shown to possess the biological activities of human native interleukin-2. *In vitro* studies performed on human cell lines demonstrate the immunoregulatory properties of PROLEUKIN, including:

enhancement of lymphocyte mitogenesis and stimulation of long-term growth of human interleukin-2 dependent cell lines;

enhancement of lymphocyte cytotoxicity;

induction of killer cell (lymphokine-activated (LAK) and natural (NK)) activity; and

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 and eosinophilia. In humans the production of cytokines including tumour necrosis factor, interleukin-1 and gamma interferon has also been demonstrated. *In vivo* experiments in some murine models have shown inhibition of implanted tumour growth. The exact mechanism by which PROLEUKIN mediates its antitumour activity in animals and humans is not completely known.

PHARMACOKINETICS

PROLEUKIN exists as biologically active, non-covalently bound microaggregates with an average size of 27 recombinant interleukin-2 molecules per microaggregate particle. The solubilising agent, sodium lauryl sulfate, may have an effect on the kinetic properties of this product.

The pharmacokinetics of PROLEUKIN has been evaluated when given by intravenous bolus, continuous intravenous infusion and subcutaneous injection.

The pharmacokinetic profile of PROLEUKIN is characterised by high plasma concentrations following a short intravenous 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 intravenous PROLEUKIN in humans indicate that upon completion of infusion, approximately 30% of the administered dose is detectable in plasma. This finding is consistent with studies in rats using radiolabelled PROLEUKIN, which demonstrate a rapid (< 1 min) uptake of the majority of the label into the lungs, liver, and kidney.

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. 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 distribution to plasma, cleared from the circulation and presented to the kidney is metabolised to amino acids in the cells lining the proximal convoluted tubules. 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 intravenous infusion. These patients were shown to have a distribution and elimination $T^{1/2}$ of 13 and 85

minutes, respectively. In humans, the mean clearance rate in cancer patients is 268 mL/min.

The relatively rapid clearance of PROLEUKIN when given intravenously has led to dosage schedules characterised by frequent, short infusions. Observed serum levels are proportional to the dose of PROLEUKIN.

When given by subcutaneous injection, the peak plasma level was not reached until 2-5 hours after the injection, and was approximately equal to the steady state following an intravenous infusion. Bioavailability of PROLEUKIN following subcutaneous injection was 35-47%. The elimination half-life was 5-9 hours.

Clinical trials

Clinical experience

15-Minute Intravenous Infusion

Two hundred fifty-five patients with metastatic renal cell cancer (metastatic RCC) were treated with single agent PROLEUKIN® (Aldesleukin) intravenously in 7 clinical studies conducted at 21 institutions. Two hundred seventy patients with metastatic 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 Performance Status (ECOG PS) of 0 or 1 and normal organ function as determined by cardiac stress test, pulmonary function tests, and creatinine \leq 1.5 mg/dL (0.12 mmol/L). Patients with brain metastases, active infections, organ allografts and diseases requiring steroid treatment were excluded.

PROLEUKIN was given by 15 minute intravenous 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 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). A summary of the clinical trials results is provided in Table 1.

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 tumour regression was observed as early as 4 weeks after completion of the first course of treatment, and in some cases, tumour regression continued for up to 12 months after the start of treatment. The median duration of objective complete responses is 54 + months and for partial response was 20 months. Thirteen patients who achieved a complete response and seven 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). Some patients with individual bulky lesions and high tumour burden achieved responses.

In the metastatic 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 objective (partial or complete) response was 9 months (2 to 106+ months); the median duration of objective complete responses is 40 + months and the median duration for partial response was 6 months. Ten patients who achieved a complete response and two 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 melanoma patients were observed in both visceral and non-visceral sites (e.g., lung, liver, lymph node, soft tissue, adrenal, subcutaneous). Some patients with individual bulky lesions and large cumulative tumour burden achieved responses.

TABLE I: Clinical response with 15-minute intravenous infusion

	METASTATIC RCC (n = 255)		METASTATIC MELANOMA (n = 270)	
	Number of Responding Patients (response rate)	Median Response Duration in Months (range)	Number of Responding Patients (response rate)	Median Response Duration in Months (range)
Complete Response (CR)	17 (7%)	54 +* (7 to 107 +)	17 (6%)	40 +* (3 to 106 +)
Partial Response (PR)	20 (8%)	20 (3 to 97 +)	26 (10%)	6 (2 to 92 +)
PR + CR	37 (15%)	54 (3 to 107 +)	43 (16%)	9 (2 to 106 +)

(+) Sign means ongoing * Median duration not yet observed; a conservative value is presented which represents the minimum median duration of response.

