**TABLE 1: Proleukin Clinical Response Data**

<table>
<thead>
<tr>
<th>Metastatic RCC</th>
<th>Number of Responding Patients (response rate)</th>
<th>Median Response Duration in Months (range)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CR's</td>
<td>17 (7%)</td>
<td>80* (7 to 131+)</td>
</tr>
<tr>
<td>PR's</td>
<td>20 (8%)</td>
<td>20 (3 to 126+)</td>
</tr>
<tr>
<td>PR's + CR's</td>
<td>37 (15%)</td>
<td>54 (3 to 131+)</td>
</tr>
</tbody>
</table>

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

**Lack of efficacy with low dose Proleukin regimens**

Sixty-five patients with metastatic renal cell cancer were enrolled in a single center, open label, non-randomized trial that sequentially evaluated the safety and anti-tumor activity of two low dose Proleukin regimens. The regimens administered 18 million International Units Proleukin as a single subcutaneous injection, daily for 5 days during week 1; Proleukin was then administered at 9 x 10^6 International Units days 3-5, weekly for an additional 3 weeks (n=40) followed by a 2 week rest or 5 weeks (n=25) followed by a 3 week rest, for a maximum of 3 or 2 treatment cycles, respectively.

These low dose regimens yielded substantially lower and less durable responses than those observed with the approved regimen. Based on the level of activity, these low dose regimens are not effective.

**Metastatic Melanoma**

Two hundred seventy patients with metastatic melanoma were treated with single agent Proleukin in 8 clinical studies conducted at 22 institutions. Metastatic melanoma patients received a median of 18 of 28 scheduled doses of Proleukin during the first course of therapy. In the metastatic melanoma studies (n=270), objective response was seen in 43 (16%) patients, with 17 (6%) complete and 26 (10%) partial responders (See Table 2). The 95% confidence interval for objective response was 12% to 21%. Responses in metastatic melanoma patients were observed in both visceral and non-visceral sites (e.g., lung, liver, lymph node, soft tissue, adrenal, subcutaneous). Responses were also observed in patients with individual bulky lesions and large cumulative tumor burden.

**TABLE 2: Proleukin CLINICAL RESPONSE DATA**

<table>
<thead>
<tr>
<th>Metastatic Melanoma</th>
<th>Number of Responding Patients (response rate)</th>
<th>Median Response Duration in Months (range)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CR's</td>
<td>17 (6%)</td>
<td>59* (3 to 122+)</td>
</tr>
<tr>
<td>PR's</td>
<td>26 (10%)</td>
<td>6 (1 to 114+)</td>
</tr>
<tr>
<td>PR's + CR's</td>
<td>43 (16%)</td>
<td>9 (1 to 124+)</td>
</tr>
</tbody>
</table>

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

**INDICATIONS AND USAGE**

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

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 treatment-related death rate (see “CLINICAL STUDIES” section and “ADVERSE REACTIONS” section). Therefore, selection of patients for treatment should include assessment of performance status.

Experience in patients with ECOG 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.

Proleukin is contraindicated for the treatment of adults with metastatic melanoma.

**WARNINGS**

Because of the severe adverse events which generally accompany Proleukin® (aldesleukin) therapy at the recommended dosages, thorough clinical evaluation should be performed to identify patients with significant cardiac, pulmonary, renal, hepatic, or CNS impairment in whom Proleukin is contraindicated. Patients with normal cardiovascular, pulmonary, hepatic, and CNS function may experience severe, life threatening or fatal adverse events. Adverse events are frequent, often serious, and sometimes fatal.

Deaths, which are frequent, may be due to the dose modification protocol, while shielding efforts are being taken to limit the number of patients who are administered the higher doses. Doses were withheld for specific toxicities (See “DOSEAGE AND ADMINISTRATION” section, “Dose Modifications” subsection and “ADVERSE REACTIONS” section).
Proleukin has been associated with exacerbation of pre-existing or initial presentation of autoimmune disease and inflammatory disorders. Exacerbation of Crohn's disease, scleroderma, thyroiditis, inflammatory arthritis, diabetes mellitus, ocular-bulbar myasthenia gravis, crescentic IgA glomerulonephritis, cholecystitis, coronary vasculitis, Stevens-Johnson syndrome and bullous pemphigoid, has been reported following treatment with IL-2.

