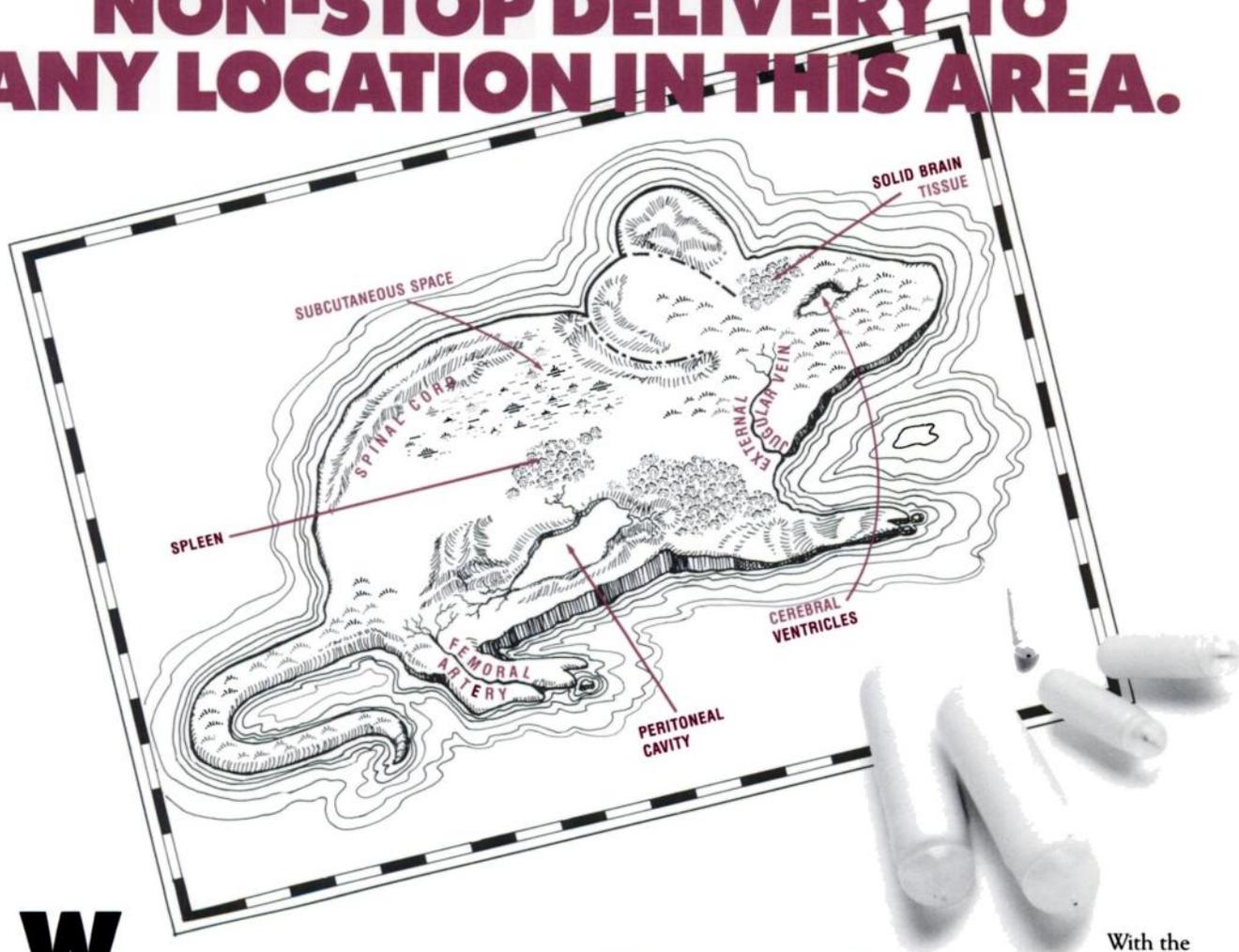


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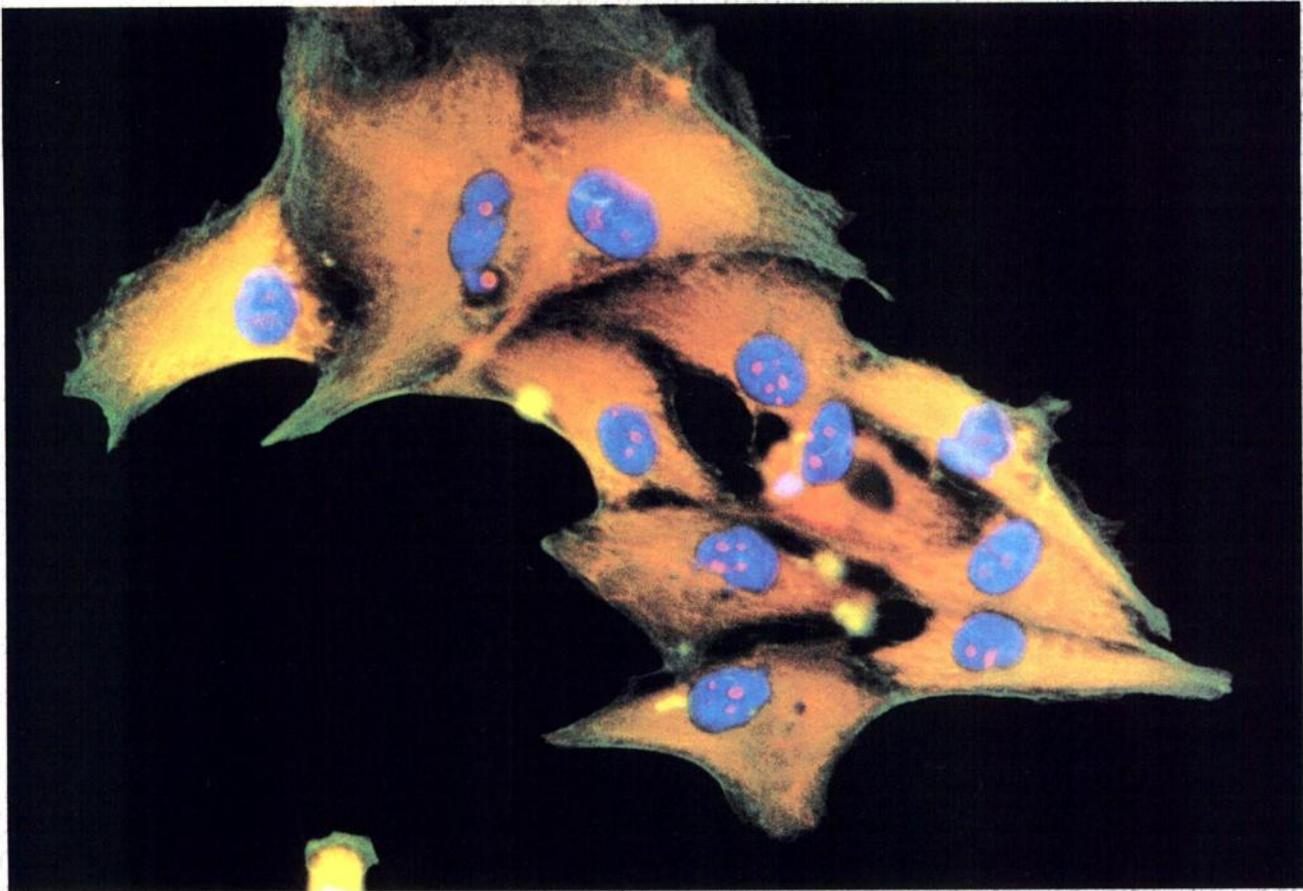
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**PROLEUKIN® (Aldesleukin)**  
**Brief Summary of Prescribing Information**  
 For full prescribing information, see Package Insert.

**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 cardio-pulmonary 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.

**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 in Package Insert. Therefore, selection of patients for treatment should include assessment of performance status, as described in Table I in Package Insert.

