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

Complete plus partial response rates were 15% in metastatic renal cell carcinoma patients and 16% in metastatic melanoma patients.

Careful patient selection is mandatory prior to the administration of Proleukin.

Please see accompanying full Prescribing Information including Boxed Warning.
Table of Contents

4  Know Your Options  
6  Kidney Cancer Basics  
8  Kidney Cancer Treatment Overview  
10  Treatments: Targeted Therapy, Chemotherapy, Clinical Trials  
12  Treatments: Immunotherapy  
16  Treatments: Proleukin® (aldesleukin) Immunotherapy (IL-2)  
18  Important Safety Information  
19  Proleukin (aldesleukin) Side Effects  
20  How Proleukin (aldesleukin) Is Administered  
21  If You Want to Know More About Proleukin  
22  Your Treatment Team  
24  Proleukin Patient Support  
25  Is Proleukin Right for You?  
26  Discussion Guide  
28  Glossary  
30  Resources
When considering treatment for metastatic kidney cancer, it is extremely important to consider every option. While surgery is the most common treatment for early disease, metastatic kidney cancer usually cannot be treated effectively by surgery alone and often requires the addition of drug therapy. You may also receive radiation treatment for the cancer that has spread to other areas of your body.

This brochure will provide you with some helpful information about the different kinds of drug therapies commonly used in the treatment of metastatic kidney cancer.

**There is information about:**
- Targeted therapy
- Chemotherapy
- Clinical trials for experimental therapies
- Immunotherapy

Receiving the diagnosis of metastatic kidney cancer can be overwhelming and frightening. There is a lot of information to take in and options to consider. While some of the information may be discouraging, there are also many inspirational stories that give hope to patients everywhere. There are treatments that can have a significant impact on the disease, and there are people still alive years after their diagnosis of metastatic kidney disease.

The information in this brochure is intended to give you an overview of your options and start you on a path of learning, but there is a lot more to learn before you can make a decision. If there is any drug, any topic, any issue that you do not fully understand, ask again and again until you get a satisfactory answer. You have a right to be—and you deserve to be—fully informed so you can make the most appropriate decision for you.

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

Please see accompanying full Prescribing Information including Boxed Warning.

Please see pages 18 and 19 for Important Safety Information and additional side effect information.
Kidney cancer is commonly called renal cell carcinoma in the medical community. Renal comes from the Latin word for kidneys, and carcinoma is another word for cancer. 

Basic facts about kidney cancer:
- More than 60,000 Americans will be diagnosed with kidney cancer in 2015
- Kidney cancer occurs roughly twice as often in males as in females and most often in men between the ages of 40 and 60
- Kidney cancer has few symptoms in its early stages so it often goes undiagnosed or misdiagnosed until the tumor is fairly large
- Kidney cancer has several types, including clear cell, papillary, sarcomatoid, transitional cell, and others

Metastatic kidney cancer means that the cancer has spread from the tumor in the kidney to other parts of the body. Kidney cancer often spreads to the lungs, liver, bones, lymph nodes, and brain.

Symptoms of kidney cancer:
- Blood in the urine (also known as hematuria) is the most common symptom of kidney cancer—seen in 40-50% of patients
- Other symptoms include a hard lump or a bulging under the skin in the stomach region or back or side pain or pressure
- Once the cancer has spread, patients may experience other symptoms; some of those symptoms may include unexplained weight loss, fevers, anemia, or high blood pressure

Diagnosis of metastatic renal cell carcinoma
- Some patients are diagnosed in early phases before the cancer has spread (metastasized) to other parts of the body
- 15-25% of patients have metastatic disease at the time of their diagnosis
- Many tumors are found accidentally on X-rays or ultrasounds being conducted for unrelated reasons

There is excellent, detailed information about kidney cancer and the different types, symptoms, diagnosis, and treatment available to you. When you are ready, there is a list of website resources in the back of this brochure that you can visit for more information, in addition to your consultation with your healthcare team.
Some patients are diagnosed with kidney cancer before it has spread to other parts of the body, while others have metastatic disease when their cancer is initially diagnosed.

In most cases, surgery is considered the primary treatment. A variety of surgical procedures are available, depending on the type, size of tumor, extent of disease, and your overall physical condition. Your doctor will discuss with you the surgical options that are most appropriate, and which drug therapies should be considered.

Consulting the guidelines

Once your specific information is gathered, your doctor may review one of the highly regarded treatment guidelines that exist. These guidelines are written by kidney cancer experts who convene on a regular basis to determine which treatment options may be recommended for each patient type. The guidelines cover when surgeries are recommended, which drug therapies are recommended as a first treatment, and which therapies might be best if additional treatment is needed.

Most doctors use these guidelines as the foundation for making treatment decisions, but your input is also of great importance. The choice of treatment, where treatment is administered, the frequency of check-ups, and many other aspects of your treatment should be determined by your doctor with input from you. It is very important to agree on a treatment plan in advance. You and your treatment team should discuss first therapy options, and try to plan ahead by also deciding what therapy options you’d be comfortable with should you require additional therapy.
Targeted therapy

Newer drugs have been developed that target some of the molecular and genetic changes that cause cancer cells to grow. These “targeted” drugs are widely used, and can attack specific cancer cells with minimal damage to normal cells and work on a molecular level. They work by interfering with cancer cell growth, preventing cell replication, or disrupting blood flow supply to the cancer cell. These drugs may be taken long term. You continue on the therapy until you can no longer tolerate the therapy or they stop working. These drugs can:

- Shrink or slow the growth of kidney cancer to help patients live longer
- Be given in a doctor’s office or other outpatient setting, either orally or by injection
- Produce unpleasant side effects, though they are generally well tolerated and are rarely life threatening
- Allow some patients to experience a period of living with the disease where it does not get worse
- Be taken for long periods of time, for example, months or years

Ask your oncologist to tell you more about the results seen with targeted therapies, and when in your treatment plan they make sense for you.

Chemotherapy

Chemotherapy, although rarely used in kidney cancer, is the name given to a group of drugs that act on cancer cells to kill or slow the growth of the tumor(s). When chemotherapy is taken by mouth or injected into a vein or muscle, the drugs enter the bloodstream and can reach cancer cells throughout the body (systemic therapy).

- Chemotherapy has been shown to help a small number of mRCC patients and is often reserved for people in whom immunotherapy or targeted drugs are not effective
- Most responses are “partial,” so tumors shrink but do not disappear completely
- Chemotherapy is usually given in an outpatient clinic or in a doctor’s office, where side effects can be monitored and managed
- Responses usually last only weeks or months before tumors begin growing again

Ask your oncologist to explain the outcomes seen with the different kinds of chemotherapy you may be considering.