An analysis of prognostic factors showed that a better ECOG PS (see Table II) was significantly associated with response.

TABLE II: Clinical response by ECOG PS

Pretreatment	METASTATIC RCC		METASTATIC 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%)

24-Hour Intravenous Infusion

Two-hundred and twenty-five patients with metastatic renal cell cancer were treated in two studies which evaluated a PROLEUKIN treatment schedule consisting of two five-day periods of 24-hour intravenous infusion of PROLEUKIN

at 18 million IU/m²/day separated by a rest period of two to six days. The induction cycle was repeated after three weeks. Patients with stable or responding tumours were eligible for additional courses of therapy, maintenance comprised of up to four cycles could be repeated at four weekly intervals. 42% (94/225) of the patients had ECOG PS = 0, 58% (131/225) had ECOG PS = 1. Prior nephrectomy was common. 77% (173/225) patients had surgery including a nephrectomy. Patients received a mean of 2.8 cycles of PROLEUKIN. The mean cumulative number of days of PROLEUKIN treatment for all cycles was 21. Objective response was seen in 28/225 (12%) patients, with 7/225 (3%) complete and 21/225 (9%) partial responders (see Table III). The 95% confidence interval for objective response was 8% to 18%. The median response duration of patients with objective complete responses was 47 months and for partial response, 10 months. The median time to follow up of the responding patients was 25.8 months. Responses were observed in both lung and non-lung sites including liver, bone, skin, lymph node, renal bed occurrences and soft tissue.

The median progression free survival for all responding patients was 12 months. The median progression free survival in patients with complete responses was 48 months (range 5 to 101 + months) for the partial responding patients 12 months (range 4 to 78 +).

TABLE III: Clinical response with 24-hour intravenous infusion

	METASTATIC RCC (n = 225)	
	Number of Responding Patients (response rate)	Median Response Duration in Months (range)
Complete Response (CR)	7 (3%)	47 (2 to 95 +)
Partial Response (PR)	21 (9%)	10 (1 to 77 +)
PR + CR	28 (12%)	12 (1 to 95 +)

Subcutaneous Injection

Two studies involving 103 patients were undertaken, using subcutaneous PROLEUKIN in the treatment of patients with metastatic renal cell carcinoma. Patients received 18 million IU of PROLEUKIN as a daily subcutaneous injection for 5 days followed by 2 days of rest. For the following 3 weeks, 18 million IU by subcutaneous injection on days 1 and 2, followed by 9 million IU on days 3 through 5. Each cycle of treatment was for 4 weeks with a 2 to 3 week rest period between cycles. Responding or stable patients could receive additional cycles, for a maximum of 12 treatment weeks. 56% (58/103) had PS 0 according to the ECOG criteria and 37% (38/103) had PS 1. Seventy-six percent (78/103) of patients had prior nephrectomy. Few had prior chemotherapy. Table IV summarises the clinical results of these patients receiving PROLEUKIN subcutaneously. Objective response was seen in 14/103 (14%) patients, with 4/103 (4%) complete and 10/103 (10%) partial responders. The 95% confidence interval for objective response was 7% to 22%.

TABLE IV: Clinical response with subcutaneous injection

	METASTATIC RCC (n = 103)	
	Number of Responding Patients (response rate)	Median Response Duration in Months (range)
Complete Response (CR)	4 (4%)	64 (24+ to 64)
Partial Response (PR)	10 (10%)	8 (3 to 30 +)
PR + CR	14 (14%)	10 (3 to 64)

Immunogenicity

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

Detectable levels of anti-PROLEUKIN antibodies (titres greater than 10) were measured in 31/58 (53%) of cancer patients treated with a variety of single-agent subcutaneous PROLEUKIN regimens. Fifteen of these patients (26%) had neutralising activity. Although the phenomenon of developing neutralising activity is generally infrequent, it does appear to be increased in patients administered subcutaneous PROLEUKIN.

Indications

PROLEUKIN® (Aldesleukin) is indicated for the treatment of adults with metastatic renal cell carcinoma (metastatic RCC).

PROLEUKIN is indicated for the treatment of adults with metastatic melanoma.

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 see "**Dosage and administration**" section for the recommended laboratory tests. **Therapy with PROLEUKIN should be restricted to patients with both normal cardiac function and normal pulmonary function.**

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 central nervous system (CNS) metastasis, an abnormal thallium stress test or abnormal pulmonary function tests and those with organ allografts.