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 (≥2 beats)
- Cardiac rhythm disturbances not controlled or unresponsive to management
- Recurrent chest pain with ECG changes, consistent with angina or myocardial infarction
- Intubation requiring >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" section.

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 in Package Insert).

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 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*. 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 hyperkalemia 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 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<sub>2</sub>O. 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 desirability of maintaining the patient's volume and 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 in Package Insert). Prolonged use of pressors, either in combination or as individual agents, at relatively high doses, may be associated with cardiac rhythm distur-

bances. 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 in Package Insert).

Recovery from CLS begins soon after cessation of PROLEUKIN (aldesleukin) 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<sub>O<sub>2</sub></sub> 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 in Package Insert.

Renal and hepatic function is 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.

**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<sub>1</sub> >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, anesthetics, sedatives, tranquilizers).

Concurrent administration of drugs possessing neurotoxic (e.g. aminoglycosides, indomethacin), myelotoxic (e.g. cytosolic chemotherapies), cardiotoxic (e.g. doxorubicin) or hepatotoxic (e.g. methotrexate, asparaginase) effects with PROLEUKIN may increase toxicity in these organ systems. The safety and efficacy of PROLEUKIN in combination with chemotherapies has not been established.

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

Beta-blockers and other antihypertensives may potentiate the hypotension seen with PROLEUKIN (aldesleukin).

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

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

**Pregnancy: Pregnancy Category C.** Animal reproduction studies have not been conducted with PROLEUKIN. It is also not known whether PROLEUKIN can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. In view of the known adverse effects of PROLEUKIN, it should only be given to a pregnant woman with extreme caution, weighing the potential benefit with the risks associated with therapy.

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

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

**ADVERSE REACTIONS**

The rate of drug related deaths in the 255 metastatic renal cell carcinoma patients on study who received single-agent PROLEUKIN was 4% (1/255).

Frequency and severity of adverse reactions to PROLEUKIN have generally been shown to be dose-related and schedule-dependent. Most adverse reactions are self-limiting and are usually, but not invariably, reversible within 2 or 3 days of discontinuation of therapy.

Examples of adverse reactions with permanent sequelae include: myocardial infarction, bowel perforation/infarction, and gangrene.

The most frequently reported serious adverse reactions include hypotension, renal dysfunction with oliguria/anuria, dyspnea or pulmonary congestion, and mental status changes (e.g. lethargy, somnolence, confusion and agitation).

Other serious toxicities have included: myocardial ischemia, myocarditis, gangrene, respiratory failure leading to intubation, GI bleeding requiring surgery, intestinal perforation/ileus, coma, seizure, sepsis and renal impairment requiring dialysis. The incidence of these events has been higher in PS 1 patients than in PS 0 patients (See "CLINICAL PHARMACOLOGY" Section, "Clinical Experience" Subsection in Package Insert).

The following data on adverse reactions are based on 373 patients (255 with renal cell cancer and 118 with other tumors) treated with the recommended every 8 hour 15-minute infusion dosing regimen. These patients had metastatic or recurrent carcinoma and were enrolled in investigational trials in the United States.

Organ systems in which reactions occurred in a significant number of the patients treated are found in the following table:

