BACKGROUND

Leukine is a recombinant human granulocyte macrophage colony stimulating factor (rhu GM-CSF) and is a hematopoietic growth factor which stimulates proliferation and differentiation of hematopoietic progenitor cells. GM-CSF induces partially committed progenitor cells to divide and differentiate in the granulocyte-macrophage pathways which include neutrophils, monocytes/macrophages, and myeloid-derived dendritic cells. Leukine is indicated for the following: 1) for use following induction chemotherapy in older adult patients with acute myelogenous leukemia (AML); 2) for the mobilization and following transplantation of autologous peripheral blood progenitor cells; 3) for use in myeloid reconstitution after autologous bone marrow transplantation; 4) for use in myeloid reconstitution after allogeneic bone marrow transplantation; and 5) use in bone marrow transplantation failure or engraftment delay.

Leukine is available as a liquid and as a lyophilized powder. Benzyl alcohol is a constituent of liquid sargramostim and Bacteriostatic Water for Injection diluent. Benzyl alcohol has been associated with a fatal “Gasing Syndrome” in premature infants and should not be given to neonates. Lyophilized Leukine is available in vials containing 250 mcg (1.4 x 10⁶ IU/vial) of Leukine in a carton of five vials. Lyophilized Leukine should be reconstituted with 1 mL Sterile Water for Injection, USP, or 1 mL Bacteriostatic Water for Injection, USP. Liquid Leukine is available in vials containing 500 mcg/mL (2.8 x 10⁶ IU/mL) in a carton of one multiple use vial or five multiple-use vials. Either preparation can be given by subcutaneous (SC) injection or intravenous (IV) infusion.

REQUIRED REVIEW AND APPROVALS

This policy involves the use of Leukine. Prior authorization is recommended for medical benefit coverage of Leukine. Coverage is recommended for those who meet the conditions of coverage in the Criteria, Dosing, Initial/Extended Approval, Duration of Therapy, and Labs/Diagnostics for the diagnosis provided. The requirement that the patient meet the Criteria for coverage of the requested medication applies to the initial authorization only. Waste Management applies for all covered conditions. Conditions Not Recommended for Approval are listed following the recommended authorization criteria and Waste Management section.

Because of the of the specialized skills required for evaluation and diagnosis of patients treated with Leukine as well as the monitoring required for adverse events and long-term efficacy, initial
approval requires Leukine to be prescribed by or in consultation with a physician who specializes in the condition being treated. All approvals for initial therapy are provided for the initial approval duration noted below; if reauthorization is required, a response to therapy is required for continuation of therapy.

DEFINITIONS
None.

INDICATIONS/Criteria
Coverage of Leukine is recommended in those who meet one of the following criteria:

FOOD AND DRUG ADMINISTRATION (FDA)-APPROVED INDICATIONS

1. Acute Myelogenous Leukemia (AML).

Criteria. Patient must meet the following criteria: Leukine is prescribed by, or in consultation with, an oncologist or hematologist.

Leukine is indicated for use following induction chemotherapy in older 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.¹ In the professional opinion of specialist physicians reviewing the data, we have adopted these criteria.

Dosing in AML: Dosing must meet the following: The dose is 250 mcg/m² per day given IV over a 4-hour period. The dose should start after the completion of induction chemotherapy.¹ Additional doses of induction chemotherapy may be needed. Consolidation chemotherapy may follow with Leukine being given after completion of chemotherapy.

Initial Approval/Extended Approval.
A) Initial Approval. Initial approval is for up to 6 months.
B) Extended Approval. Extended approval is for up to 6 months.

Duration of Therapy in AML. Therapy may be continued as long as the patient is on chemotherapy.

Labs/Diagnostics. None required.
2. **Peripheral Blood Progenitor Cell (PBPC) Collection in Patients with Cancer (Adults and Children) or Patients with Cancer (Adults and Children) who have Received Therapy with PBPC (Autologous):**

**Criteria.**  *Patient must meet the following criteria:* Leukine is prescribed by, or in consultation with, an oncologist, a hematologist, or a physician that specializes in transplantation.

Leukine is indicated for the mobilization of hematopoietic progenitor cells into peripheral blood for collection by leukapheresis. Mobilization allows for the collection of increased number of progenitor cells capable of engraftment as compared with collection without mobilization. Following myeloablative chemotherapy, the transplantation of an increased number of progenitor cells can result to more rapid engraftment, which may decrease the need for supportive care.

In the professional opinion of specialist physicians reviewing the data, we have adopted these criteria.

**Dosing in Patients with Cancer Undergoing Mobilization of PBPC:**  *Dosing must meet the following (A OR B):*  
A) 250 to 500 mcg/m² per day administered IV over 24 hours or SC once daily; OR  
B) 7.5 mcg/kg SC once daily.

**Dosing in Patients with Cancer Post PBPC Transplantation (Autologous):**  *Dosing must meet the following (A OR B):*  
A) 250 mcg/m² per day administered IV over 24 hours or SC once daily; OR  
B) 7.5 mcg/kg once daily SC.