Warnings

PROLEUKIN when administered as an intravenous infusion, should be administered in a hospital setting under the supervision of a qualified physician experienced in the use of anticancer agents. An intensive care facility and specialists skilled in cardiopulmonary or intensive care medicine must be available. PROLUEKIN® (Aldesleukin) therapy has been associated with capillary leak syndrome (CLS) which is characterised by a loss of vascular tone and extravasation of plasma proteins and fluid into the extravascular space. CLS occurs especially when PROLEUKIN is given as intensive high dose regimens intravenously. CLS results in hypotension and reduced organ perfusion, which may be severe and can result in death. CLS may be associated with cardiac dysrhythmias (supraventricular and ventricular), angina, myocardial infarction, respiratory insufficiency requiring intubation, gastrointestinal bleeding or infarction, renal insufficiency, oedema, and mental status changes.

The incidence of CLS is considerably reduced if PROLUEKIN is administered subcutaneously.

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 if PROLUEKIN therapy. Patients with indwelling central lines are particularly at risk of infection with Gram-positive microorganisms. Antibiotic prophylaxis with oxacillin, ciprofloxacin, or vancomycin has been associated with a reduced incidence of staphylococcal infections.

The incidence and severity of adverse events that accompany PROLEUKIN therapy are generally dose- and schedule-dependent, such that higher doses given intravenously are associated with the more serious adverse reactions. Serious adverse events may accompany PROLEUKIN therapy at the recommended subcutaneous dosages)See "**Adverse reactions**" section).

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

Precautions

PROLEUKIN® (Aldesleukin) should only be used under the supervision of a qualified physician, experienced in the use of cancer chemotherapeutic agents. It is recommended that patients treated with intravenous infusion be admitted to a specialised unit having the facilities of an intensive care unit for monitoring the patient's relevant clinical and laboratory parameters. Subcutaneous treatment can be administered in an outpatient setting by a suitably trained person. It is important to note that adverse effects, although sometimes serious or life-threatening, are manageable and usually, although not invariably, resolve within 1 or 2 days of cessation of PROLEUKIN therapy. The decision to resume therapy should be

based on the severity and spectrum of the clinical toxicity. In clinical trials, a small number of patients died of treatment related side effects (See "**Adverse reactions**" section).

Pretreatment Assessment.

Because of the seriousness of the adverse events that may accompany PROLEUKIN therapy, thorough clinical and investigative evaluation should be performed prior to the commencement of treatment (See "**Dosage and Administration**" section. "**Recommended Laboratory Tests**" subsection). Patients should have both normal cardiac function as defined by thallium or other diagnostic stress testing and pulmonary function confirmed by formal pulmonary function testing. Extreme caution should be used in patients who have a history of cardiac or pulmonary disease but with normal cardiac or pulmonary test results. Patients should also have normal hepatic and CNS function.

Even patients with normal cardiovascular, pulmonary, hepatic and CNS function may experience serious, life threatening or fatal adverse events.

Selection of patients for treatment should include assessment of ECOG performance status. Evaluation of clinical studies to date reveals that patients with the more favourable ECOG performance status (ECOG PS 0) at treatment initiation respond better to PROLEUKIN, with a higher response rate and lower toxicity than patients with ECOG PS >0 (See "**Pharmacology**" section "**Clinical Experience**" subsection and "**Adverse Reactions**" section).

Experience in patients with ECOG PS >1 is extremely limited.

General

It should be noted that in some patients who received higher doses of PROLEUKIN intravenously, CLS (see boxed warning) began immediately after treatment started and was marked by increased capillary permeability to protein and fluids and reduced vascular tone. In most of these patients, a concomitant drop in mean arterial blood pressure within 2 to 12 hours occurred 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 sometimes occurred. In addition, extravasation of protein and fluids into the extravascular space in some cases led to the formation of oedema and new effusions. The incidence and severity of CLS is considerably reduced when PROLEUKIN is administered subcutaneously compared to the intravenous routes of administration.

If CLS is suspected, careful monitoring of the patient's fluid balance and organ perfusion is essential. Once CLS is diagnosed frequent determination of blood pressure and monitoring of end organ function by assessment of mental status and urine output is imperative.

Administration of fluids intravenously, either colloids or crystalloids, is recommended for treatment of hypovolaemia. Correction of hypovolaemia may require large volumes of intravenous fluids but caution is required because unrestrained fluid administration may exacerbate oedema formation or effusions.

Extravascular fluid accumulation is manifest as oedema, pleural, pericardial or peritoneal effusions. Management of these events requires careful balancing of the effects of fluid shifts so that neither the consequences of fluid accumulations (e.g., pulmonary oedema) exceeds the patient's capacity to tolerate them.