All patients should have thorough evaluation and treatment of CNS metastases and have a negative scan prior to receiving Proleukin therapy. New neurologic signs, symptoms, and anatomic lesions following Proleukin therapy have been reported in patients without evidence of CNS metastases. Clinical manifestations included changes in mental status, speech difficulties, cortical blindness, limb or gait ataxia, hallucinations, agitation, obtundation, and coma. Radiological findings included multiple and, less commonly, single, cortical lesions on MRI and evidence of demyelination. Neurologic signs and symptoms associated with Proleukin therapy usually improve after discontinuation of Proleukin therapy; however, there are reports of permanent neurologic defects in a few patients. Seizures had been reported in patients with known seizure disorders. Extreme caution should be exercised as Proleukin may cause seizures.

PRECAUTIONS

General

Patients should have normal cardiac, pulmonary, hepatic, and CNS function at the start of therapy (See "PRECAUTIONS" section, "Laboratory Tests" subsection). Capillary leak syndrome (CLS) begins immediately after Proleukin® (aldesleukin) treatment starts and is marked by increased capillary permeability to proteins and fluids into the extravascular space. Severe hypovolemia, reduced vascular tone, and hypotension may occur; patients with 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 base-line) may be a cause under these circumstances. Hyperviscosity of proteins and fluids into the extravascular space will lead to the formation of edema and creation of new effusions.

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

Flexibility in fluid and pressor management is essential for maintaining organ perfusion and blood pressure. Concomitantly, extreme caution should be used in treating patients with fixed requirements for large volumes of fluid (e.g., patients with hyperviscosity, or administration of IV fluids, either colloids or crystalloids is recommended for treatment of hypovolemia. Correction of hypovolemia may require large volumes of IV fluids but caution is required; a 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) may be a cause under these circumstances. Hyperviscosity of proteins and fluids into the extravascular space will lead to the formation of edema and creation of new effusions.

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Immuneogenicity

Serum samples from patients in the clinical studies were tested by enzyme-linked immunosorbent assay (ELISA) for anti-aldesleukin antibodies. Low titers of anti-aldesleukin antibodies were detected in 57 of 77 (74%) patients with metastatic renal cell carcinoma treated with an every 8-hour PROLEUKIN regimen and in 33 of 56 (59%) patients with metastatic melanoma treated with a 50,000 International Units/kg (0.037 mg/kg) dose administered every 8 hours. In 3 of 56 patients with metastatic melanoma, antibody formation was noted. In a separate study, the effect of immuneogenicity on the pharmacokinetics of aldesleukin was evaluated in 13 patients. Following the first cycle of therapy, comparing the geometric mean aldesleukin exposure (AUC) Day 1 5 by 1. AUC Day 1, the recency model was no change was observed in the antibody-negative patients (n=2). Overall, neutralizing antibodies were detected in 12% of patients. The impact of anti-aldesleukin antibody formation on clinical efficacy and safety of Proleukin is unknown.

Immuneogenicity assay results are highly dependent on several factors including assay sensitivity and specificity; assay methodology, sample handling, timing of sample collection, concomitant medications, and underlying disease. For these reasons, no conclusions of incidence of antibodies to PROLEUKIN with the incidence of antibodies to other products may be misleading.

Post Marketing Experience

The following adverse reactions have been identified during post-approval use of Proleukin. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

- Blood and lymphatic system: neutropenia, febrile neutropenia, eosinophilia, lymphopenia
- Cardiovascular: cardiomyopathy, cardiac tamponade
- Endocrine: hyperthyroidism
- Gastrointestinal: gastritis, intestinal obstruction, colitis
- General and administration site conditions: injection site necrosis
- Immune system: anaphylaxis, angioedema, urticaria
- Infections and infestations: pneumonia (bacterial, fungal, viral), fatal endocarditis, cellulitis
- Musculoskeletal and connective tissue: myopathy, myositis, rhabdomyolysis
- Nervous system: cerebral lesions, encephalopathy, extrapyramidal syndrome, neuralgia, neuritis, demyelinating neuropathy
- Psychiatric: insomnia
- Respiratory: hypoxia, fatigue, subarachnoid hemorrhage, cerebral hemorrhage, retroperitoneal hemorrhage

