Department:	Pharmacy Management	**Original Approval:**	01/20/2016
Policy #:	PM130	**Last Approval:**	12/12/2018
Title:	Sargramostim (Leukine®)		
Approved By:	UM Committee		

REQUIRED CLINICAL DOCUMENTATION FOR REVIEW.

Documentation required to determine medical necessity for Sargramostim (Leukine): History and/or physical examination notes and relevant specialty consultation notes that address the problem and need for the service: -Diagnosis -Prescribed by or in consultation with an oncologist, hematologist or transplant specialist -Weight -Height -Dosing and duration requested -Medication list (current and past) to include start and end dates of all chemotherapy regimens.

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.[1] 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) to shorten the time to neutrophil recovery and to reduce the incidence of severe, life-threatening, or fatal infections following induction chemotherapy in adult patients ≥ 55 years of age older adult patients with acute myelogenous leukemia (AML); 2) in adult patients with cancer undergoing autologous hematopoietic stem cell transplantation for the mobilization of hematopoietic progenitor cells into peripheral blood for collection by leukapheresis; 3) for the acceleration of myeloid reconstitution after autologous peripheral blood progenitor cell or bone marrow transplantation in adult and pediatric patients 2 years of age and older with non-Hodgkin's lymphoma, acute lymphoblastic leukemia, and Hodgkin's lymphoma; 4) for acceleration of myeloid reconstitution in adult and pediatric patients ≥ 2 years of age undergoing allogeneic bone marrow transplantation from HLA-matched related donors; 5) for the treatment of adult and pediatric patients ≥ 2 years of age who have undergone allogeneic or autologous bone marrow transplantation in whom neutrophil recovery is delayed or failed; and 6) to increase survival in adult and pediatric patients from birth to 17 years of age acutely exposed to myelosuppressive doses of radiation (hematopoietic syndrome of acute radiation syndrome).[1] Leukine is given as a subcutaneous or intravenous injection.

Leukine is supplied in a carton containing 250 mcg single-dose vials. It is also available as one 500 mcg/mL multiple-dose vial and a carton containing five 500 mcg/mL multiple-dose vials. Store Leukine vials refrigerated at 2º to 8ºC (36º to 46ºF) in the original carton to protect from light. Leukine contains benzyl alcohol, which has been associated with gasping syndrome in neonates and infants. The preservative benzyl alcohol can cause serious adverse reactions and death when given intravenously to neonates and infants.

DEFINITIONS

None.

INDICATIONS/CRITERIA

Medicaid Members	Leukine is not preferred on the WA HCA Single Preferred Drug list. ***Continue to criteria for approval below.***
Medicare Members	***Step-utilization of Part D drugs not required.***

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

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 to shorten time to neutrophil recovery and to reduce the incidence of severe, life-threatening or fatal infections following induction chemotherapy adult patients ≥ 55 years of age with AML.[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/m^2 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 in adult patients with cancer undergoing autologous hematopoietic stem cell transplantation 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 myeloabalative chemotherapy, the

transplantation of an increased number of progenitor cells can result to more rapid engraftment, which may decrease the need for supportive care.[1-2]

Dosing in Patients with Cancer Undergoing Mobilization of PBPC: *Dosing must meet the following (A OR B)*:[1-2]

A) 250 to 500 mcg/m^2 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/m^2 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.[2,10] 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/mm^3 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/m^3 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.

3. Bone Marrow Transplantation (BMT). For the FDA-approved indication[1] 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.

4. 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.

Leukine is indicated to increase survival in adult and pediatric patients from birth to 17 years of age acutely exposed to myelosuppressive doses of radiation (Hematopoietic Syndrome of Acute Radiation Syndrome).[1] Administer Leukine as soon as possible after suspected or confirmed exposure to radiation doses > 2 gray (Gy).

Dosing in Radiation Syndrome (Hematopoietic Syndrome of Acute Radiation Syndrome): *Dosing must meet ONE the following **(A, B, OR C):***[1]

A) 7 mcg/kg in adult and pediatric patients > 40 kg; OR
B) 10 mcg/kg in pediatric patients ≥ 15 kg to ≤ 40 kg; OR
C) 12 mcg/kg in pediatric patients < 15 kg.

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.

Other Uses with Supportive Evidence

5. 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., aged ≥ 65 years; prior chemotherapy or radiation therapy; persistent neutropenia; bone marrow involvement by tumor; recent surgery and/or open wounds; liver and/or renal dysfunction; poor performance status; or human immunodeficiency virus [HIV] infection); OR
- **iii.** The patient has had a neutropenic complication from prior chemotherapy and did not receive prophylaxis with a colony stimulating factor (e.g., filgrastim products [Neupogen,

Zarxio, Granix, Nivestym], pegfilgrastim products [Neulasta, Fulphila], 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 **2.2018**), recommends use of CSFs in various scenarios in patients with cancer receiving myelosuppressive chemotherapy.[3] It is notable that Leukine has been removed from the list of prophylactic options based on limited use.

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 **2.2018**), 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.

6. 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 1.2019) for use in selected patients (e.g., those with recurrent or resistant infections in neutropenic patients, combination use with 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/m^2 once daily by IV infusion over 1 to 12 hours[6]; OR
B) Leukine 30 to 500 mcg/m^2 given by continuous IV infusion over 24 hours[6]; OR
C) Leukine 125 to 250 mcg/m^2 SC once daily.[7]

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.

