PDR®

47

EDITION

1993

PHYSICIANS' DESK REFERENCE®

PDR®

47 EDITION

1993

PHYSICIANS' DESK REFERENCE®

Product Manager
DANIEL B. ZURICH

Sales Manager
CHARLIE J. MEITNER

Account Managers
CHAD E. ALCORN
JAMES R. PANTALEO
MICHAEL S. SARAJIAN
JOANNE C. TERZIDES

Commercial Sales Manager
ROBIN B. BARTLETT

Direct Marketing Manager
ROBERT W. CHAPMAN

Manager, Professional Data
MUKESH MEHTA, R. Ph.

Index Editor
ADELE L. DOWD

Director of Production
MARJORIE A. DUFFY

Assistant Director of Production
CARRIE WILLIAMS

Production Manager
KIMBERLY V. HILLER

Format Editor
MILDRED M. SCHUMACHER

Production Coordinator
ELIZABETH A. KARST

Art Associate
JOAN K. AKERLIND

Medical Consultant
LOUIS V. NAPOLITANO, MD

Officers of Medical Economics Data, a division of Medical Economics Company Inc: **President and Chief Executive Officer**, Norman R. Snesil; **Executive Vice President**, Mark L. Weinstein; **Senior Vice President and Chief Financial Officer**, J. Crispin Ashworth; **Senior Vice President of Business Development**, Stephen J. Sorkenn; **Vice President of Product Management**, Curtis B. Allen; **Vice President of Sales and Marketing**, Thomas F. Rice; **Vice President of Operations**, John R. Ware; **Vice President of Information Systems and Services**, Edward J. Zecchini

Cetus—Cont.

tant congestive heart failure. Treatment consists of vigorous management of congestive heart failure with digitalis preparations and diuretics. The use of peripheral vasodilators has been recommended.

DOSAGE AND ADMINISTRATION

Care in the administration of doxorubicin hydrochloride will reduce the chance of perivenous infiltration. It may also decrease the chance of local reactions such as urticaria and erythematous streaking. On intravenous administration of doxorubicin, extravasation may occur with or without any accompanying stinging or burning sensation and even if blood returns well on aspiration of the infusion needle. If any signs or symptoms of extravasation have occurred, the injection or infusion should be immediately terminated and restarted in another vein If it is known or suspected that subcutaneous extravasation has occurred, local infiltration with an injectable corticosteroid and flooding the site with normal saline has been reported to lessen the local reaction. Because of the progressive nature of extravasation reactions, the area of injection should be frequently examined and plastic surgery consultation obtained If ulceration begins, early wide excision of the involved areas should be considered [1]

The most commonly used dosage schedule is 60–75 mg/m^2 as a single intravenous injection administered at 21-day intervals. The lower dose should be given to patients with inadequate marrow reserves due to old age, or prior therapy, or neoplastic marrow infiltration. An alternative dose schedule is weekly doses of 20 mg/m^2 which has been reported to produce a lower incidence of congestive heart failure Thirty mg/m^2 on each of three successive days repeated every four weeks has also been used. Doxorubicin dosage must be reduced if the bilirubin is elevated as follows: Serum bilirubin 1.2 to 3.0 mg/dL—give ½ normal dose, > 3 mg/dL—give ¼ normal dose.

It is recommended that doxorubicin be slowly administered into a tubing of a freely running intravenous infusion of Sodium Chloride Injection, USP or 5% Dextrose Injection, USP The tubing should be attached to a Butterfly® needle inserted preferably into a large vein. If possible, avoid veins over joints or in extremities with compromised venous or lymphatic drainage. The rate of administration is dependent on the size of the vein and the dosage. However, the dose should be administered in not less than 3 to 5 minutes. Local erythematous streaking along the vein as well as facial flushing may be indicative of too rapid an administration A burning or stinging sensation may be indicative of perivenous infiltration and the infusion should be immediately terminated and restarted in another vein. Perivenous infiltration may occur painlessly.

Doxorubicin should not be mixed with heparin or 5-fluorouracil since it has been reported that these drugs are incompatible to the extent that a precipitate may form. Until specific compatibility data are available, it is not recommended that doxorubicin be mixed with other drugs.

Doxorubicin has been used concurrently with other approved chemotherapeutic agents. Evidence is available that in some types of neoplastic disease combination chemotherapy is superior to single agents. The benefits and risks of such therapy continue to be elucidated.

