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.
KNOW YOUR options

When considering treatment for metastatic melanoma, it is extremely important to consider every option. While surgery is the most common treatment for early disease, metastatic melanoma poses treatment challenges that often require additional drug therapy to help address the cancer that has spread to other parts of the body. These treatments can include oral drugs, injected drugs, and/or radiation.

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

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

Receiving the diagnosis of metastatic melanoma 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 melanoma.

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 decide upon your treatment plan. 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. Complete response rate was 6% in metastatic melanoma patients.

As of August 2005, I have no new evidence of disease. I'm so thrilled that I just passed my 10th anniversary cancer free.

Kelli, actual Proleukin patient
Cancer free since 2005
Read more stories on Proleukin.com

Individual results may vary

Please see accompanying full Prescribing Information including Boxed Warning. Please see pages 18 and 19 for Important Safety Information and additional side effect information.
Melanoma is a cancer that begins in melanocytes, which are cells that produce the pigment melanin that colors the skin, hair, and eyes and is responsible for forming moles. Most of these pigment cells are found in the skin.

Basic facts about skin cancer:
- Melanoma is expected to affect 73,870 Americans this year
- Anyone who has more than 100 moles is at greater risk for melanoma
- Melanoma can spread to almost any other organ in the body but most commonly spreads to the liver, lungs, bones, and brain
- The majority of melanomas are black or brown. However, some melanomas are skin-colored, pink, red, purple, blue, or white

To diagnose melanoma, a skin biopsy is performed by a doctor, in which a skin sample is taken and examined under a microscope to determine if cancer cells are present, how many, and how deeply they penetrate into your skin. If necessary, more tests will be performed, including possible removal and examination of lymph nodes.

After melanoma is diagnosed, the next step is to determine the cancer’s stage, which describes the size, spread, and aggressiveness of the cancer. Staging is also important to determine the most appropriate treatment. Melanoma often starts as a single tumor or lesion. Once it spreads to distant locations, it is called advanced or metastatic melanoma.

The four basic types of melanoma:
- **Superficial spreading melanoma**: is the diagnosis in approximately 70% of melanomas; it spreads along the outer layer of skin for months or even years before penetrating more deeply. It occurs mostly on the trunks of men, the legs of women, and the upper back of both sexes.
- **Lentigo maligna melanoma**: arises from a preexisting lentigo, rather than a mole, and accounts for about 5% of melanoma cases. It typically takes years to develop and usually occurs in the elderly and the face and other sun-exposed areas.
- **Acral lentiginous melanoma**: accounts for less than 5% of all melanomas but is the most common melanoma in African Americans and Asians. It also occurs in light-skinned (Caucasian) individuals.
- **Nodular melanoma**: represents 15% to 30% of all melanomas. It grows deeper more quickly than other types of melanoma and is found most often on the trunk or head and neck.

Metastatic means that the cancer cells have spread to the lymph nodes, other organs in the body, or areas far from the original site of the tumor. There is excellent, detailed information about skin cancer and the different types, symptoms, diagnosis, and treatment available to you. When you are ready, there is a list of website resources on the inside back cover of this brochure. Please visit for more information, in addition to consulting with your healthcare team.

Most patients are diagnosed in early phases before the cancer has spread to other parts of the body. In some patients, the cancer cells have spread to nearby lymph nodes and distant sites throughout the body. If melanoma spreads beyond the initial tumor, it is more serious and poses greater risks.
Some patients are diagnosed with melanoma before it has spread to other parts of the body, while others have metastatic disease when their cancer is initially diagnosed.

Treatment of advanced metastatic melanoma focuses on:
- Shrinking or eliminating the metastases
- Preventing the disease from spreading

In most cases, it is not possible to completely eliminate or cure the cancer. Depending upon where and how big the metastases are, treatment may involve immunotherapy, chemotherapy, surgery, radiation therapy, and/or experimental therapy as part of a clinical trial.

Your doctor may discuss the surgical options that are most appropriate for you. You may also discuss which drug therapies may be recommended, as well as radiation, additional surgeries to remove distant metastases, or experimental therapies.