**TABLE III**  
**Incidence of Adverse Events**

Events by Body System	% of Patients	Events by Body System	% of Patients
<b>Cardiovascular</b>		<b>Hematologic</b>	
Hypotension	85	Anemia	77
(requiring pressors)	70	Thrombocytopenia	64
Sinus tachycardia	22	Leukopenia	34
Arrhythmias	22	Coagulation Disorders	10
Atrial	8	Leukocytosis	9
Supraventricular	5	Eosinophilia	6
Ventricular	3		
Junctional	1	<b>Abnormal Laboratory Findings</b>	
Bradycardia	7	Hypomagnesemia	16
Premature Ventricular Contractions	5	Acidosis	16
Premature Atrial Contractions	4	Hypocalcemia	15
Myocardial Ischemia	3	Hypophosphatemia	11
Myocardial Infarction	2	Hypokalemia	9
Cardiac Arrest	2	Hypocurcemia	9
Congestive Heart Failure	2	Hypalbuminemia	8
Myocarditis	1	Hyponatremia	7
Stroke	1	Hyperkalemia	4
Gangrene	1	Alkalemia	4
Pericardial Effusion	1	Hypocyclopropanemia	2
Endocarditis	1	Hypoxycyclopropanemia	2
Thrombosis	1	Hypocholesterolemia	1
		Hypercalcemia	1
		Hypernatremia	1
		Hyperphosphatemia	1
<b>Gastrointestinal</b>			
Nausea and Vomiting	87		
Diarrhea	76	<b>Renal</b>	
Stomatitis	32	Oliguria/Anuria	76
Anorexia	27	BUN Elevation	63
GI Bleeding	13	Serum Creatinine Elevation	61
(requiring surgery)	7	Proteinuria	12
Dyspepsia	7	Hematuria	9
Constipation	5	Dysuria	3
Intestinal Perforation/Ileus	<1	Renal Impairment Requiring Dialysis	2
Pancreatitis	2	Urinary Retention	1
		Urinary Frequency	1
<b>Neurologic</b>			
Mental Status Changes	73	<b>Dermatologic</b>	
Dizziness	17	Sensory Dysfunction	10
Sensory Dysfunction	10	Pruritus	48
Special Sensory Disorders	7	Erythema	41
(vision, speech, taste)	7	Rash	26
Syncope	3	Dry Skin	15
Motor Dysfunction	2	Exfoliative Dermatitis	14
Coma	1	Purpura/Petechiae	4
Seizure (grand mal)	1	Urticaria	2
		Alopecia	1
<b>Pulmonary</b>		<b>Musculoskeletal</b>	
Pulmonary Congestion	54	Arthralgia	6
Dyspnea	52	Myalgia	6
Pulmonary Edema	40	Athritis	1
Respiratory Failure (leading to intubation)	9	Muscle Spasm	1
Tachypnea	8	<b>Endocrine</b>	
Pleural Effusion	7	Hypothyroidism	<1
Wheezing	6		
Apnea	1	<b>General</b>	
Pneumothorax	1	Chills/fever	89
Hemoptysis	1	Pain (all sites)	54
		Abdominal	15
<b>Hepatic</b>		Chest	12
Elevated Bilirubin	64	Back	9
Elevated Transaminase	56	Fatigue/Weakness/Malaise	53
Elevated Alkaline Phosphatase	56	Edema	47
Jaundice	11	Infection	
Ascites	4	(including urinary tract, injection site, catheter tip, phlebitis, sepsis)	23
Hepaticomegaly	1	Weight Gain (≥10%)	23
		Headache	12
		Weight Loss (≥10%)	5
		Conjunctivitis	4
		Injection Site Reactions	3
		Allergic Reactions (non-anaphylactic)	1

Other serious adverse events were derived from trials involving more than 1,800 patients treated with PROLEUKIN-based regimens using a variety of doses and schedules. These events each occurred with a frequency of <1% and included: liver or renal failure resulting in death; duodenal ulceration; fatal intestinal perforation; bowel necrosis; fatal cardiac arrest, myocarditis, and supraventricular tachycardia; permanent or transient blindness secondary to optic neuritis; fatal malignant hyperthermia; pulmonary edema resulting in death; respiratory arrest; fatal respiratory failure; fatal stroke; transient ischemic attack; meningitis; cerebral edema; pericarditis; allergic interstitial nephritis; tracheo-esophageal fistula; fatal pulmonary emboli; severe depression leading to suicide.

**OVERDOSEAGE**

Side effects following the use of PROLEUKIN® (aldesleukin) are dose-related. Administration of more than the recommended dose has been associated with a more rapid onset of expected dose limiting toxicities. Adverse reactions generally will reverse when the drug is stopped, particularly because its serum half-life is short. (See "CLINICAL PHARMACOLOGY" Section, "Pharmacokinetics" Subsection in Package Insert). Any continuing symptoms should be treated supportively. Life threatening toxicities have been ameliorated by the intravenous administration of dexamethasone, which may result in loss of therapeutic effect from PROLEUKIN. NOTE: Prior to the use of dexamethasone, the physician should refer to the package insert for this product.