Clinical experience has shown that early administration of dopamine (1 to 5 mcg/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 mcg/kg/min or have added phenylephrine hydrochloride (1 to 5 mcg/kg/min) to low dose dopamine (See "**Adverse reactions**" section). 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 oedema formation, particularly if associated with shortness of breath from pulmonary congestion, use of diuretics, once blood pressure has normalised, has been shown to hasten recovery. **NOTE: Prior to use of any product mentioned, the physician should refer to the prescribing information for the respective product.**

PROLEUKIN treatment should be withheld if organ perfusion cannot be maintained, as demonstrated by altered mental status, reduced urine output, a fall in the systolic blood pressure below 90 mm Hg or onset of cardiac dysrhythmias (See "**Dosage and administration**" section, "**Dose Modifications**" 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 begins.

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

New neurological signs, symptoms and anatomic lesions have been reported in patients following PROLEUKIN THERAPY. Clinical manifestations included changes in mental status, speech difficulties, cortical blindness, limb and gait ataxia, hallucinations, agitation, seizures, obtundation and coma. Radiological findings included multiple and less commonly, single cortical lesions on MRI and evidence of demyelination. Neurological signs and symptoms associated with PROLEUKIN therapy usually improve after discontinuation of the drug; however, alterations in mental status may progress for several days before recovery begins and there have been reports of permanent neurological defects. PROLEUKIN administration should be withheld in patients developing moderate to severe lethargy or somnolence attributed to the drug as continued administration may result in coma.

One case of cerebral vasculitis, responsive to dexamethasone, has been reported.

Mental status changes including irritability, confusion, or depression that occur while receiving PROLEUKIN may also be indicators of bacteraemia or early bacterial sepsis, hypoperfusion or occult CNS malignancy.

PROLEUKIN is contraindicated in patients with CNS metastases and all patients should have a negative scan prior to receiving the drug. In patients with known seizure disorders, extreme caution should be exercised.

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 "**Interaction with other drugs**", subsection and "**Adverse reactions**" section). 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 have been reported following treatment with interleukin-2. Hypothyroidism sometimes preceded by hyperthyroidism, has been reported. Some of these patients required thyroid replacement therapy. Changes in thyroid function may be a manifestation of autoimmunity. Onset of symptomatic hyperglycaemia and/or diabetes mellitus has been reported during PROLEUKIN therapy.

PROLEUKIN enhancement of cellular immune function may increase the risk of graft rejection in organ transplant patients and therefore its use in such patients is contraindicated (See "**Contraindications**" section).

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

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 who have received PROLEUKIN through an indwelling central line are particularly at risk for infection with Gram-positive microorganisms.

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. This drug should not be administered to fertile persons who are not practising effective contraception.

Use in Pregnancy

Category C. PROLEUKIN has been shown to have embryo-lethal effects in rats when given in doses at 4 to 6 times the human dose (scaled by the body surface area). Significant maternal toxicities were observed in pregnant rats administered PROLEUKIN by intravenous injection at doses ranging from 0.4 to 6 times the human dose (scaled by the body surface area) during the 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 foetus.

Use in Lactation

It is not known whether PROLEUKIN 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.

Interaction with other drugs

PROLEUKIN may affect CNS function. Therefore, interactions could occur following concomitant administration of psychotropic drugs (e.g., narcotics, analgesics, antiemetics, sedatives, tranquilisers).

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.

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, cisplatin, tamoxifen and interferon- α . 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- α concurrently.

Exacerbation or the initial presentation of a number of autoimmune and inflammatory disorders has been observed following concurrent use of interferon- α 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, hyperbilirubinaemia, confusion, and dyspnoea, concomitant administration of these agents with PROLEUKIN may reduce the antitumour 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 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, diarrhoea, hypotension, oedema, and oliguria. Some clinicians have noted that these reactions resemble the immediate side effects caused by interleukin-2 administration. However the cause of these reactions is unknown. Most events were reported to occur when contrast media was given within 4 weeks after the last dose of interleukin-2. However, these events were also reported to occur when contrast media was given several months after interleukin-2 treatment.

Adverse reactions

15-Minute Intravenous Infusion

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

The following data (See Table V) 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 melanoma) treated with the recommended 15 minute short IV infusion dosing regimen.