Consulting the guidelines

Once all of the information about your cancer is gathered, your doctor may review one of the highly regarded treatment guidelines that exist. These guidelines are written by melanoma experts who convene on a regular basis to determine which treatment options may be recommended for each type of melanoma. The guidelines cover when surgeries are recommended, which drug therapies are recommended as a first treatment, and 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 both you and your doctor.

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 additional therapy options you’d be comfortable with should that be necessary.
Chemotherapy

Chemotherapy is the name given to a group of drugs that act on cancer cells to kill or slow the growth of the tumor(s). In the treatment of metastatic melanoma, the goal of chemotherapy is to destroy the cancer cells throughout the body.

- Taken by mouth or injected into a vein or muscle. The drug then enters the bloodstream and travels around the body (systemic therapy)
- Prescribed and administered by a medical oncologist, a physician specially trained in oncology
- Helps a small number of patients
- Generally given in an outpatient clinic or in a doctor’s office, where side effects can be monitored and managed

Common chemotherapy side effects
- Nausea and vomiting
- Loss of appetite
- Flu-like symptoms such as fever, chills, weakness, muscle aches, headache

Clinical trials

Clinical trials are research studies that test promising experimental cancer treatments, new ways to detect melanoma, or new ways to monitor melanoma. Clinical trials are an important part of medical research because they test new treatments in human volunteers. They also give some patients a chance to try a drug that they wouldn’t otherwise be able to use. All clinical trials have rules about who can take part and how the trial will run to try to keep patients safe.
Immunotherapy drugs work with the patient's immune system to fight cancer. This type of cancer treatment is also sometimes called biotherapy or biologic therapy because it is made up of substances that can be found within the body.

Unlike other therapy types, which kill or slow cancer cells to shrink tumors, immunotherapy gives your internal defense (immune) system a boost. The goal of immunotherapy is to increase your body's ability to produce cells that attack the cancer cells to shrink the tumor now and over time.

**The FDA-approved immunotherapies for the treatment of melanoma include**

- Interferon alpha 2-b
- High-dose interleukin-2 (HD IL-2)
- Checkpoint inhibitors of T cells (CTLA-4)
- Programmed cell death protein 1 (PD-1)

**Interferon alpha 2-b**: This may be an appropriate therapy for patients with deep melanomas, which pose a greater risk for spreading cancer cells to other parts of the body. Even after all apparent cancer has been removed by surgery, some of the melanoma cells may remain, and interferon-alpha can be used as an added therapy (adjuvant therapy) after surgery to try to prevent the melanoma cells from spreading and growing.

(continued on page 14)
Because high doses must be used in order for the interferon to be effective, many patients experience side effects that can include fever, chills, aches, depression, severe tiredness, and effects on the heart and liver.

- Patients receiving this drug should be closely monitored by an oncologist who is experienced with this treatment.
- High-dose interleukin-2 or HD IL-2 is currently used in the treatment of melanomas that have spread to other parts of the body (metastatic melanoma).

Checkpoint inhibitor of T cells (CTLA-4): These treatments work by targeting molecules that serve as checks and balances in the regulation of immune responses. By blocking inhibitory molecules, these treatments are designed to unleash or enhance preexisting anticancer immune responses.

- Immunotherapies may not be appropriate for every melanoma patient.
- Speak with a specialist who has in-depth experience with immunotherapies.
- Discuss a treatment plan to decide which therapies you will use and in which order.

Programmed cell death protein 1 (PD-1): Your immune system is normally your body’s first defense against threats like metastatic melanoma, but sometimes melanoma sends a signal that can prevent the immune system from doing its job.

- PD-1s block this melanoma signal, helping to restore the immune response against the tumor.
- While doing so, PD-1s could also affect nontumor cells.

Meeting an IL-2 specialist is a good idea and does not mean you cannot continue to work with your existing healthcare team. IL-2 specialists are happy to meet with you to discuss your treatment plan.
TREATMENTS: PROLEUKIN® (aldesleukin) immunotherapy (IL-2)

Proleukin (aldesleukin) 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 excess of 10 years in some patients with metastatic melanoma. 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 270 patients with metastatic melanoma

- 6% 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 5 years (about 59 months). The shortest response lasted 3 months, and the longest has lasted more than 10 years so far.
- There were also another 10% 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.

