



# CIGNA MEDICAL COVERAGE POLICY

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

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Coverage Policy Number ..... 6008

Subject **Sargramostim (Leukine®)**

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## Hyperlink to Related Coverage Policies

### 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. In certain markets, delegated vendor guidelines may be used to support medical necessity and other coverage determinations. Proprietary information of CIGNA. Copyright ©2011 CIGNA

## Coverage Policy

**CIGNA covers sargramostim (Leukine®) as medically necessary for treatment of ANY of the following indications:**

- acute myelogenous leukemia (AML) following induction chemotherapy in an adult 55 years of age and older
- mobilization of hematopoietic progenitor cells into peripheral blood for collection by leukapheresis
- acceleration of myeloid recovery in an individual with non-Hodgkin's lymphoma (NHL), acute lymphoblastic leukemia (ALL) or Hodgkin's disease undergoing autologous bone marrow transplantation (BMT)
- acceleration of myeloid recovery in an individual undergoing allogeneic BMT from HLA-matched related donors
- allogeneic or autologous bone marrow transplantation (BMT) when engraftment is delayed or has failed
- chemotherapy-induced febrile neutropenia in an individual who has been receiving prophylactic filgrastim or sargramostim or who has not received prophylactic colony-stimulating factors but who has risk factors for an infection-related complication

**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 sargramostim (Leukine®) therapy.**

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## **FDA Approved Indications**

### **Use Following Induction Chemotherapy in Acute Myelogenous Leukemia (AML)**

Leukine is indicated for use following induction chemotherapy in older adult patients with AML to shorten time to neutrophil recovery and to reduce the incidence of severe and life-threatening infections and infections resulting in death. The safety and efficacy of Leukine have not been assessed in patients with AML under the age of 55 years.

### **Mobilization and Engraftment of Peripheral Blood Progenitor Cells**

Leukine is indicated for the mobilization of hematopoietic progenitor cells into peripheral blood for collection by leukapheresis. Mobilization allows for the collection of increased numbers of progenitor cells capable of engraftment as compared with collection without mobilization. After myeloablative chemotherapy, the transplantation of an increased number of progenitor cells can lead to more rapid engraftment, which may result in a decreased need for supportive care. Myeloid reconstitution is further accelerated by administration of Leukine following peripheral blood progenitor cell transplantation.

### **Autologous Bone Marrow Transplantation**

Leukine is indicated for acceleration of myeloid recovery in patients with non-Hodgkin's lymphoma (NHL), acute lymphoblastic leukemia (ALL) and Hodgkin's disease undergoing autologous bone marrow transplantation (BMT). After autologous BMT in patients with NHL, ALL, or Hodgkin's disease, Leukine has been found to be safe and effective in accelerating myeloid engraftment, decreasing median duration of antibiotic administration, reducing the median duration of infectious episodes and shortening the median duration of hospitalization. Hematologic response to Leukine can be detected by complete blood count (CBC) with differential cell counts performed twice per week.

### **Allogeneic Bone Marrow Transplantation**

Leukine is indicated for acceleration of myeloid recovery in patients undergoing allogeneic BMT from HLA-matched related donors. Leukine has been found to be safe and effective in accelerating myeloid engraftment, reducing the incidence of bacteremia and other culture positive infections, and shortening the median duration of hospitalization.

### **Bone Marrow Transplantation Failure or Engraftment Delay**

Leukine is indicated in patients who have undergone allogeneic or autologous bone marrow transplantation (BMT) in whom engraftment is delayed or has failed. Leukine has been found to be safe and effective in prolonging survival of patients who are experiencing graft failure or engraftment delay, in the presence or absence of infection, following autologous or allogeneic BMT. Survival benefit may be relatively greater in those patients who demonstrate one or more of the following characteristics: autologous BMT failure or engraftment delay, no previous total body irradiation, malignancy other than leukemia or a multiple organ failure (MOF) score  $\leq$ two. Hematologic response to Leukine can be detected by complete blood count (CBC) with differential performed twice per week.

## **FDA Recommended Dosing**

### **Neutrophil Recovery Following Chemotherapy in AML**

The recommended dose is 250mcg/m<sup>2</sup>/day administered intravenously over a 4 hour period starting approximately on day 11 or four days following the completion of induction chemotherapy, if the day 10 bone marrow is hypoplastic with <5% blasts. If a second cycle of induction chemotherapy is necessary, Leukine should be administered approximately four days after the completion of chemotherapy if the bone marrow is hypoplastic with <5% blasts. Leukine should be continued until an ANC >1500 cells/mm<sup>3</sup> for 3 consecutive days or a maximum of 42 days. Leukine should be discontinued immediately if leukemic regrowth occurs. If a severe adverse reaction occurs, the dose can be reduced by 50% or temporarily discontinued until the reaction abates. In order to avoid potential complications of excessive leukocytosis a CBC with differential is recommended twice per week during Leukine therapy. Leukine treatment should be interrupted or the dose reduced by half if the ANC exceeds 20,000 cells/mm<sup>3</sup>.