TABLE V: ADVERSE EVENTS OCCURRING IN ≥10% OF PATIENTS (n=525) WITH 15-MINUTE INTRAVENOUS INFUSION

Body System	% Patient, all grades	% Patients, grade 4	Body System	% Patients, all grades	% Patients, grade 4
Body as a Whole			Metabolic and Nutritional Disorders		
Chills	52	0	Bilirubinaemia	40	2
Fever	29	1	Creatinine increase	33	1
Malaise	27	0	Peripheral oedema	28	0
Asthenia	23	0	SGOT increase	23	1
Infection	13	1	Weight gain	16	0
Pain	12	0	Oedema	15	0
Abdominal pain	11	0	Acidosis	12	1
Abdomen enlarged	10	0	Hypomagnesaemia	12	0
Cardiovascular			Hypocalcaemia	11	0
Hypotension	71	3	Alkaline phosphatase increase	10	0
Tachycardia	23	0	Nervous	34	1
Vasodilation	13	0	Confusion	22	0
Supraventricular tachycardia	12	1	Somnolence	12	0
Cardiovascular disorder ^a	11	1	Anxiety	11	0
Arrhythmia	10	0	Dizziness	43	1
Digestive			Respiratory		
Diarrhoea	67	2	Dyspnoea	24	0
Vomiting	50	1	Lung disorder ^b	11	3
Nausea	35	0	Respiratory disorder ^c	11	0
	22	0		10	0
	20	0			

Stomatitis	19	0	Cough increase		
Anorexia			Rhinitis	42	0
Nausea and vomiting	37	1	Skin and Appendages	24	0
Haemic and Lymphatic	29	0	Rash	18	0
Thrombocytopenia	16	0	Pruritis		
Anaemia			Exfoliative dermatitis	63	6
Leukopenia			Urogenital		
			Oliguria		

^a Cardiovascular disorder: fluctuations in blood pressure, asymptomatic ECG changes, CCF.

^b Lung disorder: physical findings associated with pulmonary congestion, rales, rhonchi.

^c Respiratory disorder: ARDS, CXR infiltrates, unspecified pulmonary changes.

In patients with both metastatic RCC and metastatic melanoma, those with ECOG PS of 1 or higher had a higher treatment-related mortality and serious adverse events.

Most adverse reactions are self-limiting and, usually, but not invariably, reverse or improve within 2 or 3 days of discontinuation of therapy. Examples of adverse reactions with permanent sequelae include: myocardial infarction, bowel perforation/infarction, and gangrene.

24-Hour Intravenous Infusion

The drug-related death rate was approximately 4% (8/225). Deaths were commonly associated with the CLS and hypoperfusion, however, one death was attributed to pulmonary embolism. The following data (See Table VI) 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 225 patients treated with the recommended 24-hour intravenous infusion regimen.

TABLE VI: Adverse events occurring in ≥10% of patients (n=225) with 24-hour intravenous infusion

Body System	% Patients all grades	% Patients grade 4	Body System	% Patients all grades	% Patients grade 4
Body as a Whole			Metabolic and Nutritional Disorders		
Chills	13	0	Bilirubinaemia	35	0
Fever	92	0	Creatinine increase	66	0
Malaise	16	0	Lactic dehydrogenase increase	29	< 1
Cardiovascular			SGOT increase	38	< 1
Hypotension	72	9	Alkaline phosphatase increase	58	< 1
Digestive			Nervous		
Diarrhoea	44	0	Confusion	12	0
Vomiting	16	0	Respiratory		
Nausea	22	0	Dyspnoea	20	2
Nausea and Vomiting	36	0	Skin and Appendages		
Haemic and Lymphatic			Erythema	20	0
Thrombocytopenia	12	0	Pruritis	15	0
Anaemia	77	1	Rash	28	0
			Urogenital		
			Oliguria	20	1

Subcutaneous Injection

PROLEUKIN administered by the subcutaneous route is absorbed into the lymphatic system. Following subcutaneous administration the incidence of adverse reactions attributable to secondary cytokines, such as hypotension, CLS and changes in mental status are diminished compared to those occurring when PROLEUKIN is given intravenously. The side effects associated with the CLS were hypotension, oliguria, weight gain, elevated serum creatinine, pulmonary oedema (See **Precautions** section). In two studies involving 103 patients receiving subcutaneous PROLEUKIN, grade 3 hypotension was observed in 2 (2%) patients; grade 4 hypotension was not observed in any patient.

The following life threatening (grade 4) adverse events were reported in the same clinical population (n=103); fever, 2 (2%); fatal cerebral ischaemia 1 (1%); thrombocytopenia, 1 (1%). Apart from the death resulting from cerebral ischaemia there was no other drug related death in the studies. Data on the common adverse events (reported in greater than 10% of patients, any grade, including any life-threatening (grade 4) adverse events, presented by body system, and by preferred term (COSTART) are based on the 103 patients treated with the recommended subcutaneous dosing regimen and are shown in Table VII.

Most adverse reactions are self-limiting and, usually, but not invariably, reverse or improve within 2 or 3 days of discontinuation of therapy.