Handling and Disposal: Skin reactions associated with doxorubicin have been reported. Caution in the handling of solution must be exercised and the use of gloves is recommended. If doxorubicin contacts the skin or mucosae, immediately wash thoroughly with soap and water.

Procedures for proper handling and disposal of anti-cancer drugs should be considered Several guidelines on this subject have been published [2–7] There is no general agreement that all of the procedures recommended in the guidelines are necessary or appropriate.

HOW SUPPLIED

Doxorubicin Hydrochloride Injection. USP.
Sterile, single use only, contains no preservative.
NDC 53905-235-10 10 mg vial; 2 mg/mL, 5 mL, 10 vial packs.
NDC 53905-236-06 20 mg vial; 2 mg/mL, 10 mL, 6 vial packs.
NDC 53905-237-01 50 mg vial; 2 mg/mL, 25 mL, single vial packs.
Store under refrigeration, 2°–8°C (36°–46°F), protect from light and retain in carton until time of use. Discard unused portion.
CAUTION: Federal law prohibits dispensing without prescription.

REFERENCES

1. Rudolph R *et al:* Skin Ulcers Due to Adriamycin *Cancer 38*.1087–1094, Sept. 1976
2. Recommendations for the Safe Handling of Parenteral Antineoplastic Drugs. NIH Publication No 83-2621. For sale by the Superintendent of Documents, U.S. Government Printing Office, Washington, D.C. 20402.
3. AMA Council Report. Guidelines for Handling Parenteral Antineoplastics. *JAMA*, March 15, 1985.
4. National Study Commission on Cytotoxic Exposure-Recommendations for Handling Cytotoxic Agents Available from Louis P Jeffrey, Sc.D., Director of Pharmacy Services, Rhode Island Hospital, 593 Eddy Street, Providence, Rhode Island 02902.
5. Clinical Oncological Society of Australia. Guidlines and recommendations for safe handling of antieoplastic agents. *Med J Australia 1*:426–428, 1983.
6. Jones RB, et al Safe handling of chemotherapeutic agents: A report from the Mount Sinai Medical Center. *CA-A Cancer Journal for Clinicians* Sept/Oct, 258-263, 1983.
7. American Society of Hospital Pharmacists technical assistance bulletin on handling cytotoxic drugs in hospitals. *Am J Hosp Pharm 42*:131–137, 1985.

MANUFACTURED BY:
Farmitalia Carlo Erba
Milan, Italy
DISTRIBUTED BY:
Cetus Oncology Corporation
4650 Horton Street
Emeryville, CA 94608–2997
Revised February 1, 1991 057200291 NO-P-03

LEUCOVORIN Calcium for Injection ℞

HOW SUPPLIED

Leucovorin Calcium for Injection is supplied in packs of ten individually-boxed vials.
50 mg vial: NDC 53905-051-10 Each vial contains 50 mg leucovorin as the calcium salt and 45 mg sodium chloride.
100 mg vial: NDC 53905-052-10. Each vial contains 100 mg leucovorin as the calcium salt and 90 mg sodium chloride.
Caution: Federal law prohibits dispensing without prescription.
Revised April, 1991 DD-P-02

METOCLOPRAMIDE INJECTION, USP ℞

HOW SUPPLIED

Metoclopramide Injection, USP is supplied as a Pharmacy Bulk Package containing 5 mg metoclopramide (present as the hydrochloride) per mL in the following package strengths:
NDC 53905-195-01 250 mg in 50 mL
NDC 53905-196-01 500 mg in 100 mL
Store at controlled room temperature, 15° to 30°C (59° to 86°F). Do not permit to freeze. Contains no preservative.
PROTECT FROM LIGHT. Retain in carton until time of use. Discard unused portion no later than 4 hours after initial entry.
Dilutions may be stored unprotected from light under normal light conditions up to 24 hours after preparation.
Metoclopramide Injection, USP is also supplied as a 30 mL single-dose non-Pharmacy Bulk Package containing 5 mg metoclopramide (present as the hydrochloride) per mL in a carton of six flip-top vials
NDC 53905-194-06 150 mg in 30 mL
Refer to the full prescribing information enclosed with this product for dosage and administration directions.