Clinical trials

Clinical trials are carefully designed research studies that answer specific questions about the effectiveness and safety of new drugs, combinations of drugs, treatments, surgical techniques, or medical devices. People with kidney cancer may volunteer to be studied during a clinical trial, to help leading doctors determine the efficacy of the new approaches being tested. Often, trials offer access to promising new treatment options before they are generally available.
Interferons are widely used to treat kidney cancer, alone or in combination with other drugs

- Interferons are typically self-administered by injection under the skin several times per week
- They work by “interfering” with the life processes within the cancer cell
- They prevent cancer cell growth and allow the cancer cell to be open to attack by the body’s immune system
- Response is characterized by slow shrinking of tumors
- Average time from start of treatment to noticeable tumor shrinkage is 3 to 4 months

Most common side effects of interferon therapy

- Flu-like symptoms: fever, chills, muscle aches, headache, loss of appetite, and fatigue
- Symptoms generally become less severe with continued therapy

Immunotherapy, sometimes called biologic therapy, is a form of treatment that boosts the body’s own immune defenses. It is considered one of the standard treatment options for kidney cancer patients with advanced metastatic disease.

The cytokines are an important family of immunotherapy drugs that include interferons, interleukin-2 (IL-2) and programmed cell death protein 1 (PD-1). These drugs have represented the standard in the treatment of kidney cancer, along with more recent targeted therapies.
TREATMENTS: **immunotherapy**

**IL-2 is available for the treatment of metastatic kidney cancer**
- IL-2 stimulates the growth of two types of white blood cells: T cells and “natural killer” (NK) cells.
- T cells fight against cancer by recognizing cancer cells and setting off an alarm to the body.
- The NK cells respond to this alarm and are transformed into lymphokine-activated killer (LAK) cells, capable of destroying cancer cells.

Serious side effects are known to occur with IL-2 treatment
- Side effects may include nausea, vomiting, hypertension, cardiac arrhythmias, diarrhea, loss of appetite, gastrointestinal bleeding, rashes, disorientation, hallucinations, fever, and chills.
- Most side effects are completely reversible once you stop taking the drug, but they can be severe.
- Therapy with IL-2 requires that the treating doctor be experienced in its use.
- Diligent clinical monitoring of the patient takes place throughout treatment.

Meeting specialists is a good idea and does not mean you cannot continue to work with your existing healthcare team. These specialists are happy to meet with you to discuss your treatment plan.

**Programmed cell death protein 1 (PD-1):** Your immune system is normally your body’s first defense against threats like metastatic renal cell carcinoma (RCC), but sometimes RCC sends a signal that can prevent the immune system from doing its job.
- PD-1s block this RCC signal, helping to restore the immune response against the tumor.
- While doing so, PD-1s could also affect nontumor cells.
Proleukin is FDA-approved and available as an immunotherapy treatment for metastatic renal cell carcinoma and metastatic melanoma. Proleukin is an important option to discuss with your oncologist and treatment team because it is the only therapy available that has demonstrated a complete and durable response in some patients with metastatic renal cell carcinoma. This means that in some patients who took Proleukin, their tumors disappeared completely and did not return.

Results seen with Proleukin

In clinical studies including 255 patients with metastatic kidney cancer:
- 7% of patients taking Proleukin saw their tumors disappear completely; this is known as a complete response. Among those who had a complete response, the average amount of time it took for tumors to begin growing again is estimated to be almost 7 years (about 80 months). The shortest response lasted 7 months, and the longest has lasted more than 10 years so far.
- There were also another 8% of people in the studies who experienced a partial response (A person was considered to have had a partial response only if the combined size of all their tumors shrank to at least half, and none of their tumor sites increased in size).
- Proleukin has been associated with serious side effects such as low blood pressure, diarrhea, decreased urine, chills, and vomiting. You should only receive Proleukin from a skilled physician with experience administering anticancer drugs, in a facility with equipment and staff trained to manage intensive care situations.

Warning:

Proleukin is associated with serious side effects such as low blood pressure, diarrhea, decreased urine, chills, and vomiting. You should only receive Proleukin from a skilled physician with experience administering anticancer drugs, in a facility with equipment and staff trained to manage intensive care situations.

Please see accompanying full Prescribing Information including Boxed Warning.

Please see pages 18 and 19 for Important Safety Information and additional side effect information.
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.

IMPORTANT safety INFORMATION

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

Please see accompanying full Prescribing Information.

MOST COMMON side effects

Mild to severe, occurred in more than 30% of patients

<table>
<thead>
<tr>
<th>SIDE EFFECT</th>
<th>% OF PATIENTS*</th>
</tr>
</thead>
<tbody>
<tr>
<td>LOW BLOOD PRESSURE</td>
<td>71%</td>
</tr>
<tr>
<td>DIARRHEA</td>
<td>67%</td>
</tr>
<tr>
<td>DECREASED URINE</td>
<td>63%</td>
</tr>
<tr>
<td>CHILLS</td>
<td>52%</td>
</tr>
<tr>
<td>VOMITING</td>
<td>50%</td>
</tr>
<tr>
<td>SHORTNESS OF BREATH</td>
<td>43%</td>
</tr>
<tr>
<td>RASH</td>
<td>42%</td>
</tr>
<tr>
<td>ABNORMAL BLOOD TEST FOR HOW THE LIVER WORKS (HIGH BILIRUBIN)</td>
<td>40%</td>
</tr>
<tr>
<td>LOW PLATELET COUNT INCREASING THE CHANCE OF BLEEDING</td>
<td>37%</td>
</tr>
<tr>
<td>NAUSEA</td>
<td>35%</td>
</tr>
<tr>
<td>CONFUSION</td>
<td>34%</td>
</tr>
<tr>
<td>ABNORMAL BLOOD TEST FOR HOW THE KIDNEYS WORK (HIGH CREATININE)</td>
<td>33%</td>
</tr>
</tbody>
</table>

*Out of 525.

This information is from clinical studies with patients who had metastatic kidney cancer as well as clinical studies with patients who had metastatic melanoma.

MOST SERIOUS side effects

Life-threatening severity, occurred in more than 1% of patients

<table>
<thead>
<tr>
<th>SIDE EFFECT</th>
<th>% OF PATIENTS*</th>
</tr>
</thead>
<tbody>
<tr>
<td>DECREASED URINE</td>
<td>6%</td>
</tr>
<tr>
<td>STOPPING ALL URINE</td>
<td>5%</td>
</tr>
<tr>
<td>LOW BLOOD PRESSURE</td>
<td>3%</td>
</tr>
<tr>
<td>BREATHING PROBLEMS</td>
<td>3%</td>
</tr>
<tr>
<td>ABNORMAL BLOOD TEST FOR HOW THE LIVER WORKS (HIGH BILIRUBIN)</td>
<td>2%</td>
</tr>
<tr>
<td>COPPA</td>
<td>1%</td>
</tr>
<tr>
<td>DIARRHEA</td>
<td>1%</td>
</tr>
<tr>
<td>FAST HEARTBEAT</td>
<td>2%</td>
</tr>
</tbody>
</table>

*Out of 25.