Exacerbation or initial presentation of a number of autoimmune and inflammatory disorders have been reported (see "WARNINGS" section, "PRECAUTIONS" section, "Drug Interactions" subsection). Persistent but nonprogressive vitiligo has been observed in malignant melanoma patients treated with interleukin-2. Synergistic, additive and novel toxicities have been reported with Proleukin used in combination with other drugs. Novel toxicities may be due to adverse reactions to the isolated contrast media and hypersensitivity reactions to antineoplastic agents (see "PRECAUTIONS" subsection). "Drug Interactions" subsection).

Experience has shown the following concomitant medications to be useful in the management of patients on Proleukin therapy: a) standard antipyretic therapy, including nonsteroidal anti-inflammatories (NSAIDs), start immediate to reduce fever. The function should be monitored as some NSAIDs may cause synergistic nephrotoxicity; b) meperidine used to control the rigors associated with fever; c) H+ pump inhibitors used to treat the gastrointestinal effects of interleukin-2. "section, "reactions to antineoplastic agents (See "WARNINGS" subsection). Persistent but nonprogressive vitiligo has been observed in malignant melanoma patients treated with interleukin-2. "Drug Interactions" subsection).

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

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

<table>
<thead>
<tr>
<th>Body System</th>
<th>% Patients</th>
<th>Body System</th>
<th>% Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiovascular</td>
<td>12%</td>
<td>Hypocalcemia</td>
<td>11%</td>
</tr>
<tr>
<td>Hypotension</td>
<td>11%</td>
<td>Thyroiditis</td>
<td>10%</td>
</tr>
<tr>
<td>Tachycardia</td>
<td>6%</td>
<td>Cardiac arrest</td>
<td>5%</td>
</tr>
<tr>
<td>Vomiting</td>
<td>4%</td>
<td>Cardiac tamponade</td>
<td>4%</td>
</tr>
<tr>
<td>Nausea</td>
<td>1%</td>
<td>Cardiac arrhythmia</td>
<td>1%</td>
</tr>
<tr>
<td>Anorexia</td>
<td>1%</td>
<td>Cardiac dysrhythmia</td>
<td>1%</td>
</tr>
<tr>
<td>Vasodilation</td>
<td>1%</td>
<td>Cardiac ischemia</td>
<td>1%</td>
</tr>
<tr>
<td>Pain</td>
<td>1%</td>
<td>Cardiac muscle</td>
<td>1%</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>1%</td>
<td>Cardiac myofibrosis</td>
<td>1%</td>
</tr>
<tr>
<td>Abdominal enlargement</td>
<td>1%</td>
<td>Cardiac necrosis</td>
<td>1%</td>
</tr>
</tbody>
</table>

The following adverse events (grade 4) events were reported by <1% of the 525 patients: hypophagia; shock; bradycardia; ventricular extrasystoles; myocardial ischemia; syncope; hemorrhage; atrial arrhythmia; phlebitis; AV block second degree; endocarditis; pericardial effusion; peripheral gangrene; thrombosis; coronary artery disorder; stomatitis; nausea and vomiting; liver function tests abnormal; gastrointestinal hemorrhage; hematenses; bloody diarrhea; gastrointestinal disorder; intestinal perforation; pancreatitis; anorexia; leukemia; leukopenia; leukocytosis; hypercalcemia; hyperphosphataemia increase; BUN increase; hyperuricemia; NPN increase; respiratory acidosis; somnolence; agitation; neuropathy; protonal reaction; convulsion; grand mal convulsion; delirium; asthma; lung edema; hyperventilation; hypoxia; hemoptysis; hyperventilation; purpura; myositis; pulmonary edema; pericardial effusion; vomiting; hematemesis; pericardial effusion; hypotension; thrombocytopenia; anemia; hypokalemia; hyperkalemia; and no change was observed in the antibody-negative patients (n=2). Overall, neutralizing antibodies were detected in 12% of patients. The impact of anti-aldesleukin antibody formation on clinical efficacy and safety of Proleukin is unknown.