People have benefited from Proleukin therapy. Success stories began with a patient who asked a doctor to tell them everything there is to know about all of their options, including Proleukin.

Other Proleukin stories began when a doctor recommended it without the patient even asking about it. Be sure to ask your oncologist for a detailed explanation of Proleukin, and speak to a specialist who is experienced in administering Proleukin.

Please see accompanying full Prescribing Information including Boxed Warning.
Please see pages 18 and 19 for Important Safety Information and additional side effect information.

What you should know

While Proleukin is not right for every patient, it is the only therapy that has been shown to make metastatic melanoma tumors disappear completely in a small group of patients.
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. Antibioc 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>43%</td>
</tr>
<tr>
<td>DECREASED URINE</td>
<td>43%</td>
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<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>43%</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>CONFESSION</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 melanoma as well as clinical studies with patients who had metastatic kidney cancer.

### 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>
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<tr>
<td>STRANGULATION URINE</td>
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<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>CO2PA</td>
<td>2%</td>
</tr>
<tr>
<td>DIARRHEA</td>
<td>2%</td>
</tr>
<tr>
<td>FAST HEARTBEAT</td>
<td>2%</td>
</tr>
</tbody>
</table>

*Out of 525.

This information is from clinical studies with patients who had metastatic melanoma, 4% (1/255) 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, in the process of stimulating the immune system, produces a number of side effects. The most serious are experienced while the drug is being given at the hospital and are carefully monitored and managed by the treatment team. Different patients experience different side effects, some being mild and some more severe. Every patient has a unique experience. Talk to the Proleukin treatment team about what you should expect and how they will help manage the side effects.

In patients receiving Proleukin in these studies (253 with metastatic renal cell carcinoma and 270 with metastatic melanoma), 4% (1/255) 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 (aldesleukin) is indicated for the treatment of adults with metastatic renal cell carcinoma or metastatic melanoma.

Complete response rate was 6% in metastatic melanoma patients.

Please see accompanying full Prescribing Information including Boxed Warning. Please see pages 18 and 19 for Important Safety Information and additional side effect information.

Bruce, actual Proleukin patient
Cancer free since 2006
Read more stories on Proleukin.com
Individual results may vary

I had to remind myself that the side effects generally don’t linger, and the potential for a complete, durable response makes the treatment worthwhile.

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 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.

Complete response rate was 6% in metastatic melanoma patients.
YOUR treatment TEAM

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.

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.

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.

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.

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.
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 (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, 6% of patients with metastatic melanoma 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.

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

Key Points to Remember

- Proleukin is the only therapy that offers appropriate patients the possibility of a complete and long-lasting remission for metastatic melanoma (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

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 melanoma 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.

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? (e.g., 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?

Please see accompanying full Prescribing Information including Boxed Warning.

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

- 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?

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.

Kelli, actual Proleukin patient
Cancer free since 2005
Read more stories on Proleukin.com
Individual results may vary

Complete response rate was 6% in metastatic melanoma patients.
Adjuvant therapy: Additional cancer treatment given after the primary treatment to lower the risk that the cancer will come back. Adjuvant therapy may include chemotherapy, radiation therapy, hormone therapy, targeted therapy, or biologic therapy.

Biologic therapy: A substance that is made from a living organism or its products and is used in the prevention, diagnosis, or treatment of cancer and other diseases. Biologic agents include antibodies, interleukins, and vaccines. Also called biological agent and biological drug.

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.

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.

Melanoma: A form of cancer that begins in melanocytes (cells that make the pigment melanin). It may begin in a mole (skin melanoma), but that can also begin in other pigmented tissues, such as in the eye or in the intestines.

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.

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.


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.

Stage IV melanoma: Cancer has spread to other places in the body, such as the lungs, liver, brain, bone, soft tissue, gastrointestinal (GI) tract, or to places in the skin far away from where the cancer first started.

