PROLEUKIN® (aldesleukin) FACT SHEET

IMMUNOTHERAPY THAT goes short. TREATMENT IN JUST 19 DAYS. WITH ANSWERS THAT quickly follow.

The Proleukin (IL-2) treatment course:

- **Short (5/9/5)**
  A typical Proleukin course is two 5-day cycles separated by approximately 9 days of rest. Results can be as early as 1 month following the first treatment course.

- **The majority of responders achieved a response after the first course**
  Proleukin demonstrated both durable complete responses (CRs) and partial responses (PRs) in clinical trials.

- **Well-controlled in a Proleukin Treatment Center**
  A dedicated inpatient, multidisciplinary treatment team manages the patients’ experience and answers questions during their hospital stay.

- **Most adverse events are reversible**
  Nearly all toxicities are self-limiting, rapidly reversible, and improve within 2 to 3 days of discontinuing therapy.

- **Can preserve the option for future therapies**
  Preserve the patient’s options for additional therapies, which have proven effective after cytokine therapy.

- **Insurance and financial assistance program**
  To find out more, call toll-free, 1-877-776-5385, 7:30 AM to 4:30 PM, PST, M-F.

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Important Safety Information

Proleukin 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.

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

Please see continued Important Safety Information for Proleukin® (aldesleukin) for injection, for intravenous infusion, on page 3.
PROLEUKIN® (ALDESLEUKIN) IS INDICATED FOR THE TREATMENT OF ADULTS WITH METASTATIC RENAL CELL CARCINOMA OR METASTATIC MELANOMA

QUESTIONS FOR YOUR DOCTOR

Would you consider me eligible for Proleukin treatment?

How does Proleukin fit in with my other options?

My treatment is provided at a specialized Proleukin Treatment Center; then I return here to you. Is there any treatment center or physician you recommend to share in my care?


‘Eastern Cooperative Oncology Group (ECOG) performance status.8,9
PS 0: Patient is fully active, able to carry on all predisease performance without restriction.
PS 1: Patient is restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature; eg, light housework, office work.

Careful patient selection is mandatory prior to the administration of Proleukin. See “CONTRAINDICATIONS,” “WARNINGS,” and “PRECAUTIONS” sections, in the accompanying full Prescribing Information, regarding patient screening, including recommended cardiac and pulmonary function tests and laboratory tests.

Please see continued Important Safety Information for Proleukin® (aldesleukin) for injection, for intravenous infusion, on page 3.
PROLEUKIN® (ALDESLEUKIN) IS INDICATED FOR THE TREATMENT OF ADULTS WITH METASTATIC RENAL CELL CARCINOMA OR METASTATIC MELANOMA

SUMMARY OF IMPORTANT SAFETY INFORMATION FOR PROLEUKIN® (ALDESLEUKIN) FOR INJECTION, FOR INTRAVENOUS INFUSION

WARNINGS

Therapy with Proleukin® (aldesleukin) 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 a normal thallium stress test and a normal pulmonary function test who have a history of cardiac or pulmonary disease.

Proleukin 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.

Proleukin administration has been associated with capillary leak syndrome (CLS) which is characterized by a loss of vascular tone and extravasation of plasma proteins and fluid into the extravascular space. CLS results in hypotension and reduced organ perfusion which may be severe and can result in death. CLS may be associated with cardiac arrhythmias (supraventricular and ventricular), angina, myocardial infarction, respiratory insufficiency requiring intubation, gastrointestinal bleeding or infarction, renal insufficiency, edema, and mental status changes.

Proleukin treatment is associated with impaired neutrophil function (reduced chemotaxis) and with an increased risk of disseminated infection, including sepsis and bacterial endocarditis. Consequently, preexisting bacterial infections should be adequately treated prior to initiation of Proleukin therapy. Patients with indwelling central lines are particularly at risk for infection with gram positive microorganisms. Antibiotic prophylaxis with oxacillin, nafcillin, ciprofloxacin, or vancomycin has been associated with a reduced incidence of staphylococcal infections.

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

INDICATION AND USAGE

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.