This information is from clinical studies with patients who had metastatic renal cell carcinoma and 270 with metastatic melanoma, 4% (11/255) of patients with metastatic renal cell cancer and 2% (6/270) of patients with metastatic melanoma died from treatment-related side effects of Proleukin.

In patients receiving Proleukin in these studies (255 with metastatic renal cell carcinoma and 270 with metastatic melanoma), 4% (11/255) of patients with metastatic renal cell cancer and 2% (6/270) of patients with metastatic melanoma died from treatment-related side effects of Proleukin.
Proleukin is administered via an intravenous line approximately 3 times a day for 5 days (cycle 1), followed by approximately 9 days of rest, followed by a second 5-day cycle.

Patients receiving Proleukin will be admitted into the hospital where the treatment center is located.

THE PROLEUKIN EXPERIENCE

TREATMENT CYCLE 1

5 DAYS

NO TREATMENT

9 DAYS

TREATMENT CYCLE 2

5 DAYS

Proleukin therapy has been available since 1998 for the treatment of metastatic melanoma, and since 1992 for metastatic renal cell carcinoma. Since its FDA approval, there have been many treatment centers that have developed a great deal of experience administering this therapy. While the dosing schedule described above is the standard approach, not all physicians use this exact sequence of timing and not all patients receive every dose. Speak with the physicians at your treatment center to learn about the approach they will use.

Please see accompanying full Prescribing Information including Boxed Warning.

Please see pages 18 and 19 for Important Safety Information and additional side effect information.

Proleukin (IL-2) is a specialized immunotherapy that most oncologists are familiar with by name. Most have seen the clinical results showing complete and partial responses in some patients, and they’ve also heard about the serious side effects and serious risks.

It is important to remember that most oncologists have never administered Proleukin themselves, even though it has been around for many years. The initial experiences with Proleukin led to the creation of specialized treatment centers where doctors and staff are trained and experienced in the administration of Proleukin. They are skilled at recognizing and managing the side effects.

When you and your oncologist discuss Proleukin, remember that there are nurses, physicians, and counselors with first-hand experience administering Proleukin at a treatment center who are available to answer any specific questions you may have. Visit Proleukin.com for a list of treatment centers that includes all contact information for each location. Call your oncologist or any one of these centers anytime and make an appointment if you’re interested in learning more about if Proleukin is right for you.

Proleukin (aldesleukin) is indicated for the treatment of adults with metastatic renal cell carcinoma or metastatic melanoma.
It is your responsibility and right to empower yourself by discussing treatment goals with your treatment team. You have many treatment options to explore and new information to learn about the risks and potential benefits of each therapy.

You are not alone in this process. Your treatment team should be a diverse set of people who bring different perspectives and knowledge to bear. Critical members of your team should include:

**Your oncologist**
Your oncologist can be a great source of information to help you sort through the pros and cons of various therapies. It is very important for you and your treatment team to perform a meaningful and realistic assessment of the different treatment options available to you. It’s virtually impossible to make an “apples to apples” comparison of treatment options (they all work differently and have different outcomes). So, you’ll want to learn about all of the drugs with which your oncologist is familiar.

**Care coordinators and navigators**
They may be described by various titles, but their value is clear: these team members coordinate people, information, schedules, and support, to help you make sense of treatment choices and the challenges you’re facing.

**Nurses**
Your nurses will be there for you throughout the process, from pretreatment to treatment, to home care. They will answer questions, provide information for you and your family, ease your pain, reduce anxiety, and keep your medical team informed every step of the way.

**Family members, loved ones, friends**
These people should have your priorities, your goals, and your interests at heart. They can help advocate for you, help you learn and remember all the information, sort through your emotions, and help to weigh your options.

**Oncologists with specialized experience**
Talk to and learn from healthcare professionals who have first-hand experience with certain specialized therapies with which your oncologist may not be as familiar. It helps to speak with these professionals and understand the pros and cons of the treatments they specialize in directly.

**Others who have had personal experience with your type of cancer**
Many patients find it helpful to share thoughts, fears, and experiences with others who have had a similar experience. See the Resources section in this brochure for information about advocacy groups that can help you find them.

When you combine the knowledge of your treatment team with all of the information you will soon discover, you will be better prepared to make sound decisions based on your treatment goals and feel confident in your choices.
Prometheus is committed to helping patients gain access to the therapies they need.

For any questions related to Proleukin, call toll-free 1-877-PROLEUKIN (1-877-776-5385). Specialists are available to answer your questions about health insurance plans and coverage, as well as to help you obtain “prior authorization.” They can also assist you with claims denials and locate other sources of support for which you may qualify.

You may call to inquire even if you have not yet selected or started Proleukin as your treatment choice.

Always work with your doctor and treatment team to make certain they are aware of your goals. While Proleukin is not right for every patient, 7% of patients with metastatic renal cell carcinoma who took Proleukin in clinical studies saw their tumors disappear completely. No other therapy has been proven to make tumors disappear for more than 15 years.

Treatment with Proleukin can leave other options open if Proleukin therapy is not successful for you. Because patients in good overall health have a better chance to respond, have the discussion with your doctor to determine whether Proleukin is right for you. As you plan your treatment, consider which options would make the best early treatment, and which would make more sense as second-line and third-line therapies.

Key Points to Remember
- Proleukin is the only therapy that offers appropriate patients the possibility of a complete and long-lasting remission for metastatic renal cell carcinoma (This does not always mean the cancer has been cured)
- Proleukin therapy is given only for a limited period of time. The side effects are serious and potentially life threatening but are usually limited to the duration of time you are taking the drug
- Prior treatment with Proleukin does not generally exclude patients from later treatment options
- Proleukin is not for every patient—only those determined by a physician to be healthy enough to receive treatment
- Patients may have to travel to another city or state to receive therapy
- It is not possible to identify in advance which patients will have a response to treatment

Proleukin (aldesleukin) is indicated for the treatment of adults with metastatic renal cell carcinoma or metastatic melanoma.
Kidney cancer is a very serious disease, but the treatment options described in this brochure are available to help. There are also professionals and other people on your treatment team who can help you learn and understand as much information as possible about potential therapies, as well as the benefits and risks associated with each of them.

Now is the time for you to take an active role in your treatment. It is your right and responsibility to know about every option, from the most common to the most rarely used, from the safest to the most risky, from the least effective to the most effective, so you and the members of your treatment team can make informed decisions based on your goals.

The following questions can help you and your team to decide which therapy is best for you:

- For which therapies am I a good candidate?
- Which therapies match up with my goals for therapy?
- For my specific diagnosis (stage, cell type, and overall condition), how do the different types of treatment options compare? (eg, immunotherapy, targeted therapy, chemotherapy, etc)
- What are the potential benefits for each type of therapy?
- How long do the benefits last?
- What are the potential risks?
- What is the risk/benefit ratio of each therapy?
- For my specific diagnosis, what are the potential benefits for choosing a clinical trial? What are the potential risks?
- Who else should I speak with to ensure I understand all my options?
- Does anyone on my treatment team and/or the institution at which I am considering treatment have any experience with each therapeutic option?
- Is there any benefit to treating with certain drugs in a specific order?
- Do any therapies, if used first, prevent me from using any of the others later?
- What experimental therapies are available and what are the associated risks?