Container	Total Contents*	Concentration	Administration
30 mL (single-dose vial)	150 mg	5 mg/mL	For IV infusion Only—Dilute Before Using
50 mL Pharmacy Bulk Package	250 mg	5 mg/mL	For IV infusion Only—Dilute Before Using
100 mL Pharmacy Bulk Package	500 mg	5 mg/mL	For IV infusion Only—Dilute Before Using

*Metoclopramide (present as the hydrochloride)

CAUTION: Federal law prohibits dispensing without prescription.
Revised June, 1992 JB-P-04

PROLEUKIN® ℞

[*prō-lū'-kin*]
Aldesleukin
For Injection

WARNINGS

PROLEUKIN® (aldesleukin for injection) should be administered only 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). CLS results in hypotension and reduced organ perfusion which may be severe and can result in death.

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.

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

DESCRIPTION

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 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.

Biological activities tested *in vitro* for the native non-recombinant molecule have been reproduced with Proleukin.[1,2]

Proleukin for Injection 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

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 (18 × 10^6) IU Proleukin® = 1.1 mg protein

CLINICAL PHARMACOLOGY

Proleukin® has been shown to possess the biological activity of human native interleukin-2.[1,2] *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 select murine tumor models and in the clinic 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] The exact mechanism by which Proleukin mediates its antitumor activity in animals and humans is unknown.

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 IV 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.

Studies of IV Proleukin in sheep and humans indicated that approximately 30% of the administered dose initially distributes to the plasma.

This is consistent with studies in rats that demonstrate a rapid (< 1 minute) and preferential uptake of approximately 70% of an administered dose into the liver, kidney and lung.

The serum half-life (T ½) curves of Proleukin remaining in the plasma are derived from studies done in 52 cancer patients following a 5 minute IV infusion.[5] These patients were shown to have a distribution and elimination T ½ 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 described above, 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.[6-9] 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.[9]

Immunogenicity: Fifty-eight of 76 renal cancer patients (76%) treated with the every 8 hour Proleukin regimen developed low titers of non-neutralizing anti-interleukin-2 antibodies. Neutralizing antibodies were not detected in this group of patients, but have been detected in 1/106 (<1%) patients with IV Proleukin using a wide variety of schedules and doses. The clinical significance of anti-interleukin-2 antibodies is unknown.

Clinical Experience: Two hundred and fifty-five patients with metastatic renal cell cancer were treated with single agent Proleukin. Treatment was given by the every 8 hour regimen in 7 clinical studies conducted at 21 institutions. To be eligible for study, patients were required to have bidimensionally measurable disease; Eastern Cooperative Oncology Group (ECOG) Performance Status (PS) of 0 or 1 (see Table I); and normal organ function, including normal cardiac stress test and pulmonary function tests. Patients with brain metastases, active infections, organ allografts and diseases requiring steroid treatment were excluded. In addition, it was noted that 218 of the 225 (85%) patients had undergone nephrectomy prior to treatment with Proleukin.

Proleukin was given by 15 minute 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. All patients were treated with 28 doses or until dose-limiting toxicity occurred requiring ICU-level support. Patients received a median of 20 of 28 scheduled doses of Proleukin. Doses were held for specific toxicities (See "**DOSAGE AND ADMINISTRATION**" Section, "**Dose Modification**" Subsection). A variety of serious adverse events were encountered including: hypotension; oliguria/anuria; mental status changes including coma; pulmonary congestion and dyspnea; GI bleeding; respiratory failure leading to intubation; ventricular arrhythmias; myocardial ischemia and/or infarction; ileus or intestinal perforation, renal failure requiring dialysis; gangrene; seizures; sepsis and death (See "**ADVERSE REACTIONS**" Section).

Due to the toxicities encountered during the clinical trials, investigators used the following concomitant medications. Acetaminophen and indomethacin were started immediately prior to Proleukin to reduce fever. Renal function was particularly monitored because indomethacin may cause synergistic nephrotoxicity. Meperidine was added to control the rigors associated with fever. Ranitidine or cimetidine were given for prophylaxis of gastrointestinal irritation and bleeding. Antiemetics and antidiarrheals were used as needed to treat other gastrointestinal side effects. These medications were discontinued 12 hours after the last dose of Proleukin. Hydroxyzine or diphenhydramine used to control symptoms from pruritic rashes and continued until resolution of pruritus. **NOTE: Prior to the use of any product mentioned in this paragraph, the physician should refer to the package insert for the respective product.**

For the 255 patients in the Proleukin database, objective response was seen in 15% or 37 patients with nine (4%) complete and 28 (11%) partial responders. The 95% confidence interval for response was 11 to 20%. Onset of tumor regression has been observed as early as 4 weeks after completion of the first course of treatment and tumor regression may continue for up to 12 months after the start of treatment. Durable responses were achieved with a median duration of objective (partial or complete) response by Kaplan-Meier projection at 23.2 months (1 to 50 months). The median duration of objective partial response was 18.8 months. The proportion of responding patients who will have response durations of 12 months or greater is projected to be 85% for all responders and 79% for patients with partial responses (Kaplan-Meier).