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. 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 in patients with an abnormal thallium stress test or abnormal pulmonary function tests and those with organ allografts. Retreatment with Proleukin is contraindicated in patients who have experienced the following drug-related toxicities while receiving an earlier course of therapy: Sustained ventricular tachycardia (≥5 beats), Cardiac arrhythmias not controlled or unresponsive to management, Chest pain with ECG changes, consistent with angina or myocardial infarction, Cardiac tamponade, Intubation for >72 hours, Renal failure requiring dialysis >72 hours, Coma or toxic psychosis lasting >48 hours, Repetitive or difficult to control seizures, Bowel ischemia/perforation, GI bleeding requiring surgery.

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PROLEUKIN® (ALDESLEUKIN) IS INDICATED FOR THE TREATMENT OF ADULTS WITH METASTATIC RENAL CELL CARCINOMA OR 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 serious, life threatening or fatal adverse events. Adverse events are frequent, often serious, and sometimes fatal. Should adverse events, requiring dose modification occur, dosage should be withheld rather than reduced.

Proleukin has been associated with exacerbation of pre-existing autoimmune disease and inflammatory disorders. In some cases, the onset of new autoimmune diseases, such as vitiligo, may occur. Symptomatic hyperglycemia and/or diabetes mellitus have been reported during Proleukin therapy.

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. Neurologic signs and symptoms associated with Proleukin therapy usually improve after discontinuation of Proleukin therapy; however, there are reports of permanent neurologic defects. In patients with known seizure disorders, extreme caution should be exercised as Proleukin may cause seizures.

PRECAUTIONS
Patients should have normal cardiac, pulmonary, hepatic, and CNS function at the start of therapy. Capillary leak syndrome (CLS) begins immediately after Proleukin® (aldesleukin) treatment starts and is marked by increased capillary permeability to protein and fluids and reduced vascular tone.

Proleukin® (aldesleukin) treatment should be withheld for failure to maintain organ perfusion as demonstrated by altered mental status, reduced urine output, a fall in the systolic blood pressure below 90 mm Hg or onset of cardiac arrhythmias.

Recovery from CLS begins soon after cessation of Proleukin therapy. Usually, within a few hours, the blood pressure rises, organ perfusion is restored and reabsorption of extravasated fluid and protein begins.

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

Mental status changes including irritability, confusion, or depression which occur while receiving Proleukin may be due to bacteremia or early bacterial sepsis, hypoperfusion, occult CNS malignancy, or direct Proleukin-induced CNS toxicity. Patients should be evaluated for these and other causes of mental status changes. Alterations in mental status due solely to Proleukin therapy may progress for several days before recovery begins. Rarely, patients have sustained permanent neurologic deficits.

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

Serious manifestations of eosinophilia involving eosinophilic infiltration of cardiac and pulmonary tissues can occur following Proleukin.

Please see continued Important Safety Information for Proleukin® (aldesleukin) for injection, for intravenous infusion, on next page.
ADVERSE REACTIONS

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

In clinical trials, the following life-threatening (Grade 4) adverse events were seen in >Proleukin 1% of 525 patients (255 with metastatic renal cell cancer and 270 with metastatic melanoma) treated with Proleukin: oliguria (6%), anuria (5%), hypotension (3%), respiratory disorder (3%), bilirubinemia (2%), coma (2%), diarrhea (2%), acidosis (1%), acute kidney failure (1%), apnea (1%), cardiovascular disorder (1%), coagulation disorders (1%), confusion (1%), creatinine increase (1%), dyspnea (1%), fever (1%), heart arrest (1%), infection (1%), myocardial infarct (1%), psychosis (1%), sepsis (1%), SGOT increase (1%), stupor (1%), supraventricular tachycardia (1%), thrombocytopenia (1%), ventricular tachycardia (1%), and vomiting (1%). From the same trials, the following adverse events (Grades 1-4) were seen in ≥30% of 525 patients (255 with metastatic renal cell cancer and 270 with metastatic melanoma) treated with Proleukin: hypotension (71%), diarrhea (67%), oliguria (63%), chills (52%), vomiting (50%), dyspnea (43%), rash (42%), bilirubinemia (40%), thrombocytopenia (37%), nausea (35%), confusion (34%), and creatinine increase (33%).

Please see following full Prescribing Information, including Boxed Warning, for Proleukin® (aldesleukin) for injection, for intravenous infusion.