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

Please see accompanying full Prescribing Information including Boxed Warning.

Please see pages 18 and 19 for Important Safety Information and additional side effect information.

Kidney cancer is a very serious disease, but the treatment options described in this brochure are available to help. There are also professionals and other people on your treatment team who can help you learn and understand as much information as possible about potential therapies, as well as the benefits and risks associated with each of them.

Now is the time for you to take an active role in your treatment. It is your right and responsibility to know about every option, from the most common to the most rarely used, from the safest to the most risky, from the least effective to the most effective, so you and the members of your treatment team can make informed decisions based on your goals.

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

Please see accompanying full Prescribing Information including Boxed Warning.

Please see pages 18 and 19 for Important Safety Information and additional side effect information.
**Metastatic renal cell carcinoma:** Also known as metastatic kidney cancer.

**Outcome:** A specific result or effect that can be measured. Examples of outcomes include decreased pain, reduced tumor size, and improvement of disease.

**Outpatient:** A patient who visits a healthcare facility for diagnosis or treatment without spending the night. Sometimes called a day patient.

**Partial response:** A decrease in the size of a tumor, or in the extent of cancer in the body, in response to treatment.

**Primary tumor:** The original tumor.

**Progression:** In medicine, the course of a disease, such as cancer, as it becomes worse or spreads in the body.

**Progression-free survival:** The length of time during and after treatment in which a patient is living with a disease that does not get worse. Progression-free survival may be used in a clinical study or trial to help find out how well a new treatment works. Also called PFS.

**Response rate:** The percentage of patients whose cancer shrinks or disappears after treatment.

**Stage:** The extent of a cancer within the body. If the cancer has spread, the stage describes how far it has spread from the original site to other parts of the body.

**Systemic therapy:** Treatment using substances that travel through the bloodstream, reaching and affecting cells all over the body.

**Targeted therapy:** A type of treatment that uses drugs or other substances, such as monoclonal antibodies, to identify and attack specific cancer cells. Targeted therapy may have fewer side effects than other types of cancer treatments.

**Tumor:** An abnormal mass of tissue that results when cells divide more than they should or do not die when they should. Tumors may be benign (not cancerous), or malignant. Also called neoplasm.

**Angiogenesis:** Blood vessel formation. Tumor angiogenesis is the growth of new blood vessels that tumors need to grow. This is caused by the release of chemicals by the tumor.

**Angiogenesis inhibitor:** A substance that may prevent the formation of blood vessels. In anticancer therapy, an angiogenesis inhibitor may prevent the growth of new blood vessels that tumors need to grow.

**Carcinoma:** Cancer that begins in the skin or in tissues that line or cover internal organs.

**Chemotherapy:** Treatment with drugs that kill cancer cells.

**Clinical trial:** A type of research study that tests how well new medical approaches work in people. These studies test new methods of screening, prevention, diagnosis, or treatment of a disease. Also called clinical study.

**Complete response:** The disappearance of all signs of cancer in response to treatment. This does not always mean the cancer has been cured. Also called complete remission.

**Immunotherapy:** Treatment to boost or restore the ability of the immune system to fight cancer infections, and other diseases. Also used to lessen certain side effects that may be caused by some cancer treatments. Agents used in biological therapy include monoclonal antibodies, growth factors, and vaccines. These agents may also have a direct antitumor effect. Also called biological response modifier (BRM) therapy or biotherapy.

**Kidney cancer:** Cancer that originates in the kidneys. Your kidneys are two bean-shaped organs, each about the size of your fist. They’re located behind your abdominal organs, with one kidney on each side of your spine. In adults, the most common type of kidney cancer is renal cell carcinoma.

**Lymph node:** A rounded mass of lymphatic tissue that is surrounded by a capsule of connective tissue. Lymph nodes filter lymph (lymphatic fluid), and they store lymphocytes (white blood cells). They are located along lymphatic vessels. Also called lymph gland.

**Metastasis:** The spread of cancer from one part of the body to another. A tumor formed by cells that have spread is called a metastatic tumor or a metastasis. The metastatic tumor contains cells that are like those in the original (primary) tumor. The plural form of metastasis is metastases.

**Metastatic renal cell carcinoma:** Also known as metastatic kidney cancer.

**Outcome:** A specific result or effect that can be measured. Examples of outcomes include decreased pain, reduced tumor size, and improvement of disease.

**Outpatient:** A patient who visits a healthcare facility for diagnosis or treatment without spending the night. Sometimes called a day patient.

**Partial response:** A decrease in the size of a tumor, or in the extent of cancer in the body, in response to treatment.

**Primary tumor:** The original tumor.

**Progression:** In medicine, the course of a disease, such as cancer, as it becomes worse or spreads in the body.

**Progression-free survival:** The length of time during and after treatment in which a patient is living with a disease that does not get worse. Progression-free survival may be used in a clinical study or trial to help find out how well a new treatment works. Also called PFS.

**Response rate:** The percentage of patients whose cancer shrinks or disappears after treatment.

**Stage:** The extent of a cancer within the body. If the cancer has spread, the stage describes how far it has spread from the original site to other parts of the body.

**Systemic therapy:** Treatment using substances that travel through the bloodstream, reaching and affecting cells all over the body.

**Targeted therapy:** A type of treatment that uses drugs or other substances, such as monoclonal antibodies, to identify and attack specific cancer cells. Targeted therapy may have fewer side effects than other types of cancer treatments.

**Tumor:** An abnormal mass of tissue that results when cells divide more than they should or do not die when they should. Tumors may be benign (not cancerous), or malignant. Also called neoplasm.
The following resources refer to websites maintained by third parties over whom Prometheus has no control. As such, Prometheus makes no representation as to the accuracy, completeness, adequacy, or any other aspect of the information contained on such websites.