Complete Responders	Partial Responders	Response Rate	Onset of Response	Median Duration of Response
9 (4%)	28 (11%)	15%	1 to 12 mos.	23.2 months (range 1-50)

TABLE I
PERFORMANCE STATUS SCALE

Performance Status Equivalent		Performance Status Definitions
ECOG*	Karnofsky	
0	100	Asymptomatic
1	80-90	Symptomatic; fully ambulatory
2	60-70	Symptomatic; in bed less than 50% of day
3	40-50	Symptomatic, in bed more than 50% of day
4	20-30	Bedridden

Zubrod, CG, et al J Chron Dis 11:7-33, 1960

TABLE II
PROLEUKIN RESPONSE ANALYZED BY ECOG* PERFORMANCE STATUS (PS)

Pre-Treatment ECOG PS	No. of Patients Treated (n=255)	Response CR	Response PR	% of Patients Responding	On-Study Death Rate
0	166	9	21	18%	4%
1	80	0	7	9%	6%
≥2	9	0	0	0%	0%

* Eastern Cooperative Oncology Group

Response was observed in both lung and non-lung sites (e.g. liver, lymph node, renal bed recurrences, soft tissue). Patients with individual bulky lesions (> 5 × 5 cm) as well as large cumulative tumor burden (> 25 cm^2 tumor area) achieved durable responses.

An analysis of prognostic factors showed that performance status as defined by the ECOG (see Table I) was a significant predictor of response. PS 0 patients had an 18% overall rate of objective response, which included all 9 complete response patients and 21 of 28 partial response patients. PS 1 patients had a lower rate of response (9%), all of which were partial responses. In this group it was notable that 6 of the 7 responders had resolution of tumor related symptoms and improved performance status to PS 0. All seven patients were fully functional and 4 of the 7 returned to work, suggesting that responses among the PS 1 patients were clinically meaningful as well (see Table II).

In addition, the frequency of toxicity was related to the performance status. As a group, PS 0 patients, when compared with PS 1 patients, had lower rates of adverse events with fewer on-study deaths (4% vs. 6%), less frequent intubations (8% vs. 25%), gangrene (0% vs. 6%), coma (1% vs. 6%), GI bleeding (4% vs. 8%), and sepsis (6% vs. 18%). These differences in toxicity are reflected in the shorter mean time to hospital discharge for PS 0 patients (2 vs. 3 days) as well as the smaller percentage of PS 0 patients experiencing a delayed (> 7 days) discharge from the hospital (8% vs. 19%). [See Table I and Table II above.]

INDICATIONS AND USAGE

Proleukin (aldesleukin) is indicated for the treatment of adults (≥ 18 years of age) with metastatic renal cell carcinoma.

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 "**CLINICAL PHARMACOLOGY**" Section, "**Clinical Experience**" Subsection). Therefore, selection of patients for treatment should include assessment of performance status, as described in Table I.

Experience in patients with PS > 1 is extremely limited.

CONTRAINDICATIONS

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

Patients with an abnormal thallium stress test or pulmonary function tests are excluded from treatment with Proleukin. Patients with organ allografts should be excluded as well. In addition, retreatment with Proleukin is contraindicated in patients who experienced the following toxicities while receiving an earlier course of therapy:

- Sustained ventricular tachycardia (≥ 5 beats)
- Cardiac rhythm disturbances not controlled or unresponsive to management
- Recurrent chest pain with ECG changes, consistent with angina or myocardial infarction
- Intubation required > 72 hours
- Pericardial tamponade
- Renal dysfunction 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

See boxed "**WARNINGS**"

Proleukin (aldesleukin) administration has been associated with capillary leak syndrome (CLS) which results from extravasation of plasma proteins and fluid into the extravascular space and loss of vascular tone. CLS results in hypotension and reduced organ perfusion which may be severe and can result in death. The CLS may be associated with cardiac arrhythmias (supraventricular and ventricular), angina, myocardial infarction, respiratory insufficiency requiring intubation, gastrointestinal bleeding or infarction, renal insufficiency, 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 exclude from treatment patients with significant cardiac, pulmonary, renal, hepatic or CNS impairment.