REFERENCES

The same treatment dose and schedule was employed in all studies demonstrating efficacy. Proleukin was given

Safety and efficacy were studied in a series of single and multicenter, historically controlled studies enrolling

kidney is metabolized to amino acids in the cells lining the proximal convoluted tubules. In humans, the mean

may account for the preservation of clearance in patients with rising serum creatinine values. Greater than

Following the initial rapid organ distribution, the primary route of clearance of circulating Proleukin is the

is detectable in plasma. This finding is consistent with studies in rats using radiolabeled Proleukin, which

on the kinetic properties of this product.

Proleukin exists as biologically active, non-covalently bound microaggregates with an average size of 27

Pharmacokinetics

The

is likely to be different from that of native interleukin-2.

The in vitro biological activities of the native noncombinant molecule have been reproduced with Proleukin.1,4

Proleukin is a sterile, white to off-white, lyophilized cake in single-use vials intended for intra-

adenal, subcutaneous. Responses were also observed in patients with individual bulky lesions and large, cummulative 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 11+)</td>
</tr>
<tr>
<td>PR's + CR's</td>
<td>43 (16%)</td>
<td>9 (1 to 12+)</td>
</tr>
</tbody>
</table>

(2) sign means ongoing

(3) median observed; a conservative value is presented which represents the minimum median duration of response.

Malignant Melanoma

Two hundred seventy patients with metastatic melanoma were treated with single agent Proleukin in 8 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 II). 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). Response rates were also observed in patients with individual bulky lesions and large cumulative tumor burden.

INDICATIONS AND USAGE

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 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. In patients with an abnormal thallium stress test or abnormal pulmonary function tests, Proleukin is contraindicated in patients with abnormal thallium stress test or abnormal pulmonary function tests and those with organ allotransplants. Treatment with Proleukin is contraindicated in patients who have experienced the five drug-related toxicities while receiving an earlier course of therapy.

Contraindications

Proleukin® (aldesleukin) is contraindicated in patients with a known history of hypersensitivity to interleukin-2 or any component of the Proleukin formulation. Proleukin is contraindicated in patients with an abnormal thallium stress test or abnormal pulmonary function tests and those with organ allotransplants. Treatment with Proleukin is contraindicated in patients who have experienced the five drug-related toxicities while receiving an earlier course of therapy.

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Hypersensitivity reactions have been reported in patients receiving combination regimens containing sequential high dose Proleukin and antineoplastic agents, specifically, dacarbazine, cis-platinum, tamoxifen and interferon-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 rhadio-
myopathy 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 interleukin-2 alone or in combination with other immunosuppressive agents, such as cyclosporine, prednisone, azathioprine, dapsone, hydroxychloroquine, antimalarial drugs, anticoagulants, and calcium-channel antagonists. These reactions include fever, chills, vomiting, diarrhea, hypotension, edema, and oliguria. Some clinicians have noted that these reactions resemble the immediate side effects caused by interleukin-2 administration, however the cause of these events is unknown. These reactions were reported to occur 2 to 9 days after administration of interleukin-2.

It is recommended that this drug be administered to persons of either gender not practicing effective contraception.

Pregnancy

Pregnancy Category C.

Proleukin has been shown to have embryolethal effects in rats when given in doses at 2 to 37 times the human dose (scaled by body weight). Significant maternal toxicity was observed in pregnant rats administered Proleukin by IV injection at doses 2.1 to 36 times higher than the human dose during critical period of organogenesis. Some of these reactions included ventricular tachycardia, atrial fibrillation, and death. Some of these patient's required cardioversion, ventricular pacing, and CPR. Proleukin may reduce the antitumor effectiveness of Proleukin and thus should be avoided.

Proleukin enhancement of cellular immune function may increase the risk of alloagraft rejection in transplant patients.

Serious Manifestations of Eosinophilia

Serious manifestations of eosinophilia involving eosinophilic infiltration of cardiac and pulmonary tissues can occur following Proleukin administration. Proleukin® (aldesleukin) treatment should be withheld for failure to maintain organ perfusion as demonstrated by altered mental status, reduced urine output, a fall in the systolic blood pressure below 90 mm Hg or onset of cardiac arrhythmias, and electrocardiographic changes. Proleukin® (aldesleukin) treatment should be withheld if there has been excessive loss of weight at least 10% of body weight if associated with shortness of breath from pulmonary congestion, use of diuretics, once blood pressure has normalized, has been shown to hasten recovery. Prior to the use of any product mentioned, the physician should refer to the package insert for the respective product.