American Cancer Society
1-800-ACS-2345 (227-2345)
www.cancer.org

Association of Cancer Online Resources (ACOR)
www.acor.org

Cancer Care
1-800-813-HOPE (4673)
www.cancercare.org
www.cancercare.org/diagnosis/kidney_cancer

Cancer.net
www.cancer.net

Kidney Cancer Association
1-800-850-9132
www.kidneycancer.org

Kidney Cancer Association Nurse Hotline
1-503-215-7921

Mayo Clinic
www.mayoclinic.com

National Cancer Institute
1-800-4-CANCER (422-6237)
www.cancer.gov

National Comprehensive Cancer Network® (NCCN®)
www.nccn.org/patients/guidelines/kidney/index.html

National Institutes of Health
www.nih.gov

National Kidney Foundation (NKF)
www.kidney.org

Prevent Cancer Foundation
www.preventcancer.org

Society for Immunotherapy of Cancer
1-414-271-2456
www.sitcancer.org

US Food and Drug Administration
www.fda.gov

Financial Assistance
Cancer Care
www.cancercare.org/financial
www.cancercarecopay.org

Patient Services, Inc.
1-800-366-7741
www.patientservicesinc.org/
For-Patients/Types-Of-Assistance

THE OPPONENT IS FORMIDABLE. BUT YOU ARE empowered.
Proleukin® (aldesleukin) is indicated for the treatment of adults with metastatic renal cell carcinoma or metastatic melanoma.
PROLEUKIN® (aldesleukin)
for injection, for intravenous infusion
Rx Only

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 antinecancer agents. An intensive care facility and specialists skilled in cardiorespiratory 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.

DESCRIPTION

Proleukin® (aldesleukin), a human recombinant interferon-2 product, is a highly purified protein with a molecular weight of approximately 15,300 daltons. The chemical name is des-α-1,4-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 interferon-2 gene. Genetic engineering techniques were used to modify the human IL-2 gene, and the resulting expression clone encodes a modified human interferon-2. This recombinant form differs from native interferon-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 aggregate state of Proleukin is likely to be different from that of native interferon-2.

The in vitro biological activities of the native nonrecombinant molecule have been reproduced with Proleukin.1-7 Proleukin is supplied as a sterile, white to off-white, lyophilized cake in single-use vials intended for intravenous administration. When reconstituted with 1.2 mL sterile Water for Injection, USP, each mL contains 18 million International Units (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 present product.

Proleukin biological potency is determined by a lymphocyte proliferation bioassay and is expressed in International Units as established by the World Health Organization 1st International Standard for Interleukin-2 (human).

The relationship between the biological activity and protein mass is as follows:

18 million International Units Proleukin = 1.1 mg protein

CLINICAL PHARMACOLOGY

Proleukin® (aldesleukin) has been shown to possess the biological activities of human native interferon-2.1-7 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 animals and humans produces multiple immunological effects. These 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. In vivo studies in murine tumor models have shown inhibition of tumor growth. The exact mechanisms 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 intravenous infusion, rapid distribution into the extravascular space and elimination from the body by metabolism in the kidneys with little or no bioactive protein excreted in the urine. Studies of intravenous Proleukin in sheep and humans indicate that upon completion of infusion, approximately 30% of the administered dose is detectable in plasma. This finding is consistent with studies in rats using radio labeled Proleukin, which demonstrated a rapid (<1 min) uptake of the majority of the label into the lungs, liver, kidney, and spleen.

The serum half-life (T 1/2) curves of Proleukin remaining in the plasma are derived from studies done in 52 cancer patients following a 5-minute intravenous infusion. These patients were shown to have a distribution and elimination half-life of 12 ± 3 minutes and 58 ± 3 minutes respectively.

Following the initial rapid organ distribution, the primary route of clearance of circulating Proleukin is the kidney. In humans and animals, Proleukin is cleared from the circulation by both glomerular filtration and peritubular transport in the kidney. The relative rapid clearance of Proleukin has led to dosage schedules characterized by frequent, short infusions. Observed serum levels are proportional to the dose of Proleukin.

CLINICAL STUDIES

Safety and efficacy were studied in a series of single and multicenter, historically controlled studies enrolling a total of 525 patients with metastatic renal cell carcinoma or melanoma. Eligible patients had an Eastern Cooperative Group (ECOG) Performance Status (PS) of 0 or 1 and normal organ function as determined by cardiac stress test, pulmonary function tests, and creatinine ≤1.5 mg/dL. Studies excluded patients with brain metastases, active infections, organ allografts and diseases requiring steroid treatment.

The same treatment dose and schedule was employed in all studies demonstrating efficacy. Proleukin was given by 15 min intravenous infusion every 8 hours for up to 5 days (maximum of 14 doses). No treatment was given on days 6 to 14 and the same dosing was repeated for up to 5 days on days 15 to 19 (maximum of 14 doses). These 2 cycles constituted 1 course of therapy. Patients could receive a maximum of 28 doses during a course of therapy. In practice greater than 60% of patients had doses withheld. Doses were withheld for specific toxicities (See "DOSEAGE AND ADMINISTRATION" section, "Dose Modifications" subsection and ADVERSE REACTIONS section).

Metastatic Renal Cell Cancer

Two hundred fifty-five patients with metastatic renal cell cancer (metastatic RCC) were treated with single agent Proleukin in 7 clinical studies conducted at 21 institutions. Metastatic RCC patients received a median of 20 of 28 scheduled doses of Proleukin. In the renal cell cancer studies (n=255), objective response was seen in 37 (15%) patients, with 17 (7%) complete and 20 (8%) partial responders (See Table I). The 95% confidence interval for objective response was 11% to 23%. Onset of tumor regression was observed as early as 4 weeks after completion of the first course of treatment, and in some cases, tumor regression continued for up to 12 months after the start of treatment. Responses were observed in both lung and non-lung sites (e.g., liver, lymph node, renal bed occurrences, soft tissue). Responses were also observed in patients with individual bulky lesions and high tumor burden.

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>

(-) sign means ongoing

* 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 x10^6 International Units days 1-2 and 18 x10^6 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, of which the first dose was seen as 43 (16%) patients, with 17 (8%) 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). Responses were also observed in patients with individual bulky lesions and large cumulative tumor burden.

*)
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 test 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 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 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
- Infiltration for >24 hours
- Renal failure requiring dialysis >72 hours
- Coma or toxic psychosis lasting >48 hours
- Repetitive or difficult to control seizures
- Bowel ischemia
- Gil bleeding requiring surgery

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, which require dose modification occur, Proleukin should be withheld rather than reduced (See “DOSE AND ADMINISTRATION” section, “Dose Modifications” subsection). 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 arthritides, diarrheal disease, vasculitis, occlusive retinopathy, crescentic IgA glomerulonephritis, cholecystitis, cerebral 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. Radiographic 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. One case of possible cerebral vasculitis, responsive to dexamethasone, has 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 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 the formation of edema and creation of new effusions.

Medical management of CLS begins with 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 cathereterization and central pressure monitoring and hypovolemia is assessed by catheterization and central pressure monitoring. Management of CLS begins with fluid accumulation, edema is common and ascites, pleural or pericardial fluid may develop. 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) exceed the patient’s tolerance.

Clinical experience has shown that early administration of dopamine (1 to 5 mcg/kg/min) to patients manifesting capillary leak syndrome, before the onset of hypotension, can help to maintain organ perfusion and blood pressure. Consequently, extreme caution should be used in treating patients with fixed requirements for large volumes of fluid (e.g., patients with hypercalciemia). 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 caustion is required because unrestrictly administered fluid administration may exacerbate problems associated with edema formation or effusions. With extravascular fluid accumulation, edema is common and ascites, pleural or pericardial effusions may develop. 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) exceed the patient’s tolerance.