Patients with indwelling central lines have a higher risk of infection with gram positive organisms. 9-11 hours after the last dose of Proleukin.

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 reducing the dose to be given. Decisions to stop, hold, or restart Proleukin therapy must be made after a rest period of at least 7 weeks from the date of hospital discharge. Each treatment course should be separated by a rest period of at least 7 weeks from the date of hospital discharge. For these reasons, no conclusions of incidence of antibodies to PROLEUKIN with the incidence of antibodies to other products may be misleading.

Dose Modifications

If toxicity for toxicity should be avoided. NOTE: Prior to the use of any product mentioned, the physician should refer to the package insert for the respective product.

Dosage and Administration

The recommended Proleukin (aldesleukin) treatment regimen is administered by a 15-minute intravenous infusion every 8 hours. Before initiating treatment, carefully review the "INDICATIONS AND USAGE", "WARNINGS", "PRECAUTIONS", "ADVERSE REACTIONS" and "DRUG INTERACTIONS" sections, particularly regarding patient selection, possible serious adverse events, patient monitoring and withholding dosage. The following schedule has been used to treat adult patients with metastatic renal cell carcinoma (clear-cell RCC) or metastatic melanoma. Each course of treatment consists of two 5-day treatment cycles separated by a rest period.

600,000 International U/kg (0.037 mg/kg) dose 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, for a maximum of 28 doses per course, as tolerated. During clinical trials, doses were frequently withheld for toxicity (See "CLINICAL STUDIES" section and "Dose Modifications" subsection). Metastatic renal cell carcinoma patients treated with this schedule received a median of 20 of the 28 doses during the first course of therapy. Metastatic melanoma patients received a median of 18 doses during the first course of therapy.

Retreatment

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

The following adverse reactions are self-limiting and, usually, not invariably, reversible or improved within 2 or 3 days of discontinuation of therapy. Examples of adverse reactions with permanent sequelae include: myocardial infarction, bowel perforation/infarction, and gangrene.
Retreatment with Proleukin is contraindicated in patients who have experienced the following toxicities:

<table>
<thead>
<tr>
<th>Body System</th>
<th>Dose should be held and restarted according to the following:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiovascular</td>
<td>Infarction, supraventricular tachycardia or bradycardia that requires treatment or is recurrent or persistent</td>
</tr>
<tr>
<td>Respiratory</td>
<td>O2 saturation ≤90%</td>
</tr>
<tr>
<td>Urogenital</td>
<td>Persistent oliguria, urine output of &lt;10 mL/hour for 16 to 24 hours with rising serum creatinine</td>
</tr>
<tr>
<td>Digestive</td>
<td>Stool guaiac repeatedly ≥3+</td>
</tr>
</tbody>
</table>

Doses should be held and restarted according to the following:

- **Cardiovascular**: Infarction, supraventricular tachycardia or bradycardia that requires treatment or is recurrent or persistent.
- **Respiratory**: O2 saturation ≤90%.
- **Urogenital**: Persistent oliguria, urine output of <10 mL/hour for 16 to 24 hours with rising serum creatinine.
- **Digestive**: Stool guaiac repeatedly ≥3+.

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

**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.

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

2. **Dosage:** The dose of Proleukin, reconstituted with Sterile Water for Injection, USP (without preservative) should be diluted aseptically in 50 mL of 5% Dextrose Injection, USP (D5W) and infused over a 15-minute period. Dilution and delivery of Proleukin outside of this concentration range should be avoided.

3. **Preparation:** Before and after reconstitution and dilution, store in a refrigerator at 2° to 8°C (36° to 46°F). DO NOT SHAKE.

4. **Reconstitution:** Proleukin should not be coadministered with other drugs in the same container.

5. **Administration:** Do not reconstitute or dilute Proleukin in a refrigerator at 2° to 8°C (36° to 46°F). PROTECT FROM LIGHT. Store vials of lyophilized Proleukin in a refrigerator at 2° to 8°C (36° to 46°F). PROTECT FROM LIGHT. Store vials of lyophilized Proleukin in a refrigerator at 2° to 8°C (36° to 46°F). PROTECT FROM LIGHT.