TABLE VII: Adverse events occurring in ≥10% of patients (n=103) receiving proleukin by subcutaneous injection

Body System	% Patients all grades	% Patients grade 4	Body System	% Patients all grades	% Patients grade 4
Body as a Whole			Haemic and Lymphatic		
Chills	55	0	Anaemia	59	0
Fever	87	2	Injection Site		
Malaise	12	0	Injection site reaction	42	0
Asthenia	13	0	Metabolic and Nutritional Disorders		
Hypothermia	13	0	Creatinine increase	16	0
Pain	11	0	SGOT increase	24	0
Cardiovascular			Lactic dehydrogenase increase	53	0
Hypotension	12	0	Alkaline phosphatase increase	21	0
Digestive			Skin and Appendages		
Diarrhoea	39	0	Rash	10	0
Vomiting	21	0	Pruritis	14	0
Nausea	27	0			
Anorexia	27	0			
Nausea and vomiting	42	0			

In additional clinical population treated with PROLEUKIN-based regimens using a variety of doses and schedules (e.g., subcutaneous, continuous infusion, administration with lymphokine activated killer cells (LAK)) the following serious adverse events were reported: cerebral oedema; myocarditis; pericarditis; supraventricular tachycardia, transient ischaemic attacks; bowel necrosis; duodenal ulceration; meningitis; allergic interstitial nephritis and tracheoesophageal fistula and permanent or transient blindness secondary to optic neuritis.

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

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

Exacerbation or initial presentation of a number of autoimmune and inflammatory disorders have been reported (See "**Warnings**" section, "**precautions**" section, "**Interactions with other drugs**" subsection). 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, "**Interactions with other drugs**" subsection).

Capillary leak syndrome

Cardiac arrhythmias (supraventricular and ventricular), angina pectoris, myocardial infarction, respiratory insufficiency requiring intubation, gastrointestinal bleeding or infarction, renal insufficiency, oedema and mental status changes may be associated with capillary leak syndrome (see "**Warnings**"). The frequency and severity of capillary leak syndrome are lower after subcutaneous administration than with continuous intravenous infusion.

Severe manifestations of eosinophilia

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 have been reported, involving eosinophilic infiltration of cardiac and pulmonary tissues.

Cerebral vasculitis

Cerebral vasculitis, both isolated and in combination with other manifestations, has been reported. Cutaneous and leukocytoclastic hypersensitivity vasculitis has been reported. Some of these cases are responsive to corticosteroids.

Adverse drug reactions with concurrent interferon alpha treatment

The following undesirable effects have been reported rarely in association with concurrent interferon alpha treatment: crescentic IgA glomerulonephritis, oculo-bulbar myasthenia gravis, inflammatory arthritis, thyroiditis, bullous pemphigoid, rhabdomyolysis and Stevens-Johnson syndrome. Severe rhabdomyolysis and

myocardial injury, including myocardial infarction, myocarditis and ventricular hypokinesia appear to be increased in patients receiving Proleukin (intravenously) and interferon-alpha concurrently (see "**Interactions with other drugs**").

Bacterial infection

Bacterial infection or exacerbation of bacterial infection, including septicaemia, bacterial endocarditis, septic thrombophlebitis, peritonitis, pneumonia, and local catheter site infection have been reported mainly after intravenous administration (see "**Precautions**").

Patients with indwelling central lines have a high risk of infection with gram positive organisms. A reduced incidence of staphylococcal infections in PROLEUKIN studies has been associated with the use of antibiotic prophylaxis which includes the use of oxacillin, ciprofloxacin, or vancomycin. Steroids should be avoided.

Leukoencephalopathy

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.

Dosage and administration

Before initiating treatment, carefully review the "**Indications**"; "**Contraindications**"; "**Warnings**"; "**Precautions**"; and "**Adverse effects**" sections, particularly regarding patient selection, possible serious adverse events, patient monitoring and withholding dosage. PROLEUKIN (Aldesleukin) can be administered either as a 15-minute intravenous infusion, a 24-hour intravenous infusion, or by subcutaneous injection.

15-Minute Intravenous Infusion

In this treatment regimen PROLEUKIN® (Aldesleukin) for injection is administered by a 15-minute intravenous infusion every 8 hours. The following schedule has been used to treat adult patients with metastatic RCC or metastatic melanoma.

600,000 IU/kg (0.037 mg/kg) administered every 8 hours by a 15-minute intravenous infusion for 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 course, provided this is tolerated. During clinical trials, doses were frequently withheld for toxicity (See "**Clinical Experience**" and "**Dose Modifications**" subsections).