Due to the use of the product mentioned, the physician should refer to the package insert for the respective product. 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 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 the formation of edema and creation of new effusions.

Medical management of CLS begins with 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 and hypovolemia is assessed by catheterization and central pressure monitoring. Management of CLS begins with fluid accumulation, edema is common and ascites, pleural or pericardial effusions may develop. 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) exceed the patient’s tolerance.

Clinical experience has shown that early administration of dopamine (1 to 5 mcg/kg/min) to patients manifesting capillary leak syndrome, before the onset of hypotension, can help to maintain organ perfusion particularly to the kidneys and thus prevent renal output. If organ perfusion and blood pressure are not sustained by dopamine therapy, clinical investigators have increased the dose of dopamine to 6 to 10 mcg/kg/min or have added phenylephrine hydrochloride (1 to 5 mcg/kg/min) to low dose dopamine (See “ADVERSE REACTIONS” section). Prolonged use of pressors, either in combination or as individual agents, at relatively high doses, may be associated with cardiac rhythm disturbances. If there has been excessive weight gain or edema formation, particularly if associated with shortness of breath from pulmonary congestion, use of diuretics should be considered. 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) exceed the patient’s tolerance.

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 (See “DOSE AND ADMINISTRATION” section, “Dose Modifications” subsection). Recovery from CLS begins soon after cessation of Proleukin therapy. Usually, within a few hours, the blood pressure rises, organ perfusion is restored and reabsorption of extravesal fluid and protein begins.

Serious Manifestations of Eosinophilia
Serious manifestations of eosinophilia involving eosinophilic infiltration of cardiac and pulmonary tissues can occur during Proleukin therapy.

Laboratory Tests
The following a 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

Serum creatinine should be ≤1.5 mg/dL prior to initiation of Proleukin treatment. All patients should have baseline pulmonary function tests with arterial blood gases. Adequate pulmonary function should be documented (FEV1 >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 further testing is suggested to exclude significant coronary artery disease.

Daily monitoring during therapy with Proleukin should include vital signs (temperature, pulse, blood pressure, and respiration rate), weight, and fluid intake and output. In a patient with a decreased systolic blood pressure, especially less than 90 mm Hg, constant cardiac rhythm monitoring should be conducted. If an abnormal complex or rhythm is seen, an ECG should be performed. Vital signs in these hypertensive patients should be taken hourly. Drug 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 tachy) should be further assessed with arterial blood gas determination. These tests are to be repeated as often as clinically indicated.

Cardiac function should be 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 cardiac enzyme evaluation. Evidence of myocardial injury, including findings compatible with myocardial infarction or myocarditis, has been reported. Ventricular hypokinesia due to myocarditis may be persistent for several months. If there is evidence of cardiac ischemia or congestive heart failure, Proleukin therapy should be held, and a repeat thallium study should be done.

TABLE 2: Proleukin Clinical RESPONSE DATA

<table>
<thead>
<tr>
<th>Number of Responding Patients (response rate)</th>
<th>Median Response Duration in Months (range)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Metastatic Melanoma</strong></td>
<td></td>
</tr>
<tr>
<td>CR's</td>
<td>17 (6%)</td>
</tr>
<tr>
<td>PR's</td>
<td>28 (10%)</td>
</tr>
<tr>
<td>PR's + CR's</td>
<td>43 (16%)</td>
</tr>
<tr>
<td>Median Duration not yet observed; a conservative value is presented which represents the minimum median duration of response.</td>
<td></td>
</tr>
</tbody>
</table>

(*) sign means ongoing
Drug Interactions

Proleukin may affect central nervous function. Therefore, interactions could occur following concomitant administration of psychotropic drugs (e.g., narcotics, anxiolytics, anticonvulsants, sedatives, tranquilizers).

Concurrent administration of drugs possessing nephrotoxic (e.g., aminoglycosides, indomethacin), myelotoxic (e.g., cytotoxic chemotherapy), cardiotoxic (e.g., doxorubicin) or hepatotoxic (e.g., methotrexate, aspirin) actions may increase toxicity in these organ systems. The safety and efficacy of Proleukin in combination with any antineoplastic agents have not been established.

In addition, reduced kidney and liver function secondary to Proleukin treatment may delay elimination of concomitant medications and increase the risk of adverse events from those drugs.

Hypersensitivity reactions have been reported in patients receiving combination regimens containing sequential high dose Proleukin and antineoplastic agents, specifically dacarbazine, cis-platinum, tamoxifen and interferon-alfa. These reactions consisted of erythema, pruritus, and hypotension and occurred within hours of administration of chemotherapy. These events required medical intervention in some patients.

Myocardial injury, including myocardial infarction, myocarditis, ventricular hypokinesia, and severe rhabdomyolysis appear to be increased in patients receiving Proleukin and interferon-alfa concurrently.

In a small group of 525 patients treated with Proleukin, the rate of drug-related deaths in the 255 metastatic RCC patients who received single-agent Proleukin was 4% (11/255); the rate of drug-related deaths in the 270 metastatic melanoma patients who received single-agent Proleukin was 2% (5/270).

Delayed Adverse Reactions to Iodinated Contrast Media

A review of the literature revealed that 12.6% (range 11-28%) of 501 patients treated with various interleukin-2 containing regimens who were subsequently administered radiographic iodinated contrast media experienced acute, atypical adverse reactions. The onset of symptoms usually occurred within hours (most commonly 1 to 4 hours) following the administration of contrast media. These reactions include fever, chills, nausea, vomiting, pruritus, rash, 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 contrast reactions after interleukin-2 therapy is unknown. Most events were reported to occur when contrast media was given within 4 weeks after the last dose of interleukin-2. These events were also reported to occur when contrast media was given several months after interleukin-2 treatment.

Carcinogenesis, Mutagenesis, Impairment of Fertility

There have been no studies conducted assessing the carcinogenic or mutagenic potential of Proleukin.

Pregnancy

Pregnancy Category C.

Proleukin has been shown to have embryolethal effects in rats when given in doses at 27 to 36 times the human dose (scaled by body weight). Significant maternal toxicities were 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. No evidence of teratogenicity was observed other than that attributed to maternal toxicity. There are no adequate well-controlled studies of Proleukin in pregnant women. Proleukin should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

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.

Geriatric Use

There were a small number of patients aged 65 and over in clinical trials of Proleukin; experience is limited to 27 patients, eight with metastatic melanoma and nineteen with metastatic renal cell carcinoma. The response rates were similar in patients 65 years and over as compared to those less than 65 years of age. The median number of courses and the median number of doses per course were similar between older and younger patients.