Dosing should continue at the same dose through the period of PBPC collection. Leukine has been used as a single agent, as well as with Neupogen® (filgrastim injection); Leukine was administered as 7.5 mcg/kg SC in the evening while Neupogen was administered in the morning. The optimal schedule for PBPC collection has not been established. Collection of PBPC is usually begun by Day 5 and performed daily until protocol specified targets were achieved. Exceptions may be made based upon transplant-center protocols.

**Initial Approval/Extended Approval.**

- **Patients with Cancer Undergoing Mobilization of PBPC:**  
  A) *Initial Approval.* Initial approval is for 5 to 7 days. Exceptions may be made based upon transplant center protocols.  
  B) *Extended Approval.* Not applicable.

- **Patients with Cancer Post PBPC Transplantation (Autologous):**  
  A) *Initial Approval.* Initial approval is for 14 days or until the absolute neutrophil count (ANC) is > 1,500 cells/mm³ for 3 consecutive days. Exceptions may be made based upon transplant center protocols.
B) **Extended Approval.** Approve for an additional 14 days if ANC is not at a sustainable level (> 1,500 cells/m³ for 3 consecutive days). Exceptions may be made based upon transplant center protocols.

**Duration of Therapy in PBPC:**

- **Patients with Cancer Undergoing Mobilization of PBPC:** 5 days. Exceptions may be made based upon transplant center protocols.
- **Patients with Cancer post PBPC Transplantation (Autologous):** 14 days. Approve for another 14 days if the ANC is not at a sustainable level according to the prescribing physician. Most patients have a response after 28 days.¹

**Labs/Diagnostics.** None required.

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3. **Bone Marrow Transplantation (BMT).** For the FDA-approved indication¹ in autologous BMT; allogeneic BMT from a Human Leukocyte Antigen (HLA)-Matched Related Donors; and for BMT failure or engraftment delay in patients who have undergone allogeneic or autologous BMT, forward to the Medical Director for review. Coverage criteria are not addressed in this document but will be considered on a case-by-case basis.

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**Other Uses with Supportive Evidence**

4. **Patients with Cancer Receiving Myelosuppressive Chemotherapy.**

**Criteria.** *The patient must meet the following criteria (A AND B):*

A) The agent is prescribed by, or in consultation with, an oncologist or hematologist; AND

B) The patient meets ONE of the following conditions (i, ii, iii, or iv):

i. The patient is receiving myelosuppressive anti-cancer medications that are associated with a high risk of febrile neutropenia (the risk of febrile neutropenia is at least 20% based on the chemotherapy regimen); OR

ii. The patient is receiving myelosuppressive anti-cancer medications that are associated with a risk of febrile neutropenia but the risk is less than 20% based on the chemotherapy regimen and the patient has one or more risk factors for febrile neutropenia according to the prescribing physician (e.g., older patient [aged ≥ 65 years]; history of previous chemotherapy or radiation therapy; pre-existing neutropenia; open wounds or active infection; poor performance status); OR

iii. The patient has had a neutropenic complication from prior chemotherapy and did not receive prophylaxis with a colony stimulating factor (Neupogen® [filgrastim injection], Zarxio™ [filgrastim-sndz injection], Neulasta® [pegfilgrastim injection], Granix™ [tbo-filgrastim injection], Leukine) and a reduced dose or frequency of chemotherapy may compromise treatment outcome; OR
iv. The patient who has received chemotherapy has febrile neutropenia and has at least one risk factor for poor clinical outcomes or for developing infection-associated complications according to the prescribing physician\(^3\)\(^4\) (e.g., neutropenia expected to be \(> 10\) days in duration; severe neutropenia [ANC \(< 100\) cells/mm\(^3\)]; age greater than 65 years; prior episode of febrile neutropenia; invasive fungal infection, and other clinically documented infections).

The National Comprehensive Cancer Network (NCCN) guidelines for myeloid growth factors (version 2.2014), recommends use of CSFs in various scenarios in patients with cancer receiving myelosuppressive chemotherapy.\(^3\) In the professional opinion of specialist physicians reviewing the data, we have adopted these criteria.

**Dosing in Patients with Cancer Receiving Myelosuppressive Chemotherapy.** *Dosing must meet the following:* The dose is 250 mcg/m\(^2\) per day by SC injection.\(^3\)

According to the NCCN guidelines for myeloid growth factors (version 2.2014), Leukine therapy starts the next day up to 3 to 4 days after the completion of chemotherapy and is treated through post-nadir recovery.\(^3\) Because the duration of neutropenia often increases with each cycle of chemotherapy, longer periods of Leukine therapy may be required for later chemotherapy cycles than for early cycles.

**Initial Approval/Extended Approval.**
A) *Initial Approval.* Approve for up to 6 months.
B) *Extended Approval.* Approve at 6-month intervals if the patient continues to receive myelosuppressive chemotherapy.

**Duration of Therapy in Patients with Cancer Receiving Myelosuppressive Chemotherapy.** Therapy may be continued as long as the patient is receiving myelosuppressive chemotherapy.