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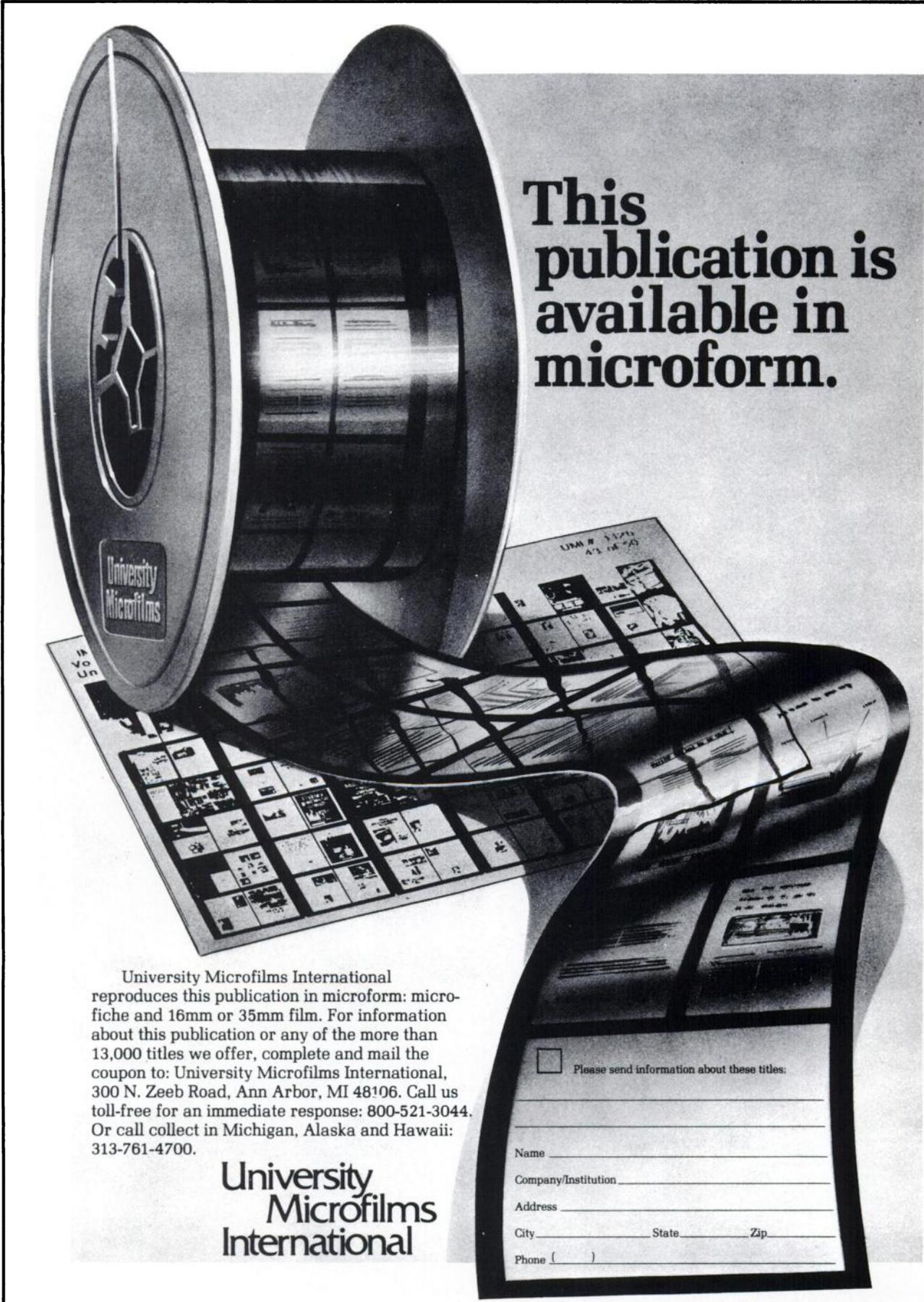