### **Mobilization of Peripheral Blood Progenitor Cells**

The recommended dose of sargramostim is 250 mcg/m<sup>2</sup>/day given by continuous IV infusion over 24 hours or by subcutaneous injection once daily. This same dose should be continued throughout the period of PBPC collection. The optimal schedule for PBPC collection has not been established; however, in clinical studies, PBPC collection was usually started by day five and performed daily until protocol-specified targets were achieved. Sargramostim dosage should be reduced by 50% if WBC > 50,000 cells/mm<sup>3</sup>. Other mobilization therapy should be considered if adequate numbers of progenitor cells are not collected.

### **Autologous or Allogeneic Bone Marrow Transplantation**

The recommended dose of sargramostim is 250 mcg/m<sup>2</sup>/day given once daily by IV infusion over a two-hour period beginning two to four hours after bone marrow infusion, and not less than 24 hours after the last dose of chemotherapy or radiotherapy. Sargramostim therapy should not be initiated until the post-marrow infusion ANC is less than 500 cells/mm<sup>3</sup> and should be continued until the ANC is greater than 1500 cells/mm<sup>3</sup> for three consecutive days.

### **Bone Marrow Transplantation Failure or Engraftment Delay**

The recommended dose of sargramostim is 250 mcg/m<sup>2</sup>/day given once daily for 14 days as an IV infusion given over two hours. The dose can be repeated after seven days off therapy if engraftment has not occurred. If engraftment still has not occurred after the second course of therapy, a third course of 500 mcg/m<sup>2</sup>/day for 14 days can be tried after another seven days off therapy. If no improvement is observed after the third course of sargramostim therapy, it is unlikely that further dose escalation will be beneficial.

### **Post-Peripheral Blood Progenitor Cell Transplantation**

The recommended dose of sargramostim is 250 mcg/m<sup>2</sup>/day given by continuous IV infusion over 24 hours or by subcutaneous injection once daily beginning immediately following infusion of PBPC and continuing until an ANC > 1500 cells/mm<sup>3</sup> for three consecutive days is achieved.

### **Drug Availability**

Liquid Leukine is available in vials containing 500 mcg/mL (2.8 x 10<sup>6</sup> IU/mL) sargramostim. Lyophilized Leukine is available in vials containing 250 mcg (1.4 x 10<sup>6</sup> IU/vial) sargramostim. Each dosage form is supplied as follows: Lyophilized Leukine - carton of five vials of lyophilized Leukine 250 mcg. Liquid Leukine - carton of one multiple-use vial; each vial contains 1 mL of preserved 500 mcg/mL liquid Leukine - carton of five multiple-use vials; each vial contains 1 mL of preserved 500 mcg/mL liquid Leukine.

### **General Background**

#### **Pharmacology**

Sargramostim, a recombinant human granulocyte-macrophage colony stimulating factor (GM-CSF), is a biosynthetic hematopoietic growth factor that stimulates the proliferation and differentiation of a variety of hematopoietic progenitor cells. It principally influences leukopoiesis. GM-CSF is a multilineage colony-stimulating factor that principally affects the proliferation, differentiation, and activation of granulocytes and macrophages by inducing partially committed progenitor cells to divide and differentiate in the granulocyte-macrophage pathways which include: neutrophils, monocytes/macrophages, and myeloid-derived dendritic cells. GM-CSF also enhances certain functions of mature neutrophils and monocytes, including chemotaxis, phagocytosis, and antibody-dependent cellular cytotoxicity (ADCC).

Sargramostim can be administered intravenously or subcutaneously. Sargramostim is rapidly absorbed following subcutaneous injection; it is detected in the serum within five minutes, and peak serum concentrations generally are attained within 1–3 hours following rapid subcutaneous injection. The elimination half-life of sargramostim is approximately one hour for intravenous administration (two-hour infusion) and approximately three hours for subcutaneous administration.

#### **Guidelines**

The National Comprehensive Cancer Network (NCCN) recommends Leukine as follows:

## Chemotherapy Induced Neutropenia

### Grade 2A

Treatment of chemotherapy-induced febrile neutropenia in patients who have been receiving prophylactic filgrastim or sargramostim or who have not received prophylactic colony-stimulating factors but who have risk factors for an infection-related complication.

### Adverse Reactions

There are relatively few side effects directly associated with sargramostim, and it is generally well-tolerated. Side effects reported include: capillary leak syndrome, fluid retention, peripheral edema, pleural and/or pericardial effusion, fever, asthenia, chills, diarrhea, excessive leukocytosis, shortness of breath, myalgia, bone pain, headache, skin rash, itching, and redness or pain at site of subcutaneous injection.