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

Proleukin may exacerbate disease symptoms in patients with clinically unrecognized or untreated CNS metastases. All patients should have thorough evaluation and treatment of CNS metastases prior to receiving Proleukin therapy. They should be neurologically stable with a negative CT scan. In addition, extreme caution should be exercised in treating patients with a history of seizure disorder because Proleukin may cause seizures.

Intensive Proleukin treatment is associated with impaired neutrophil function (reduced chemotaxis) and with an increased risk of disseminated infection, including sepsis and bacterial endocarditis, in treated patients. Consequently, pre-existing bacterial infections should be adequately treated prior to initiation of Proleukin therapy. Additionally, all patients with indwelling central lines should receive antibiotic prophylaxis effective against *S. aureus*.[10-12] Antibiotic prophylaxis which has been associated with a reduced incidence of staphylococcal infections in Proleukin studies includes the use of: oxacillin, nafcillin, ciprofloxacin, or vancomycin. 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 package insert for the respective product.**

PRECAUTIONS

General: Patients should have normal cardiac, pulmonary, hepatic and CNS function at the start of therapy. Patients who have had a nephrectomy are still eligible for treatment if they have serum creatinine levels ≤ 1.5 mg/dL.

Adverse events are frequent, often serious, and sometimes fatal.

Capillary leak syndrome (CLS) begins immediately after Proleukin 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 edema formation and creation of effusions.

Medical management of CLS begins with careful monitoring of the patient's fluid and organ perfusion status. This is

Continued on next page

Cetus—Cont.

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*).

Patients with hypovolemia are managed by administering IV fluids, either colloids or crystalloids. 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 some patients may develop ascites or pleural effusions. 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) exceeds 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. (See "**CLINICAL PHARMACOLOGY**" Section, "**Clinical Experience**" Subsection). Prolonged use of pressors, either in combination or as individual agents, at relatively high doses, may be associated with cardiac rhythm disturbances. **NOTE: Prior to the use of any product mentioned in this paragraph, the physician should refer to the package insert for the respective product.**

Failure to maintain organ perfusion, demonstrated by altered mental status, reduced urine output, a fall in the systolic blood pressure below 90 mm Hg or onset of cardiac arrhythmias, should lead to holding the subsequent doses until recovery of organ perfusion and a return of systolic blood pressure above 90 mm Hg are observed. (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 resorption of extravasated fluid and protein begins. 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.

Oxygen is given to the patient if pulmonary function monitoring confirms that P_aO_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 "**CLINICAL PHARMACOLOGY**" Section, "**Clinical Experience**" Subsection

Renal and hepatic function are impaired during Proleukin treatment. Use of concomitant medications known to be nephrotoxic or hepatotoxic may further increase toxicity to the kidney or liver. 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.

Patients may experience mental status changes including irritability, confusion, or depression while receiving Proleukin These mental status changes may be indicators of bacteremia or early bacterial sepsis. Mental status changes due solely to Proleukin are generally reversible when drug administration is discontinued. However, alterations in mental status may progress for several days before recovery begins.

Impairment of thyroid function has been reported following Proleukin treatment. A small number of treated patients went on to require thyroid replacement therapy. This impairment of thyroid function may be a manifestation of autoimmunity, consequently, extra caution should be exercised when treating patients with known autoimmune disease Proleukin (aldesleukin) enhancement of cellular immune function may increase the risk of allograft rejection in transplant patients.