Proleukin is known to be substantially excreted by the kidney, and the risk of toxic reactions to this drug may be greater in patients with impaired renal function. The pattern of organ system toxicity and the proportion of patients with severe toxicities by organ system were generally similar in patients 65 years and older and younger patients. There was a trend, however, towards an increased incidence of severe urogenital toxicities and dyspnea in the older patients.

ADVERSE REACTIONS

The rate of drug-related deaths in the 255 metastatic RCC patients who received single-agent Proleukin was 4% (11/255); the rate of drug-related deaths in the 270 metastatic melanoma patients who received single-agent Proleukin was 2% (5/270).

The following data on common adverse events (reported in greater than 10% of patients, any grade), presented by body system, decreasing frequency and by preferred term (COSTART) are based on 525 patients (255 with renal cell cancer and 270 with metastatic melanoma) treated with the recommended infusion dosing regimen.

### TABLE 3: ADVERSE EVENTS OCCURRING IN ≥10% OF PATIENTS (n=525)

<table>
<thead>
<tr>
<th>Body System Body as a Whole</th>
<th>% Patients</th>
<th>Body System Metabolic and Nutritional Disorders</th>
<th>% Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chills</td>
<td>52</td>
<td>Bilirubinemia</td>
<td>40</td>
</tr>
<tr>
<td>Fever</td>
<td>29</td>
<td>Creatinine increase</td>
<td>33</td>
</tr>
<tr>
<td>Malaise</td>
<td>27</td>
<td>Perinephric edema</td>
<td>28</td>
</tr>
<tr>
<td>Anesthesia</td>
<td>23</td>
<td>SGOT increase</td>
<td>23</td>
</tr>
<tr>
<td>Infection</td>
<td>13</td>
<td>Weight gain</td>
<td>16</td>
</tr>
<tr>
<td>Pain</td>
<td>12</td>
<td>Edema</td>
<td>15</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>11</td>
<td>Acodis</td>
<td>12</td>
</tr>
<tr>
<td>Abdomen enlarged</td>
<td>10</td>
<td>Hypogonadism</td>
<td>12</td>
</tr>
<tr>
<td>Cardiovascular</td>
<td></td>
<td>Hippocalcemia</td>
<td>11</td>
</tr>
<tr>
<td>Hypotension</td>
<td>71</td>
<td>Alkaline phosphatase increase</td>
<td>10</td>
</tr>
<tr>
<td>Tachycardia</td>
<td>23</td>
<td>Nervous</td>
<td></td>
</tr>
<tr>
<td>Vasodilation</td>
<td>13</td>
<td>Confusion</td>
<td>34</td>
</tr>
<tr>
<td>Supraventricular tachycardia</td>
<td>12</td>
<td>Somnolence</td>
<td>22</td>
</tr>
<tr>
<td>Cardiovascular disorder</td>
<td>11</td>
<td>Anxiety</td>
<td>12</td>
</tr>
<tr>
<td>Anhydramia</td>
<td>10</td>
<td>Dizziness</td>
<td>11</td>
</tr>
<tr>
<td>Digestive</td>
<td></td>
<td>Respiratory</td>
<td></td>
</tr>
<tr>
<td>Diarrhea</td>
<td>67</td>
<td>Dyspneia</td>
<td>43</td>
</tr>
<tr>
<td>Vomiting</td>
<td>50</td>
<td>Lung disordera</td>
<td>24</td>
</tr>
<tr>
<td>Nausea</td>
<td>35</td>
<td>Respiratory disordera</td>
<td>11</td>
</tr>
<tr>
<td>Stomatitis</td>
<td>22</td>
<td>Cough increase</td>
<td>11</td>
</tr>
<tr>
<td>Anorexia</td>
<td>20</td>
<td>Ribulose</td>
<td>10</td>
</tr>
<tr>
<td>Nausea and vomiting</td>
<td>19</td>
<td>Skin and Appendages</td>
<td></td>
</tr>
<tr>
<td>Hemic and Lymphatic</td>
<td></td>
<td>Rash</td>
<td>42</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>37</td>
<td>Pruritus</td>
<td>24</td>
</tr>
<tr>
<td>Anemia</td>
<td>29</td>
<td>Exfoliative dermatitis</td>
<td>18</td>
</tr>
<tr>
<td>Leukopenia</td>
<td>16</td>
<td>Urogenital</td>
<td>63</td>
</tr>
</tbody>
</table>

* Cardiotoxic disorder: fluctuations in blood pressure, asymptomatic ECG changes, CHF.
* Lung disorder: physical findings associated with pulmonary congestion, rales, rhonchi.
* Respiratory disorder: ARDS, CRR infiltrates, unspecified pulmonary changes.
The following data on life-threatening adverse events (reported in greater than 1% of patients, grade 4), presented by body system, and by 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>(%)</th>
<th>Body System</th>
<th>(%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiovascular</td>
<td>4 (1%)</td>
<td>Acute kidney failure</td>
<td>3 (1%)</td>
</tr>
<tr>
<td>Hypotension</td>
<td>15 (3%)</td>
<td>Nervous</td>
<td>5 (1%)</td>
</tr>
<tr>
<td>Supraventricular tachycardia</td>
<td>3 (1%)</td>
<td>Confusion</td>
<td>5 (1%)</td>
</tr>
<tr>
<td>Coagulation disorder*</td>
<td>7 (1%)</td>
<td>Shupor</td>
<td>3 (1%)</td>
</tr>
<tr>
<td>Myocardial infarct</td>
<td>7 (1%)</td>
<td>coma</td>
<td>6 (2%)</td>
</tr>
<tr>
<td>Ventricular tachycardia</td>
<td>5 (1%)</td>
<td>Psychosis</td>
<td>7 (1%)</td>
</tr>
<tr>
<td>Cardiac arrest</td>
<td>4 (1%)</td>
<td>Respiratory</td>
<td>2 (1%)</td>
</tr>
<tr>
<td>Digestive</td>
<td></td>
<td>Dypsnea</td>
<td>5 (1%)</td>
</tr>
<tr>
<td>Dianrhea</td>
<td>10 (2%)</td>
<td>Respiratory disorder*</td>
<td>14 (3%)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>7 (1%)</td>
<td>Apnea</td>
<td>5 (1%)</td>
</tr>
<tr>
<td>Hemic and Lymphatic</td>
<td></td>
<td>Unurinal</td>
<td>2 (1%)</td>
</tr>
</tbody>
</table>
| Thrombocytopenia | 5 (1%) | Oliguria | 33 (60%)
| Coagulation disorder* | 4 (1%) | Anuria | 25 (50%)

* Cardiovascular disorder: fluctuations in blood pressure.
* Coagulation disorder: intravascular coagulopathy.
* Respiratory disorder: ARDS, respiratory failure, intubation.

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

In an additional population of greater than 1,800 patients treated with Proleukin-based regimens using a variety of doses and schedules (e.g., subcutaneous, continuous infusion, administration with LAK cells) the following serious adverse events were reported: dudional ulceration; bowel necrosis; myocardial; supraventricular tachycardia; permanent or transient blindness secondary to optic neuritis; transient ischemic attacks; meninges; cerebral edema; pericarditis; allergic interstitial nephritis; tracheo-esophageal fistula.