Interactions between sargramostim and other drugs have not been fully evaluated. Therefore, drugs which may potentiate the myeloproliferative effects of sargramostim, such as corticosteroids and lithium, should be used with caution. Sargramostim should not be used concomitantly with, or within 24 hours preceding or following, cytotoxic chemotherapy or radiotherapy because of the potential sensitivity of rapidly dividing hematopoietic progenitor cells.

Sargramostim is contraindicated in the following situations: for concomitant use with chemotherapy and radiotherapy; in patients with known hypersensitivity to GM-CSF, yeast-derived products, or any component of the product; in patients with excessive leukemic myeloid blasts in the bone marrow or peripheral blood ( $\geq 10\%$ ). Sargramostim injection containing 1.1% benzyl alcohol and sargramostim lyophilized powder that is reconstituted with bacteriostatic water for injection containing 0.9% benzyl alcohol should not be administered to neonates because benzyl alcohol has been reported to be associated with a fatal "Gasping Syndrome" in premature infants. Sargramostim should be used with caution in patients with preexisting fluid retention, pulmonary infiltrates, or congestive heart failure because edema, capillary leak syndrome, and pleural and/or pericardial effusion have been reported in patients after sargramostim administration. Sargramostim should be used with caution in patients with preexisting lung disease and/or hypoxia because sequestration of granulocytes in the pulmonary circulation and dyspnea have been reported in patients treated with sargramostim. Sargramostim should also be used with caution in patients with preexisting cardiac disease because occasional transient, reversible, supraventricular arrhythmia has been reported in some patients receiving sargramostim. Although a direct causal relationship has not been established, the manufacturer recommends that renal and/or hepatic function be monitored every other week when sargramostim is used in patients with preexisting renal and/or hepatic dysfunction because sargramostim has induced elevation of serum creatinine or bilirubin and hepatic enzymes in these patients.

Following the first administration of sargramostim in a particular cycle, a syndrome characterized by respiratory distress, hypoxia, hypotension, flushing, syncope, and/or tachycardia has been reported. These signs resolve with symptomatic treatment and usually do not recur with subsequent doses in the same cycle of treatment. Complete blood cell counts (CBCs) with differential should be performed twice weekly during sargramostim therapy to avoid the potential complications of excessive leukocytosis and/or thrombocytosis. If the absolute neutrophil count (ANC) exceeds 20,000 cells/mm<sup>3</sup> or if the platelet count exceeds 500,000/mm<sup>3</sup>, sargramostim therapy should be temporarily discontinued or the dosage reduced by half. Excessive blood cell counts usually return to normal or baseline levels within three to seven days after sargramostim therapy is stopped.

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## Coding/Billing Information

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

**Covered when medically necessary:**

HCPSC Codes	Description
J2820	Injection, sargramostim (GM-CSF), 50 mcg

ICD-9-CM	Description
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<b>Diagnosis Codes</b>	
200.00-200.88	Non-Hodgkin's lymphoma
201.00-201.98	Hodgkin's disease
202.00-202.28	Non-Hodgkin's lymphoma
202.80-202.88	Non-Hodgkin's lymphoma
204.0	Acute lymphoblastic leukemia (ALL)
205.0	Acute myeloid leukemia (AML)
996.85	Complications of bone marrow transplant
V10.61	Personal history of lymphoid leukemia
V10.62	Personal history of myeloid leukemia
V10.72	Personal history of Hodgkin's disease
V42.81	Bone marrow replaced by transplant
V42.82	Peripheral stem cells replaced by transplant

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## References

1. Bayer Healthcare Pharmaceuticals. Sargramostim (Leukine®) injection package insert. Seattle, WA: Bayer Healthcare Pharmaceuticals. July 2009.
2. Facts and Comparisons 4.0. Sargramostim. St. Louis (MO): Facts and Comparisons, 2011. Available from: <http://online.factsandcomparisons.com/>
3. Korzenik JR, Dieckgraefe BK, Valentine JF, Hausman DF, Gilbert MJ. Sargramostim for active Crohn's disease. *New England Journal of Medicine*. 2005 May 26; 352(21):2193-201.
4. McEvoy GK, ed. AHFS 2011 Drug Information. Bethesda, MD: American Society of Health-Systems Pharmacists, Inc. 2011.
5. NCCN Drugs & Biologics Compendium™. Leukine® (sargramostim). Copyright 2011, National Comprehensive Cancer Network (NCCN).
6. Sandborn WJ. What's new: innovative concepts in inflammatory bowel disease. *Colorectal Dis*. 2006 May;8 Suppl 1:3-9.

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## Policy History

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<b>Pre-Merger Organizations</b>	<b>Last Review Date</b>	<b>Policy Number</b>	<b>Title</b>
CIGNA HealthCare Great-West Healthcare	8/15/2008	6008	Sargramostim (Leukine <sup>®</sup> )

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