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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 assessing mental status and alteration of mental status, by auscultation of chest for adventitious sounds and central pressure monitoring. Hypovolemia is assessed by catherization 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 cardiac failure). Administration of hypotonic solutions is not recommended for treatment of hypovolemia. Correction of hypovolemia may require large volumes of IV fluids based on clinical signs and symptoms and may require administration of pressor agents, (e.g., dopamine) in order to achieve adequate perfusion 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 dopamine dose to 5 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 loss of weight at least 10% of body weight if associated with shortness of breath from pulmonary congestion, use of diuretics, once blood pressure has normalized, has been shown to hasten recovery. Prior to the use of any product mentioned, the physician should refer to the package insert for the respective product.

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Clinical experience has shown that early administration of dopamine (1 to 5 mcg/kg/min) to patients manifesting capillary leak syndrome (CLS) can help to maintain organ perfusion distally 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 dopamine dose to 5 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 loss of weight at least 10% of body weight if associated with shortness of breath from pulmonary congestion, use of diuretics, once blood pressure has normalized, has been shown to hasten recovery. Prior to the use of any product mentioned, the physician should refer to the package insert for the respective product.

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The following life-threatening adverse events (reported in greater than 1% of patients), grade 4, were identified: hypertension, fatal subdural and subarachnoid hemorrhage, cerebral hemorrhage, psychiatric: insomnia.

Patients with indwelling central lines have a higher 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, nafcillin, ciprofloxacin, or vancomycin. Hydroxyurea or diphenylhydantoin has been used to control the seizures associated with high aldesleukin (aldesleukin) concentrations and continued until resolution of pruritus. Topical creams and ointments should be applied as needed for skin manifestations. Preparations containing a steroid (e.g., hydrocortisone) should be avoided. NOTE: Prior to 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”, “CONTRAINDICATIONS”, “WARNINGS”, “PRECAUTIONS”, and “ADVERSE REACTIONS” sections, particularly regarding patient selection for serious adverse events, patient monitoring and withholding dosage. The following schedule has been used to treat adult patients with metastatic renal cell carcinoma (metastatic RCC) or metastatic melanoma. Each course of treatment consists of two 5-day treatment cycles separated by a rest period.

600,000 International Units (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, for a maximum of 28 doses per course, as tolerated. During clinical trials, doses were frequently withheld due to toxicity (See “CLINICAL STUDIES” section and “Dose Modifications” subsection). Metastatic RCC 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.

Dose Modifications

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

1. If the patient cannot continue treatment due to toxicity, the physician should refer to the package insert for the respective product.

TREATMENT WITH PROLEUKIN IS CONTRAINDICATED IN PATIENTS WHO HAVE EXPERIENCED THE FOLLOWING TOXICITIES

Doses should be held and restarted according to the following:

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.

The impact of antialdesleukin antibody formation on clinical efficacy and safety of Proleukin is unknown.

The following data on life-threatening adverse events (reported in greater than 1% of patients, grade 4), separated by a rest period of at least 7 weeks from the date of hospital discharge.

The following life-threatening (grade 4) adverse events were reported by <1% of the 525 patients: hypertension; shivering; bradycardia; ventricular extrasystoles; myocardial infarction; hypoglycemia; anaphylactoid reactions, hypothermia; atrial arrhythmia; phelebitis; AV block second degree; endocarditis; pericardial effusion; peripheral gangrene; thrombosis; coronary artery disorder; stomatitis; nausea and vomiting; liver function tests abnormal; gastrointestinal hemorrhage; hematemesis; bloody diarrhea; gastrointestinal disorder; intestinal perforation; pancreatitis; anemia; leukemia; leukocytosis; hypocalcemia; alkaline phosphatase increase; BUN increase; hyperuricemia; NPN increase; respiratory acidosis; somnolence; agitation; neuropathy; paroxysmal reaction; convulsion; grand mal convulsion; delirium; asthma; lung edema; hypotension; hypoxia; hemoptysis; hyperventilation; pneumonia; myasthenia; pupillary disorder; kidney function abnormal; kidney failure; acute tubular necrosis.