**Labs/Diagnostics.** None required.

5. **Treatment of Myelodysplastic Syndrome (MDS) in Adults.**

**Criteria.** *The patient must meet the following criteria:* Leukine is prescribed by, or in consultation with, an oncologist or hematologist.

Leukine is recommended in NCCN guidelines for MDS (version 1.2016) for use in selected patients (e.g., those with recurrent or resistant infections in neutropenic patients, combination use with Epogen\(^9\)/Procrit\(^8\) [epoetin alfa injection]).\(^5\) This criterion is recommended based on the professional opinion of specialized and other physicians.
Dosing in MDS in Adults. *Dosing must meet ONE of the following (A, B OR C):*

A) Leukine 15 to 500 mcg/m² once daily by IV infusion over 1 to 12 hours; OR
B) Leukine 30 to 500 mcg/m² given by continuous IV infusion over 24 hours; OR
C) Leukine 125 to 250 mcg/m² SC once daily.

Initial Approval/Extended Approval.

A) *Initial Approval.* Approve at 3-month intervals.

B) *Extended Approval.* Approve at 3-month intervals.

Duration of Therapy in MDS in Adults. Therapy is usually intermittent.

Labs/Diagnostics. None required.

6. **Radiation Syndrome (Hematopoietic Syndrome of Acute Radiation Syndrome).**

Criteria. *The patient must meet the following criteria:* Leukine is prescribed by, or in consultation with, a physician with expertise in treating acute radiation syndrome.

The Strategic National Stockpile Radiation Working Group published recommendations for the medical management of acute radiation syndrome in 2004. In any adult with a whole body or significant partial body exposure greater than 3 Grays, therapy with a CSF should be started as soon as biodosimetry results indicate that exposure has occurred or when clinical signs and symptoms indicate a level 3 or 4 degree of hematotoxicity. People at the extremes of age (children < 12 years of age and adults > 60 years of age) may be more susceptible to irradiation and therefore a lower threshold exposure dose (2 Grays) for initiation of CSF therapy is appropriate, as well as in patients who have major trauma injuries or burns. The Radiation Injury Treatment Network updated guidelines in September 2010 for the treatment of acute radiation syndrome (injury). CSF therapy is recommended in a variety of clinical scenarios in patients who have experienced radiation injury (syndrome) based on factors such as the radiation dose. This criterion is recommended based on the professional opinion of specialized and other physicians.

**Dosing in Radiation Syndrome (Hematopoietic Syndrome of Acute Radiation Syndrome):** *Dosing must meet the following:* 250 mcg/m² SC once daily.

Initial Approval/Extended Approval.

A) *Initial Approval.* Approve for 1-month.

B) *Extended Approval.* Approve at 1-month intervals.

Duration of Therapy in Radiation Syndrome (Hematopoietic Syndrome of Acute Radiation Syndrome). Usually only one course of Leukine is needed until the ANC is adequate.
Labs/Diagnostics. None required.

7. **Pediatric Patients with High-Risk Neuroblastoma.**

**Criteria.** *Patient must meet the following criteria (A AND B):*

A) The agent is prescribed by, or in consultation with, an oncologist; AND
B) The patient is receiving Leukine in a regimen with Unituxin™ (dinutuximab injection for intravenous use).

Unituxin is indicated for use in combination with GM-CSF, interleukin-2 (IL-2), and 13-cis-retinoic acid for the treatment of pediatric patients with high-risk neuroblastoma who achieve at least a partial response to first-line, multiagent, multimodality therapy.

**Dosing in Pediatric Patients with High-Risk Neuroblastoma:** *Dosing must meet the following:* The dose is 250 mcg/m² per day by SC injection or IV infusion administered over 2 hours.

According to the Unituxin prescribing information, Leukine 250 mcg/m² per day is given by SC injection (recommended) or by IV infusion over 2 hours for 14 continuous days of a 28-day cycle during Cycles 1, 3, and 5.

**Initial Approval/Extended Approval.**

A) *Initial Approval.* Approve for up to 6 months.
B) *Extended Approval.* Approve at 6-month intervals.

**Duration of Therapy in Pediatric Patients with High-Risk Neuroblastoma.** For most circumstances, Leukine therapy would be given in Cycles 1, 3, and 5 for 14 days of 28 day cycles for a total of six cycles.

Labs/Diagnostics. None required.

**Waste Management for All Indications.**

Vials contain 250 mcg or 500 mcg. Use the lowest amount of Leukine possible to achieve the dose required.

**SPECIAL CONSIDERATIONS**

Leukine has not been shown to be effective, or there are limited or preliminary data or potential safety concerns that are not supportive of general approval for the following conditions. Rationale for non-coverage for these specific conditions is provided below. (Note: This is not an exhaustive list of Conditions Not Recommended for Approval.)
1. Coverage is not recommended for circumstances not listed in the *Recommended Authorization Criteria*. Criteria will be updated as new published data are available.

**LIMITATIONS/EXCLUSIONS**

Please refer to a product line’s certificate of coverage for benefit limitations and exclusions for these services:

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