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 Academy of Dermatology
www.aad.org

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

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

Cancer Care, Inc.
1-800-813-HOPE (813-4673)
www.cancercare.org

Cancer Education
www.cancereducation.com

Cancer Guide
www.cancerguide.org

Cancer.net
www.cancer.net

Melanoma Patients’ Information Page
www.mpip.org

Melanoma Research Foundation
1-877-MRF-6460 (673-6460)
www.melanoma.org

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

National Coalition for Cancer Survivorship
1-877-NCCS-YES (622-7937)
www.canceradvocacy.org

National Comprehensive Cancer Network® (NCCN®)
www.nccn.org

National Institutes of Health
www.nih.gov

Prevent Cancer Foundation
www.preventcancer.org

Skin Cancer Foundation
www.skincancer.org

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

US Food and Drug Administration
www.fda.gov

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.
DESCRIPTION

Proleukin® (aldesleukin), a human recombinant interleukin-2 product, is a highly purified protein with a molecular weight of approximately 15,300 daltons. The chemical name is des-ala-1, serine-125 human interleukin-2. Proleukin, a lymphokine, is produced by recombinant DNA technology using a genetically engineered E. coli strain containing an analog of the human interleukin-2 gene. Genetic engineering techniques were used to modify the human IL-2 gene, and the resulting expression clone encodes a modified human interleukin-2. This recombinant form differs from native interleukin-2 in the following ways: a) Proleukin is not glycosylated because it is derived from E. coli; b) the molecule has no N-terminal alanine; the codon for this amino acid was deleted during the genetic engineering procedure; c) the molecule has serine substituted for cysteine at amino acid position 125; this was accomplished by site specific manipulation during the genetic engineering procedure; and d) the aggregation state of Proleukin is likely to be different from that of native interleukin-2.

The in vitro biological activities of the native nonrecombinant molecule have been reproduced with Proleukin.1,2

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 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 interleukin-2.1,2 In vitro studies performed on human cell lines demonstrate the immunoregulatory properties of Proleukin, including:

- enhancement of lymphocyte mitogenesis and stimulation of long-term growth of human interleukin-2 dependent cell lines;
- enhancement of lymphocyte cytotoxicity;
- induction of killer cell (lymphokine-activated LAK) and natural (NK) activity;
- and induction of interferon-gamma production.

The in vivo administration of Proleukin in animals and humans produces multiple immunological effects, such as:

- General effects: fever, hypotension, and hypovolemic shock;
- Specific effects: platelet aggregation, myeloid cells, and changes in leukocyte populations.

The relatively 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 through 14 and the treatment was resumed on 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, > 60% of patients had doses withheld. Doses were withheld for specific toxicities (See “DOSE 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 20%. 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>
<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

Table: Proleukin Clinical Response Data

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 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, starting the first dose was seen in 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.

**INDICATIONS AND USAGE**

Proleukin® (aldesleukin) 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 results 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 thalidomide 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 (≥6 beats)
- Cardiac arrhythmias not controlled or unresponsive to management
- Chest pain with ECG changes, consistent with angina or myocardial infarction
- Cardiac tamponade
- Intubation for >2 hours
- Renal failure requiring dialysis for >72 hours
- Coma or toxic psychosis lasting >48 hours
- Repetitive or difficult to control seizures
- Boxed ischemia
- GI 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® (aldesleukin) therapy should be withheld rather than reduced (See “DOSAGE 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, dermatomyositis, uveitis, 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. Radiological findings included multiple and, less commonly, single cortical lesions on MRI and evidence of demyelination. Neurologic signs and symptoms associated with Proleukin therapy usually improve after discontinuation of Proleukin therapy; however, there are reports of permanent neurologic defects. 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 extracellular space will lead to the formation of edema and creation of new effusions.

Medical management of CLS begins with careful monitoring of the patient’s fluid and organ perfusion status. This is achieved by frequent determination of blood pressure and pulse, and by monitoring organ function, which includes assessment of mental status and urine output. Hypovolemia is assessed by catheterization and central pressure monitoring of Proleukin. Recovery from CLS begins soon after cessation of Proleukin therapy. Usually, within a few hours, the blood pressure and urine output improve. Recovery of renal function usually begins by 6 to 12 hours after the last dose 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.

**Mental status changes including irritability, confusion, or depression which occur while receiving Proleukin may be indicators of bacteremia or early bacterial sepsis, hypoperfusion, occult CNS malignancy, or direct Proleukin-induced CNS toxicity. Alterations in mental status due solely to Proleukin therapy may progress for several days before recovery begins. Rarely, patients have sustained permanent neurologic deficits (See “PRECAUTIONS” section “Drug Interactions” subsection).”