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

Immunogenicity

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 8-hour 600,000 International Units/kg (0.037 mg/kg) dose administered every 8 hours by a 15-minute intravenous infusion regimen and in 33 of 50 (66%) patients with metastatic melanoma treated with a variety of intravenous regimens. In a separate study, the effect of immunogenicity on the pharmacokinetics of aldesleukin was evaluated in 13 patients. Following the first cycle of therapy, the geometric mean area under the curve (AUC) Day 15 to Day 1, there was an average 68% increase in 11 patients who developed anti-aldesleukin antibodies and no change was observed in the antibody-negative patients (n=2). Overall, neutralizing antibodies were detected in 1 patient. The impact of antialdesleukin antibody formation on clinical efficacy and safety of Proleukin is unknown.

The following adverse effects following the use of Proleukin 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 8-hour 600,000 International Units/kg (0.037 mg/kg) dose administered every 8 hours by a 15-minute intravenous infusion regimen and in 33 of 50 (66%) patients with metastatic melanoma treated with a variety of intravenous regimens. In a separate study, the effect of immunogenicity on the pharmacokinetics of aldesleukin was evaluated in 13 patients. Following the first cycle of therapy, the geometric mean area under the curve (AUC) Day 15 to Day 1, there was an average 68% increase in 11 patients who developed anti-aldesleukin antibodies and no change was observed in the antibody-negative patients (n=2). Overall, neutralizing antibodies were detected in 1 patient. The impact of antialdesleukin antibody formation on clinical efficacy and safety of Proleukin is unknown.

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The following adverse effects following the use of Proleukin 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 8-hour 600,000 International Units/kg (0.037 mg/kg) dose administered every 8 hours by a 15-minute intravenous infusion regimen and in 33 of 50 (66%) patients with metastatic melanoma treated with a variety of intravenous regimens. In a separate study, the effect of immunogenicity on the pharmacokinetics of aldesleukin was evaluated in 13 patients. Following the first cycle of therapy, the geometric mean area under the curve (AUC) Day 15 to Day 1, there was an average 68% increase in 11 patients who developed anti-aldesleukin antibodies and no change was observed in the antibody-negative patients (n=2). Overall, neutralizing antibodies were detected in 1 patient. The impact of antialdesleukin antibody formation on clinical efficacy and safety of Proleukin is unknown.
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 (1.1 mg) OF PROLEUKIN AND SHOULD BE RECONSTITUTED ASEPTICALLY WITH 1.2 mL OF STERILE WATER FOR INJECTION, USP. WHEN RECONSTITUTED AS DIRECTED, EACH mL CONTAINS 18 MILLION 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. During reconstitution, the Sterile Water for Injection, USP should be directed at the side of the vial and the contents gently swirled to avoid excess foaming. DO NOT SHAKE.

3. The dose of Proleukin, reconstituted with Sterile Water for Injection, USP (without preservative) should be diluted aseptically in 50 mL of 5% Dextrose Injection, USP (D5W) and infused over a 15-minute period. In cases where the total dose of Proleukin is 1.5 mg or less (e.g., a patient with a body weight of less than 40 kilograms), the dose of Proleukin should be diluted in a smaller volume of D5W. Concentrations of Proleukin below 0.03 mg/mL and above 0.07 mg/mL have shown increased variability in drug delivery. Dilution and delivery of Proleukin outside of this concentration range should be avoided.

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

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

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

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

HOW SUPPLIED
Proleukin® (aldesleukin) is supplied in individually boxed single-use vials. Each vial contains 22 million International Units of Proleukin. Discard unused portion.

NDC 65483-116-07 Individually boxed single-use vial
Store vials of lyophilized Proleukin in a refrigerator at 2° to 8°C (36° to 46°F). PROTECT FROM LIGHT. Store in carton until time of use.
Reconstituted or diluted Proleukin is stable for up to 48 hours at refrigerated and room temperatures, 2° to 25°C (36° to 77°F). However, since this product contains no preservative, the reconstituted and diluted solutions should be stored in the refrigerator.

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

REFERENCES

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