24-Hour Intravenous Infusion

PROLEUKIN should be administered by 24-hour intravenous infusion according to the following cycle:

18 million IU per m² per 24-hours as a continuous infusion for 5 days, followed by 2-6 days without drug, an additional 5 days of intravenous PROLEUKIN as a

continuous infusion and three weeks without drug. This constitutes an induction cycle. After the 3-week rest period of the first cycle, a second cycle should be given. Up to 4 maintenance cycles consisting of 5 days 18 million IU per m² per 24-hours once a month may be given to patients who respond or have disease stabilisation.

Subcutaneous Injection

PROLEUKIN should be administered subcutaneously according the following four week cycle:

For the first week: 18 million IU is administered as a subcutaneous injection every day on days 1 to 5. On days 6 and 7 no treatment is administered.

For each of the following 3 weeks, 18 million IU is administered by subcutaneous injection on days 1 and 2 or each week followed by 9 million IU on days 3 to 5. On days 6 and 7 no treatment is administered.

After a one-week rest period, a second four-week cycle should be given. Patients should be evaluated for response approximately 4 weeks after completion of this second cycle. Maintenance cycles may be given to patients who have a response defined as shrinkage or stabilisation of tumours.

Injection site reactions are common, rarely leading to necrosis. This effect can be reduced by varying the injection site on the body.

Retreatment

Patients should be evaluated for response approximately 4 weeks after completion of a cycle of therapy and again immediately prior to the scheduled start of the next treatment cycle. Additional cycles of treatment should be given to patients only if there is some tumour shrinkage following the last cycle and retreatment is not contraindicated (See tabulation below). Data from the clinical studies do not permit recommendations to be made on the optimum number of further treatment cycles. Maintenance cycles should be based on the individual patient's response and clinical needs.

Retreatment with PROLEUKIN is contraindicated in patients who have experiences the following drug-related toxicities while receiving an earlier cycle of therapy:

Body System

Cardiovascular	Sustained ventricular tachycardia (≥ 5 beats) Cardiac rhythm disturbances not controlled or unresponsive to treatment 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 ischaemia/perforation Gastrointestinal bleeding requiring surgery

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 complete assessment of the patient. With this in mind, the following guidelines should be used:

Body System	Withhold dose if these occur	Subsequent doses may be given if
Cardiovascular	Atrial fibrillation, supraventricular tachycardia, or bradycardia that requires treatment or is recurrent or persistent Systolic BP <90 mm Hg with increasing requirements for pressors Any ECG change consistent with MI, ischaemia or myocarditis with or without chest pain; suspicion of cardiac ischaemia	Patient is asymptomatic with full recovery to normal sinus rhythm Systolic BP ≥90 mm Hg and stable or lessening requirements for pressors Patient is asymptomatic, MI and myocarditis have been ruled out, clinical suspicion of angina is low; there is no evidence of ventricular hypokinesia
Respiratory	Arterial O ₂ saturation (SaO ₂) < 90%	Arterial O ₂ saturation (SaO ₂) > 90%
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 >0.36 mmol/L (>4.5 mg/dL) or a serum creatinine of ≥0.32 mmol/L (≥4 mg/dL) in the presence of severe volume overload, acidosis, or hyperkalaemia Persistent oliguria, urine output of <10 mL/hour for 16 to 24 hours with rising serum creatinine	Serum creatinine <0.32 mmol/L (<4 mg/dL) and fluid and electrolyte status is stable Urine output >10 mL/hour with a decrease of serum creatinine >0.12 mmol/L or normalisation of serum creatinine
Digestive	Signs of hepatic failure including encephalopathy, increasing ascites, liver pain, hypoglycaemia Faecal occult blood test positive	All signs of hepatic failure have resolved* Faecal occult blood test 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 cycle. A new cycle of treatment if warranted, should be initiated no sooner than 7 weeks after cessation of adverse event and hospital discharge.*

Recommended Laboratory Tests

- The following investigations are recommended for all patients, prior to beginning treatment and periodically thereafter. Standard haematological tests- including FBC, differential and platelets counts
- Blood chemistry - including electrolytes, renal and hepatic function tests
- Chest x-rays

Serum creatinine should be less than or equal to 0.12mmol/L (1.5mg/dL) prior to initiation and resumption of PROLEUKIN treatment.

Monitoring during therapy with PROLEUKIN should include vital signs (temperature, pulse, blood pressure and respiration rate), weight, and fluid balance. In a patient with 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 is recommended.

Patients should be screened for normal cardiac function with a thallium or other diagnostic stress testing.

All patients should have baseline pulmonary function tests and arterial blood gases or pulse oximetry as required. Adequate pulmonary functions should be recorded prior to initiating therapy.