Exacerbation of pre-existing autoimmune disease or initial presentation of autoimmune and inflammatory disorders has been reported following Proleukin alone or in combination with interferon (See “PRECAUTIONS” section “Drug Interactions” subsection and “ADVERSE REACTIONS” section). Hypothyroidism, sometimes preceded by hyperthyroidism, has been reported following Proleukin treatment. Some of these patients required thyroid replacement therapy. Changes in thyroid function may be a manifestation of autoimmune. Onset of symptomatic hyperglycemia and/or diabetes mellitus has been reported during Proleukin therapy. Proleukin enhancement of cellular immune function may increase the risk of allograft rejection in transplant patients.

**Serious Manifestations of Eosinophilia**

Serious manifestations of eosinophilia involving eosinophilic infiltration of cardiac and pulmonary tissues can occur in patients receiving Proleukin.

**Laboratory Tests**

The following clinical 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 chemistry-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 the physician should refer to the package insert for the respective product.

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.

**Drug Interactions**

Proleukin enhancement of cellular immune function may increase the risk of allograft rejection in transplant patients.
Drug Interactions
Proleukin may affect central nervous function. Therefore, interactions could occur following concomitant administration of psychotropic drugs (e.g., narcotics, analgesics, antiemetics, sedatives, tranquillizers).

Concurrent administration of drugs possessing nephrotoxic (e.g., aminoglycosides, indomethacin), myelotoxic (e.g., cytotoxic chemotherapy), cardiotoxic (e.g., doxorubicin) or hepatotoxic (e.g., methotrexate, asparaginase) effects with Proleukin may increase toxicity in these organ systems. The safety and efficacy of Proleukin in combination with 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 interfer-on-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.

Exacerbation or the initial presentation of a number of autoimmune and inflammatory disorders has been observed following concurrent use of interferon-alfa and Proleukin, including crescentic IgA glomerulonephritis, ocular-malar vasculitis, myasthenia gravis, inflammatory arthritis, thyroiditis, bullous pemphigoid, and Stevens-Johnson syndrome.

Although glucocorticoids have been shown to reduce Proleukin-induced side effects including fever, renal insufficiency, hyperbilirubinemia, confusion, and dyspnea, concomitant administration of these agents with Proleukin may reduce the antitumor effectiveness of Proleukin and thus should be avoided.12 Beta-blockers and other antihypertensives may potentiate the hypotension seen with Proleukin.

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.13

Carcinogenesis, Mutagenesis, Impairment of Fertility
There have been no studies conducted assessing the carcinogenic or mutagenic potential of Proleukin.

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

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 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 (aldesleukin) 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>Periarticular edema</td>
<td>28</td>
</tr>
<tr>
<td>Asthenia</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>Acuteon</td>
<td>12</td>
</tr>
<tr>
<td>Abdomen enlarged</td>
<td>10</td>
<td>Hypogonadaliai</td>
<td>12</td>
</tr>
<tr>
<td>Cardiovascular</td>
<td></td>
<td></td>
<td></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>Vasodilatation</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>Anemia</td>
<td>10</td>
<td>Dizziness</td>
<td>11</td>
</tr>
<tr>
<td>Digestive</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diarrhea</td>
<td>67</td>
<td>Dyspnea</td>
<td>43</td>
</tr>
<tr>
<td>Vomiting</td>
<td>50</td>
<td>Lung disorderc</td>
<td>24</td>
</tr>
<tr>
<td>Nausea</td>
<td>35</td>
<td>Respiratory disorderc</td>
<td>11</td>
</tr>
<tr>
<td>Sinusitis</td>
<td>22</td>
<td>Cough increase</td>
<td>11</td>
</tr>
<tr>
<td>Anorexia</td>
<td>23</td>
<td>Rhinitis</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></td>
<td></td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>37</td>
<td>Rash</td>
<td>42</td>
</tr>
<tr>
<td>Anemia</td>
<td>29</td>
<td>Pruritus</td>
<td>24</td>
</tr>
<tr>
<td>Leukopenia</td>
<td>16</td>
<td>Eosinophil dermatitis</td>
<td>18</td>
</tr>
<tr>
<td>Urogenital</td>
<td></td>
<td></td>
<td>63</td>
</tr>
</tbody>
</table>

