



CIGNA MEDICAL COVERAGE POLICY

The following Coverage Policy applies to all plans administered by CIGNA Companies including plans administered by Great-West Healthcare, which is now a part of CIGNA.

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Subject **Aldesleukin (Proleukin®)**

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INSTRUCTIONS FOR USE

Coverage Policies are intended to provide guidance in interpreting certain **standard** CIGNA HealthCare benefit plans. Please note, the terms of a customer's particular benefit plan document [Group Service Agreement (GSA), Evidence of Coverage, Certificate of Coverage, Summary Plan Description (SPD) or similar plan document] may differ significantly from the standard benefit plans upon which these Coverage Policies are based. For example, a customer's benefit plan document may contain a specific exclusion related to a topic addressed in a Coverage Policy. In the event of a conflict, a customer's benefit plan document **always supercedes** the information in the Coverage Policies. In the absence of a controlling federal or state coverage mandate, benefits are ultimately determined by the terms of the applicable benefit plan document. Coverage determinations in each specific instance require consideration of 1) the terms of the applicable benefit plan document in effect on the date of service; 2) any applicable laws/regulations; 3) any relevant collateral source materials including Coverage Policies and; 4) the specific facts of the particular situation. Coverage Policies relate exclusively to the administration of health benefit plans. Coverage Policies are not recommendations for treatment and should never be used as treatment guidelines. Proprietary information of CIGNA. Copyright ©2011 CIGNA

Coverage Policy

CIGNA covers aldesleukin (Proleukin®) as medically necessary for adults with normal cardiac and pulmonary functions as defined by thallium stress testing and formal pulmonary function testing for any of the following:

- metastatic renal cell carcinoma (RCC)
- metastatic melanoma

When coverage is available and medically necessary, the dosage, frequency, site of administration, and duration of therapy should be reasonable, clinically appropriate, and supported by evidence-based literature and adjusted based upon severity, alternative available treatments, and previous response to aldesleukin (Proleukin®) therapy.

FDA Approved Indications

Proleukin (aldesleukin) is indicated for the treatment of adults with metastatic renal cell carcinoma (metastatic RCC). Proleukin is indicated for the treatment of adults with metastatic melanoma. Careful patient selection is mandatory prior to the administration of Proleukin. Evaluation of clinical studies to date reveals that patients with more favorable ECOG performance status (ECOG PS 0) at treatment initiation respond better to Proleukin, with a higher response rate and lower toxicity. Therefore, selection of patients for treatment should include assessment of performance status. Experience in patients with ECOG PS >1 is extremely limited.

FDA Recommended Dosing

The recommended Proleukin for injection treatment regimen is administered by a 15-minute IV infusion every 8 hours. 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 IU/kg (0.037 mg/kg) dose administered every 8 hours by a 15-minute IV 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. 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.

For 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. Each treatment course should be separated by a rest period of at least 7 weeks from the date of hospital discharge. Proleukin should be administered only 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.

Black Box Warning

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.

Drug Availability

Proleukin is supplied in individually boxed single-use vials. Each vial contains 22 million International Units of Proleukin.

General Background

Pharmacology

Aldesleukin, a human recombinant interleukin-2 product, is a highly purified protein produced by recombinant deoxyribonucleic acid (DNA) technology using a genetically engineered *Escherichia coli* strain containing an analog of the human interleukin-2 gene. The exact mechanism by which aldesleukin mediates its antitumor activity in animals and humans is unknown.

The pharmacokinetic profile of aldesleukin is characterized by high plasma concentrations following a short intravenous (IV) 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. In humans, the mean clearance rate in cancer patients is 268 mL/minute (min). The relatively rapid clearance of aldesleukin has led to dosage

schedules characterized by frequent, short infusions. Observed serum levels are proportional to the dose of aldesleukin.

Guidelines

The National Comprehensive Cancer Network (NCCN) recommends Proleukin for the following:

Melanoma

Grade 2A

High-dose single agent or in combination with cisplatin and vinblastine with either dacarbazine or temozolomide, with or without interferon alfa for unresectable stage III in-transit metastases; local, satellitosis, and/or in-transit unresectable recurrence; incompletely resected nodal recurrence; limited recurrence or metastatic disease; disseminated recurrence or metastatic disease without brain metastases in patients with good performance status. High-dose interleukin-2 should not be used for patients with active, untreated brain metastases.

RCC

Grade 2A

First-line therapy as a high-dose single agent for selected patients with predominant clear cell histology with medically unresectable stage IV disease or who have relapsed.