In the same clinical population, the following fatal adverse effects occurred with a frequency of <1%: malignant hyperthermia; cardiac arrest; myocardial infarction; pulmonary emboli; stroke; intestinal perforation; liver or renal failure; severe depression leading to suicide; pulmonary edema; respiratory arrest; respiratory failure. In patients with both metastatic RCC and metastatic melanoma, those with ECOG PS of 1 or higher had a higher treatment-related mortality and serious adverse events.

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

### 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 every 8-hour PROLEUKIN® 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 aldolusleukin was evaluated in 13 patients. Following the first cycle of therapy, comparing the geometric mean aldolusleukin exposure (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 anti-aldesleukin antibody formation on clinical efficacy and safety of Proleukin is unknown.

Immunogenicity 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, comparison 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, lympho cytopenia
- **Cardiac:** cardiomyopathy, cardiac tamponade
- **Endocrine:** hyperthyroidism
- **Gastrointestinal:** gastritis, intestinal obstruction, colitis
- **General and administration site conditions:** injection site necrosis
- **Hepatobiliary:** hepatitis, hepatosplenomegaly, cholecystitis
- **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
- **Vascular:** hypertension, fatal subdural and subarachnoid hemorrhage, cerebral hemorrhage, retnoprophthalic 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 interferon-2. Synergistic, additive and novel toxicities have been reported with Proleukin used in combination with other drugs. Novel toxicities include delayed adverse reactions to iodinated contrast media and hypersensitivity reactions to antineoplastic agents (See "WARNINGS" section, "Drug Interactions" subsection).

Exacerbation 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), started immediately prior to Proleukin to reduce fever. Renal function should be monitored as some NSAIDs may cause synergistic nephrotoxicity; b) meperidine used to control the rigors associated with fever; c) hydroxyzine or diphenhydramine has been used to control symptoms from pruritic rashes 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 the use of any product mentioned, the physician should refer to the package insert for the respective product.

### OVERDOSAGE
Side effects following the use of Proleukin® (aldesleukin) appear to be dose-related. Exceeding the recommended dose has been associated with a more rapid onset of expected dose-limiting toxicities. Symptoms which persist after cessation of Proleukin should be monitored and treated supportively. Life-threatening toxicities may be ameliorated by the intravenous administration of dexamethasone, which may also result in loss of the therapeutic effects of Proleukin. NOTE: Prior to the use of 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", "CONTRA-INDICATIONS", "WARNINGS", "PRECAUTIONS", and "ADVERSE REACTIONS" 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 (metastatic RCC) or metastatic melanoma. Each course of treatment consists of two 5-day treatment cycles separated by a rest period.

600,000 International Untis § (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 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.

### Retreatment
Patients should be evaluated for response approximately 4 weeks after completion of a course of therapy and again 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 hospital discharge.
### 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:

**Retreatment with Proleukin is contraindicated in patients who have experienced the following toxicities:**

<table>
<thead>
<tr>
<th>Body System</th>
<th>Toxicity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiovascular</td>
<td>Sustained ventricular tachycardia (≥5 beats)</td>
</tr>
<tr>
<td></td>
<td>Cardiac rhythm disturbances not controlled or unresponsive to management</td>
</tr>
<tr>
<td></td>
<td>Chest pain with ECG changes, consistent with angina or myocardial infarction</td>
</tr>
<tr>
<td>Respiratory</td>
<td>Intubation for &gt;72 hours</td>
</tr>
<tr>
<td>Urogenital</td>
<td>Renal failure requiring dialysis &gt;72 hours</td>
</tr>
<tr>
<td>Nervous</td>
<td>Coma or toxic psychosis lasting &gt;48 hours</td>
</tr>
<tr>
<td>Digestive</td>
<td>Bowel ischemia/perforation</td>
</tr>
<tr>
<td></td>
<td>GI bleeding requiring surgery</td>
</tr>
</tbody>
</table>

### Doses should be held and restarted according to the following:

<table>
<thead>
<tr>
<th>Body System</th>
<th>Hold dose for</th>
<th>Subsequent doses may be given if</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiovascular</td>
<td>Atrial fibrillation, supraventricular tachycardia or bradycardia that requires treatment or is recurrent or persistent</td>
<td>Patient is asymptomatic with full recovery to normal sinus rhythm</td>
</tr>
<tr>
<td></td>
<td>Systolic bp &lt;90 mm Hg with increasing requirements for pressors</td>
<td>Systolic bp ≥90 mm Hg and stable or improving requirements for pressors</td>
</tr>
<tr>
<td></td>
<td>Any ECG change consistent with MI, ischemia or myocarditis with or without chest pain; suspicion of cardiac ischemia</td>
<td>Patient is asymptomatic, MI and myocarditis have been ruled out, clinical suspicion of angina is low; there is no evidence of ventricular hypokinesia</td>
</tr>
<tr>
<td>Respiratory</td>
<td>O₂ saturation &lt;90%</td>
<td>O₂ saturation ≥90%</td>
</tr>
<tr>
<td>Nervous</td>
<td>Mental status changes, including moderate confusion or agitation</td>
<td>Mental status changes completely resolved</td>
</tr>
<tr>
<td>Body as a Whole</td>
<td>Sepsis syndrome, patient is clinically unstable</td>
<td>Sepsis syndrome has resolved, patient is clinically stable, infection is under treatment</td>
</tr>
<tr>
<td>Urogenital</td>
<td>Serum creatinine &gt;4.5 mg/dL or a serum creatinine of ≥4 mg/dL in the presence of severe volume overload, acidosis, or hyperkalemia</td>
<td>Serum creatinine &lt;4 mg/dL, and fluid and electrolyte status is stable</td>
</tr>
<tr>
<td></td>
<td>Persistent oliguria, urine output of &lt;10 mL/hour for 16 to 24 hours with rising serum creatinine</td>
<td>Urine output &gt;10 mL/hour with a decrease of serum creatinine &gt;1.5 mg/dL, or normalization of serum creatinine</td>
</tr>
<tr>
<td>Digestive</td>
<td>Signs of hepatic failure including encephalopathy, increasing ascites, liver pain, hypoglycemia</td>
<td>All signs of hepatic failure have resolved*</td>
</tr>
<tr>
<td></td>
<td>Stool guaiac repeatedly &gt;3-4+</td>
<td>Stool guaiac negative</td>
</tr>
<tr>
<td>Skin</td>
<td>Bullous dermatitis or marked worsening of pre-existing skin condition, avoid topical steroid therapy</td>
<td>Resolution of all signs of bullous dermatitis</td>
</tr>
</tbody>
</table>

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

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 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.

1. 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.

2. 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.

3. 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.

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 studies 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