TABLE III
Incidence of Adverse Events

Events by Body System	% of Patients	Events by Body System	% of Patients
Cardiovascular		Gastrointestinal	
Hypotension	85	Nausea and Vomiting	87
(requiring pressors)	71	Diarrhea	76
Sinus Tachycardia	70	Stomatitis	32
Arrhythmias	22	Anorexia	27
Atrial	8	GI Bleeding	13
Supraventricular	5	(requiring surgery)	2
Ventricular	3	Dyspepsia	7
Junctional	1	Constipation	5
Bradycardia	7	Intestinal Perforation/Ileus	2
Premature Ventricular Contractions	5	Pancreatitis	<1
Premature Atrial Contractions	4	Neurologic	
Myocardial Ischemia	3	Mental Status Changes	73
Myocardial Infarction	2	Dizziness	17
Cardiac Arrest	2	Sensory Dysfunction	10
Congestive Heart Failure	1	Special Sensory Disorders	
Myocarditis	1	(vision, speech, taste)	7
Stroke	1	Syncope	3
Gangrene	1	Motor Dysfunction	2
Pericardial Effusion	1	Coma	1
Endocarditis	1	Seizure (grand mal)	1
Thrombosis	1		
Pulmonary		Renal	
Pulmonary Congestion	54	Oliguria/Anuria	76
Dyspnea	52	BUN Elevation	63
Pulmonary Edema	10	Serum Creatinine Elevation	61
Respiratory Failure		Proteinuria	12
(leading to intubation)	9	Hematuria	9
Tachypnea	8	Dysuria	3
Pleural Effusion	7	Renal Impairment Requiring Dialysis	2
Wheezing	6	Urinary Retention	1
Apnea	1	Urinary Frequency	1
Pneumothorax	1	Dermatologic	
Hemoptysis	1	Pruritus	48
Hepatic		Erythema	41
Elevated Bilirubin	64	Rash	26
Elevated Transaminase	56	Dry Skin	15
Elevated Alkaline Phosphatase	56	Exfoliative Dermatitis	14
Jaundice	11	Purpura/Petechiae	4
Ascites	4	Urticaria	2
Hepatomegaly	1	Alopecia	1
Hematologic		Musculoskeletal	
Anemia	77	Arthralgia	6
Thrombocytopenia	64	Myalgia	6
Leukopenia	34	Arthritis	1
Coagulation Disorders	10	Muscle Spasm	1
Leukocytosis	9	Endocrine	
Eosinophilia	6	Hypothyroidism	<1
Abnormal Laboratory Findings		General	
Hypomagnesemia	16	Fever and/or Chills	89
Acidosis	16	Pain (all sites)	54
Hypocalcemia	15	Abdominal	15
Hypophosphatemia	11	Chest	12
Hypokalemia	9	Back	9
Hyperuricemia	9	Fatigue/Weakness/Malaise	53
Hypoalbuminemia	8	Edema	47
Hypoproteinemia	7	Infection	23
Hyponatremia	4	including urinary tract, injection site, catheter tip, phlebitis, sepsis)	
Hyperkalemia	4		
Alkalosis	4	Weight Gain (≥ 10%)	23
Hypoglycemia	2	Headache	12
Hyperglycemia	2	Weight Loss (≥ 10%)	5
Hypocholesterolemia	1	Conjunctivitis	4
Hypercalcemia	1	Injection Site Reactions	3
Hypernatremia	1	Allergic Reactions (non-anaphylactic)	1
Hyperphosphatemia	1		

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 CBC, differential and platelet counts
- Blood chemistries—including electrolytes, renal and hepatic function tests
- Chest x-rays

All patients should have baseline pulmonary function tests with arterial blood gases Adequate pulmonary function should be documented (FEV_1 > 2 liters or ≥ 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 of questionable significance, a stress echocardiogram to document normal wall motion may be useful to exclude significant coronary artery disease.

Daily monitoring during therapy with Proleukin should include vital signs (temperature, pulse, blood pressure and respiration rate) and weight. In a patient with a decreased blood pressure, especially less than 90 mm Hg, constant cardiac monitoring for rhythm 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 and central venous pressure (CVP) checked.

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 is 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 CPK evaluation. If there is evidence of cardiac ischemia or congestive heart failure, 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, tranquilizers)

DOCKET ALARM

Explore Litigation Insights

Docket Alarm provides insights to develop a more informed litigation strategy and the peace of mind of knowing you're on top of things.

Real-Time Litigation Alerts

Keep your litigation team up-to-date with **real-time alerts** and advanced team management tools built for the enterprise, all while greatly reducing PACER spend.

Our comprehensive service means we can handle Federal, State, and Administrative courts across the country.

Advanced Docket Research

With over 230 million records, Docket Alarm's cloud-native docket research platform finds what other services can't. Coverage includes Federal, State, plus PTAB, TTAB, ITC and NLRB decisions, all in one place.

Identify arguments that have been successful in the past with full text, pinpoint searching. Link to case law cited within any court document via Fastcase.

Analytics At Your Fingertips

Learn what happened the last time a particular judge, opposing counsel or company faced cases similar to yours.

Advanced out-of-the-box PTAB and TTAB analytics are always at your fingertips.

API

Docket Alarm offers a powerful API (application programming interface) to developers that want to integrate case filings into their apps.

LAW FIRMS
Build custom dashboards for your attorneys and clients with live data direct from the court.

Automate many repetitive legal tasks like conflict checks, document management, and marketing.

FINANCIAL INSTITUTIONS
Litigation and bankruptcy checks for companies and debtors.

E-DISCOVERY AND LEGAL VENDORS
Sync your system to PACER to automate legal marketing.