During treatment, pulmonary function should be monitored on a regular basis by clinical examination, assessment of vital signs and, if necessary, pulse oximetry. A decrease in arterial oxygen saturation (Sa_{O_2}) may be associated with CLS. Signs and symptoms of respiratory impairment should be further assessed with arterial blood gas determination.

Cardiac function should be assessed 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 secondary to myocarditis may persist for several months. If there is evidence of cardiac ischaemia or congestive heart failure, PROLEUKIN therapy should be withheld, and further evaluation performed.

Reconstitution and dilution directions

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

- To facilitate reconstitution, and subsequent product aspiration, the use of a locking Luer adapter plug is suggested. Vials should be entered only once for reconstitution in order to minimise the risk of microbial contamination. Any unused portion of the reconstituted agent should be discarded.
- Each vial of PROLEUKIN should be reconstituted aseptically with only 1.2 mL of Water for Injections B.P. When reconstituted as directed, each mL contains 1.1 mg or 18 million IU of PROLEUKIN.
- To avoid foaming during reconstitution, the Water for Injections B.P. should be directed carefully at the sides of the vial and the contents of the vial gently swirled. **The vial should not be shaken.**
- Reconstitution with either Bacteriostatic Water for Injection or 0.9% Sodium Chloride for Injection **must be avoided** because of increased aggregation.
- PROLEUKIN is an unpreserved sterile product. Since this product contains no preservative, the reconstituted and diluted solutions must be stored in a refrigerator.
- After reconstitution, store in a refrigerator at 2 to 8°C. Do not freeze. To avoid microbial contamination, it is recommended that the product is used

immediately, otherwise ensure that PROLEUKIN is used within 24 hours of reconstitution. The product should be inspected visually for particulate matter or discoloration and brought to room temperature immediately prior to administration .

For 15-minute intravenous infusion only:

After reconstitution with Water for Injections B.P., the product should be diluted aseptically in 50 mL 5% Dextrose for Injection (D5W). **(After aspiration of the reconstituted solution, DO NOT RINSE THE VIAL WITH DILUENT. Each vial contains sufficient product to ensure that the correct amount is withdrawn).**

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 mcg/mL and above 70 mcg/mL have shown increased variability in drug delivery. When it is necessary to achieve concentrations below 30 mcg/mL, the addition of 0.1 % Human Serum Albumin (HSA) is recommended

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.

24-hour intravenous infusion

Administration of PROLEUKIN via 24-hour intravenous infusion can be accomplished by various methods, including the use of infusion bags and other drug delivery devices.

- For continuous infusion using plastic bags, dilute PROLEUKIN in an appropriate volume of D5W containing 0.1% HSA for delivery. **(After aspiration of the reconstituted solution, DO NOT RINSE THE VIAL WITH DILUENT. Each vial contains sufficient product to ensure that the correct amount is withdrawn).** When reconstituted and diluted according to directions, PROLEUKIN is stable for up to 24 hours in plastic bags (e.g., PVC bags) when refrigerated (2 to 8°C). The solution should be brought to room temperature prior to infusion in the patient.
- PROLEUKIN can be diluted with D5W for a final diluted concentration equal to or greater than 100 mcg/mL. For concentrations of 1-70 mcg/mL, pre-addition of HSA to a final concentration of 0.1% is necessary for full recovery and stability.
- At final concentrations above 100 mcg/mL, PROLEUKIN solutions remain stable when diluted in D5W alone.
- At final PROLEUKIN concentrations of 1 to 70 mcg/mL (in D5W), visual precipitation and/or decreased bioactivity occur. PROLEUKIN solution containing 0.1% HSA remains stable.

At final concentrations between 70 and 100 mcg/mL, all solutions are unstable whether or not HSA is present. It is recommended that these concentrations be avoided.

Subcutaneous Use

Reconstitute PROLEUKIN as directed above. Further dilution with Dextrose for Injection (D5W) is not required.

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, which may also result in loss of the therapeutic effects of PROLEUKIN. **NOTE: Prior to the use of dexamethasone, the physician should refer to the dexamethasone prescribing information.**

Presentation

PROLEUKIN[®](Aldesleukin) powder for injection is supplied as 18 million IU in individually boxed single-use vials.

Store vials of lyophilised PROLEUKIN in a refrigerator at 2 to 8°C. Avoid exposure to heat and light.

Store reconstituted or diluted PROLEUKIN for up to 24 hours at refrigerated temperatures, 2 to 8°C.

Do not use beyond the expiry date printed on the vial. **NOTE:** This product does not contain a preservative. Discard unused portion.

Medicine classification

Prescription medicine

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