Clinical Efficacy

The removal of the HIV and leukemia indications was based on studies published in the last five years that indicate there is no clinical benefit for the use of Proleukin in either of these two conditions.

HIV

The study of aldesleukin with and without antiretroviral therapy (STALWART) (Tavel, 2010) evaluated whether intermittent interleukin-2 (IL-2) alone or with antiretroviral therapy (ART) around IL-2 cycles increased CD4⁺ counts compared to no therapy. A total of 267 participants were randomized. At week 32, the mean CD4⁺ count was 134 cells greater in the IL-2 alone group ($p < 0.001$), and 133 cells greater in the IL-2 plus ART group ($p < 0.001$) compared to the no therapy group. Twelve participants in the IL-2 groups compared to 1 participant in the group assigned to no therapy experienced an opportunistic event or died ($p = 0.009$). IL-2 alone or with per-cycle HAART increases CD4⁺ counts but was associated with a greater number of opportunistic events or deaths compared to no therapy. These results call into question the immunoprotective significance of IL-2-induced CD4⁺ cells.

Leukemia

In patients with acute myeloid leukemia (AML), induction chemotherapy is based on standard doses of anthracyclines and cytarabine (Pautas, 2010). High doses of cytarabine have been reported as being too toxic for patients older than age 50 years, but few studies have evaluated intensified doses of anthracyclines. In this randomized study, high doses of daunorubicin or idarubicin were compared with standard doses of idarubicin for remission induction in patients age 50 to 70 years, with an event-free survival (EFS) end point. After two consolidation courses based on intermediate doses of cytarabine, patients in continuous remission were randomly assigned to receive or not receive maintenance therapy with recombinant interleukin-2 (rIL-2; 5×10^6 U/m² \times 5 days each month) for a total duration of 12 months. A total of 468 patients entered the study. Overall complete remission rate was 77% with significant differences among the three randomization arms (83%, 78%, and 70% in the IDA3, IDA4, and DNR arms, respectively; $P = .04$). However, no significant differences were observed in relapse incidence, EFS, or overall survival among the three arms. In the 161 patients randomly assigned for maintenance therapy, no difference in outcome was observed between the rIL-2 and the no further treatment arms. Neither intensification of anthracycline doses nor maintenance with rIL-2 showed a significant impact on AML course, at least as scheduled in this trial.

Adverse Reactions/Contraindications

In addition to the Black Box Warning information, aldesleukin may affect central nervous function. Therefore, interactions could occur following concomitant administration of psychotropic drugs (e.g., narcotics, analgesics, antiemetics, sedatives, tranquilizers). In addition, reduced kidney and liver function secondary to aldesleukin treatment may delay elimination of concomitant medications and increase the risk of adverse events from those drugs.

Coding/Billing Information

Note: This list of codes may not be all-inclusive.

Covered when medically necessary:

HCPSC Codes	Description
J9015	Injection, aldesleukin, per single use vial

ICD-9-CM Diagnosis Codes	Description
172.0-172.9	Malignant melanoma of skin
189.0	Malignant neoplasm of kidney, except pelvis
189.1	Malignant neoplasm of renal pelvis

References

1. Bayer Healthcare Pharmaceuticals, Inc. Proleukin® (aldesleukin) injection prescribing information. Emeryville, CA: Bayer Healthcare Pharmaceuticals, Inc. Aug 2010.
2. Jorge A. Tavel, et.al. Effects of Intermittent IL-2 Alone or with Peri-Cycle Antiretroviral Therapy in Early HIV Infection: The STALWART Study. PLoS One. 2010; 5(2): e9334. Published online Feb 23, 2010.
3. McEvoy GK, ed. AHFS 2011 Drug Information. Bethesda, MD: American Society of Health-Systems Pharmacists, Inc; 2011.
4. NCCN Drugs & Biologics Compendium™. Proleukin® (aldesleukin). Copyright 2011, National Comprehensive Cancer Network (NCCN).
5. Pautas, C., et.al. Randomized Study of Intensified Anthracycline Doses for Induction and Recombinant Interleukin-2 for Maintenance in Patients With Acute Myeloid Leukemia Age 50 to 70 Years: Results of the ALFA-9801 Study. 2010 by American Society of Clinical Oncology.

Policy History

Pre-Merger Organizations	Last Review Date	Policy Number	Title
CIGNA HealthCare Great-West Healthcare	3/15/2008	6102	Aldesleukin (Proleukin®)

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