* Cardiac vascular disorder: fluctuations in blood pressure, asymptomatic ECG changes, CHF.
* Lung disorder: physical findings associated with pulmonary congestion, rales, rhonchi.
* Respiratory disorder: ARDS, CIR infiltrates, unspecified pulmonary changes.
TABLE 4: LIFE-THREATENING (GRADE 4) ADVERSE EVENTS (n=525)

<table>
<thead>
<tr>
<th>Body System</th>
<th># (%) Patients</th>
<th>Body System</th>
<th># (%) Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Body as a Whole</td>
<td></td>
<td>Metabolic and Nutritional Disorders</td>
<td></td>
</tr>
<tr>
<td>Fever</td>
<td>5 (1%)</td>
<td>Bilirubinemia</td>
<td>13 (2%)</td>
</tr>
<tr>
<td>Infection</td>
<td>7 (1%)</td>
<td>Creatinine increase</td>
<td>5 (1%)</td>
</tr>
<tr>
<td>Sepsis</td>
<td>6 (1%)</td>
<td>SGOT increase</td>
<td>3 (1%)</td>
</tr>
<tr>
<td>Cardiovascular</td>
<td></td>
<td>Acidosis</td>
<td>4 (1%)</td>
</tr>
<tr>
<td>Hypotension</td>
<td>15 (3%)</td>
<td>Nervous</td>
<td></td>
</tr>
<tr>
<td>Supraventricular tachycardia</td>
<td>3 (1%)</td>
<td>Confusion</td>
<td>5 (1%)</td>
</tr>
<tr>
<td>Cardiac 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>8 (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></td>
</tr>
<tr>
<td>Digestive</td>
<td></td>
<td>Dypneaa</td>
<td>5 (1%)</td>
</tr>
<tr>
<td>Diarrhea</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>Unrogenital</td>
<td></td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>5 (1%)</td>
<td>Oliguria</td>
<td>33 (6%)</td>
</tr>
<tr>
<td>Coagulation disorder*</td>
<td>4 (1%)</td>
<td>Anuria</td>
<td>25 (5%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Acute kidney failure</td>
<td>3 (1%)</td>
</tr>
</tbody>
</table>

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

The following life-threatening (grade 4) events were reported by <1% of the 525 patients: hypothyroidia; shock; bradycardia; ventricular extrasystoles; myocardial ischemia; syncope; hemorraghe; atrial arrhythmia; phlebitis; AV block second degree; endocarditis; pericardial effusion; peripheral gangrene; thrombosis; coronary artery disorder; stomatitis; nausea and vomiting; liver function tests abnormal; gastrointestinal hemorrhage; hematemesis; bloody diarrhea; gastritis; gastrointestinal disorder; intestinal perforation; pancreatitis; anemia; leukopenia; 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; pneumothorax; 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: ducational ulceration; bowel necrosis; mycarditis; supraventricular tachycardia; permanent or transient blindness secondary to optic neuritis; transient ischemic attacks; meningitis; cerebral edema; pericarditis; allergic interstitial nephritis; tracheo-esophageal fistula.

In the same clinical population, the following fatal events each 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 adverse 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: myoccardial 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 titer 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 aldesleukin was evaluated in 13 patients. Following the first cycle of therapy, comparing the geometric mean aldesleukin exposure (AUC) Day 15 to Day 1, there was an average 68% increase in 11 patient 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, lymphocytopenia
- Cardiac: cardiomyopathy, cardiac tamponade
- Endocrine: hyperthyroidism
- Gastrointestinal: gastrointestinal 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, neuroalgia, neuritis, demyelinating neuropathy
- Psychiatric: insomnia
- Vascular: hypertension, fatal subdural and subarachnoid hemorrhage, cerebral hemorrhage, retropitoneal hemorrhage

Exacerbation or initial presentation of a number of autoimmune and inflammatory diseases have been reported (See "WARNINGS" section, "PRECAUTIONS" section, "Drug Interactions" section). Persistent but nonprogressive vitiligo has been observed in malignant melanoma patients treated with interleukin-2. Synergistic, additive and novel toxicities have been reported with Proleukin used in combination with other drugs. Novel toxicities include delayed adverse reactions to samples containing irradiated media and hyperresponsivity reactions to antineoplastic agents (See "PRECAUTIONS" section, "Drug Interactions" section).