7. Pediatric Patients with High-Risk Neuroblastoma.[11]

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.[11]

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

According to the Unitixin prescribing information, Leukine 250 mcg/m^2 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.

Conditions Not Recommended for Approval

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.

Coverage is not recommended for circumstances *not* listed in the *Recommended Authorization Criteria*. Criteria will be updated as new published data are available.

SPECIAL CONSIDERATIONS

None.

LIMITATIONS/EXCLUSIONS

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

PRODUCT LINE	LINK TO CERTIFICATE OF COVERAGE
MEDICARE ADVANTAGE	http://healthfirst.chpw.org/for-members/resource-library/handbooks-and-guides
WASHINGTON APPLE HEALTH	http://chpw.org/our-plans/apple-health/
INTEGRATED MANAGED CARE	http://chpw.org/our-plans/apple-health/

Citations & References

References

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2. Pusic I, DiPersio JF. The use of growth factors in hematopoietic stem cell transplantation. *Curr Pharm Des.* 2008;14(20):1950-1961.
3. The NCCN Myeloid Growth Factors Clinical Practice Guidelines in Oncology (Version 1.2018 – March 2, 2018). ® 2018 National Comprehensive Cancer Network, Inc. Available at: http://www.nccn.org. Accessed on July 24, 2018.
4. Smith TJ, Bohlke K, Lyman GH, Carson KR, et al. Recommendations for the use of WBC growth factors: American Society of Clinical Oncology Clinical Practice Guideline Update. *J Clin Oncol*. 2015;33(28):3199-3212. Available at: http://jco.ascopubs.org/content/early/2015/07/08/JCO.2015.62.3488.full.pdf+html Accessed on July 30, 2018.

5. The NCCN Myelodysplastic Syndromes Clinical Practice Guidelines in Oncology (Version 1.2019 – July 16, 2018). ® 2018 National Comprehensive Cancer Network, Inc. Available at: http://www.nccn.org. Accessed on July 30, 2018.
6. Sargramostim. American Hospital Formulary Service Drug Information®. Bethesda, MD: American Society of Health-System Pharmacists. 2013:1581-1590.
7. Gradishar WJ, LeBeau MM, O'Laughlin R, et al. Clinical and cytogenetic responses to granulocyte-macrophage colony-stimulating factor in therapy-related myelodysplasia. *Blood*. 1992;80(10):2463-2470.
8. Waselenko JK, MacVittie TJ, Bladely WF, et al. Medical management of the acute radiation syndrome: recommendations of the strategic national stockpile radiation working group. *Ann Intern Med*. 2004;140:1037-1051.
9. Radiation Injury Treatment Network (RITN). Acute Radiation Syndrome Treatment Guidelines. March 2016. Available at: https://ritn.net/treatment/. Accessed on July 30, 2018.
10. Lonial S, Akhtari M, Kaufman J, et al. Mobilization of haemtopoietic progenitors from normal donors using the combination of granulocyte-macrophage colony-stimulating factor and granulocyte colony-stimulating factor results in fewer plasmacytoid dendritic cells in the graft and enhanced donor T cell engraftment with Th1 polarization: results from a randomized clinical trial. *Biol Blood Marrow Transplant*. 2013;19:460-467.
11. Unituxin™ injection for intravenous use [prescribing information]. Silver Springs, MD: United Therapeutic Corporation; March 2017.

OTHER REFERENCES UTILIZED

- The NCCN Acute Myeloid Leukemia Clinical Practice Guidelines in Oncology (Version 1.2018). ® 2018 National Comprehensive Cancer Network, Inc. Available at: http://www.nccn.org. Accessed on July 30, 2018.
- DiCarlo AL, Maher C, Hick JL, et al. Radiation injury after a nuclear detonation: medical consequences and the need for scarce resources allocation. *Diaster Med Public Health Prep*. 2011;5 Suppl 1:S32-S44.
- Singh VK, Newman VL, Seed TM. Colony-stimulating factors for the treatment of the hematopoietic component of the acute radiation syndrome (H-ARS): a review. *Cytokine*. 2015;71:22-37.

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CFR		
WAC	WAC 284-43-2050	
RCW		
Contract Citation	☐ WAH	
	☐ IMC	
	☐ MA	
Other Requirements		
NCQA Elements		

Revision History

Revision Date	Revision Description	Revision Made By
01/13/2016	New	Kelly Force; Yusuf Rashid, RPh
01/20/2016	Approval	MMLT
01/12/2017	No revisions	Fran McGaugh
01/13/2017	Approval	MMLT
07/24/2017	Criteria completely updated and revised	Michael Sporck, Pharmacy Intern Sophia Yun, PharmD
07/25/2017	Approved	MMLT
03/09/2018	Reassigned from UM141 to PM130	Cindy Bush
04/27/2018	Transferred to new template	Cindy Bush
05/25/2018	No revisions	Jennifer Farley, PharmD
06/14/2018	Approval	Cindy Bush
11/27/2018	Revised from ESI annual update	Jennifer Farley, PharmD
12/12/2018	Approval	UM Committee