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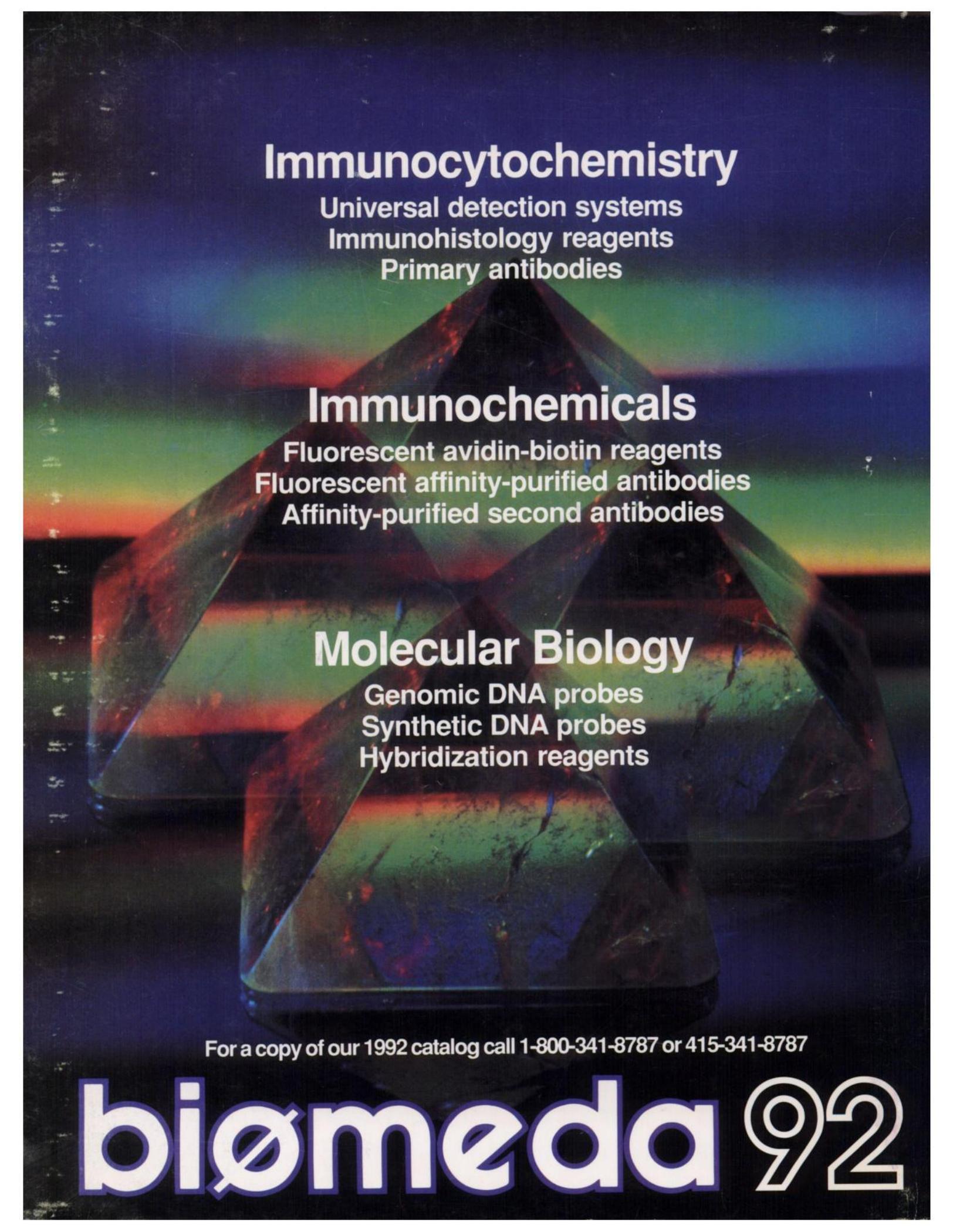
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