Experience has shown the following concomitant medications to be useful in the management of Proleukin side effects: a) standard antihypertensive 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) H+ antagonists given for prophylaxis of gastrointestinal irritation and bleeding; d) antiepileptics and antianxiety drugs used as needed to treat other gastrointestinal side effects. Generally these medications were discontinued 12 hours after the last dose of Proleukin.

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 diphencypramidine 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 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.

Oncology Study:

<table>
<thead>
<tr>
<th>Body System</th>
<th># (%) Patients</th>
<th>Body System</th>
<th># (%) Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Coagulation disorder</td>
<td>4 (1%)</td>
<td>Oliguria</td>
<td>33 (6%)</td>
</tr>
<tr>
<td>Digestive</td>
<td></td>
<td>Dypneaa</td>
<td>5 (1%)</td>
</tr>
<tr>
<td>Diarrhea</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>Unrogenital</td>
<td></td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>5 (1%)</td>
<td>Oliguria</td>
<td>33 (6%)</td>
</tr>
<tr>
<td>Coagulation disorder*</td>
<td>4 (1%)</td>
<td>Anuria</td>
<td>25 (5%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Acute kidney failure</td>
<td>3 (1%)</td>
</tr>
</tbody>
</table>

The following table includes a list of the adverse reactions that have been reported with Proleukin. The table includes both the incidence of grade 3 and 4 adverse reactions and the number of patients affected.

<table>
<thead>
<tr>
<th>Body System</th>
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</tr>
</tbody>
</table>

NOTE: Prior to the use of any product mentioned, the physician should refer to the package insert for the respective product.
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>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>
</tbody>
</table>

Doses should be held and restarted according to the following:

<table>
<thead>
<tr>
<th>Body System</th>
<th>Hold dose for</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiovascular</td>
<td>Atrial fibrillation, supraventricular tachycardia or bradycardia that requires treatment or is recurrent or persistent</td>
</tr>
<tr>
<td>Respiratory</td>
<td>O₂ saturation &lt;90%</td>
</tr>
<tr>
<td>Nervous</td>
<td>Mental status changes, including moderate confusion or agitation</td>
</tr>
<tr>
<td>Body as a Whole</td>
<td>Sepsis syndrome, patient is clinically unstable</td>
</tr>
<tr>
<td>Urogenital</td>
<td>Urine output &gt;10 mL/hour with a decrease of serum creatinine &gt;1.5 mg/dL</td>
</tr>
<tr>
<td>Digestive</td>
<td>Signs of hepatic failure including encephalopathy, increasing ascites, liver pain, hypoglycemia</td>
</tr>
<tr>
<td>Skin</td>
<td>Stool guaiac repeated ≥3-4+</td>
</tr>
</tbody>
</table>

Subsequent doses may be given if

<table>
<thead>
<tr>
<th>Body System</th>
<th>Hold dose for</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiovascular</td>
<td>Patient is asymptomatic with full recovery to normal sinus rhythm</td>
</tr>
<tr>
<td>Respiratory</td>
<td>O₂ saturation &gt;90%</td>
</tr>
<tr>
<td>Nervous</td>
<td>Mental status changes completely resolved</td>
</tr>
<tr>
<td>Body as a Whole</td>
<td>Sepsis syndrome has resolved, patient is clinically stable, infection is under treatment</td>
</tr>
<tr>
<td>Urogenital</td>
<td>Serum creatinine &lt;4 mg/dL, and fluid and electrolyte status is stable</td>
</tr>
<tr>
<td>Digestive</td>
<td>All signs of hepatic failure have resolved*</td>
</tr>
<tr>
<td>Skin</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.

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.

Rx Only

REFERENCES


Manufactured by:
Prometheus Laboratories Inc.
San Diego, CA 92121
U.S. License No. 1848
At
Boehringer Ingelheim Pharma
BiberachRiss, Germany

For additional information, contact Prometheus Laboratories Inc. 1-877-PROLEUKIN (1-877- 776-5385)

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REV: January 2015 PR001H