Leukine (sargramostim)
Policy Number: C2439-A

CRITERIA EFFECTIVE DATES:

ORIGINAL EFFECTIVE DATE	LAST REVIEWED DATE	NEXT REVIEW DUE BY OR BEFORE
12/1/2017	12/2/2020	1/26/2022
HCPCS CODING	**TYPE OF CRITERIA**	**LAST P&T APPROVAL/VERSION**
J2820-injection, sargramostim (gm-csf), 50mcg	RxPA	Q1 2021 20210127C2439-A

PRODUCTS AFFECTED:
Leukine (sargramostim)

DRUG CLASS:
Granulocyte/Macrophage Colony-stimulating Factor (GM-CSF)

ROUTE OF ADMINISTRATION:
Intravenous or Subcutaneous

PLACE OF SERVICE:
Specialty Pharmacy or Buy and Bill

AVAILABLE DOSAGE FORMS:
Leukine (sargramostim) 250mcg single dose vial, 500mcg single dose vial

FDA-APPROVED USES:
LEUKINE is a leukocyte growth factor indicated:

- To shorten time to neutrophil recovery and to reduce the incidence of severe and life-threatening infection and infections resulting in death following induction chemotherapy in adult patients 55 years and older with acute myeloid leukemia (AML).
- For the mobilization of hematopoietic progenitor cells into peripheral blood for collection by leukapheresis and autologous transplantation in adult patients.
- For the acceleration of myeloid reconstitution following autologous bone marrow or peripheral blood progenitor cell transplantation in adult and pediatric patients 2 years of age and older.
- For the acceleration of myeloid reconstitution following allogeneic bone marrow transplantation in adult and pediatric patients 2 years of age and older.
- For treatment of delayed neutrophil recovery or graft failure after autologous or allogeneic bone marrow transplantation in adult and pediatric patients 2 years of age and older.
- 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 [H- ARS])

COMPENDIAL APPROVED OFF-LABELED USES:
Prophylaxis of febrile neutropenia in non-myeloid malignancies following myelosuppressive chemotherapy, zidovudine-induced neutropenia, ganciclovir-induced neutropenia

COVERAGE CRITERIA: INITIAL AUTHORIZATION

DIAGNOSIS:
FDA approved uses and prophylaxis of febrile neutropenia in non-myeloid malignancies following myelosuppressive chemotherapy, pulmonary alveolar proteinosis, zidovudine-induced neutropenia, aplastic anemia, ganciclovir-induced neutropenia, malignant melanoma, myelodysplastic syndrome (MDS), neuroblastoma

REQUIRED MEDICAL INFORMATION:
BIOSIMILAR DRUGS are preferred when requested as a physician administered drug and/or pharmacy formulary product per applicable state regulations and there is a lack of dat demonstrating clinical superiority of reference drugs over the FDA approved biosimilar drugs. A reference medication is approved under the following conditions:

1. Treatment with at least two (2) associated biosimilar drug(s) has been ineffective, not tolerated, or is contraindicated (i.e. an allergic reaction to a specific inactive ingredient in the preferred biologic product or biosimilar OR an adverse reaction to a specific inactive ingredient in the preferred biologic product or biosimilar OR therapeutic success while taking a non-preferred biologic product or biosimilar and therapeutic failure while taking the preferred biologic product or biosimilar documented by patient diary or medical charted notes)
   [DOCUMENTATION REQUIRED-Document when the preferred biologic product or biosimilar was tried and the length of the trial period, Provide specific clinical documentation of therapeutic failure on the preferred biologic product or biosimilar whenever possible. Describe the medical problem caused by the preferred referenced biologic. Vague and non-descriptive symptoms are not adequate rationale (e.g., stomachache)]

A. FEBRILE NEUTROPENIA PROPHYLAXIS IN NON-MYELOID MALIGNANCIES:
   1. Documented diagnosis of non-myeloid malignancy
      AND
   2. Documentation that sargramostim is being used following myelosuppressive chemotherapy
      [Documentation of current chemotherapy regimen, any previous chemotherapy regimens and anticipated treatment plan]
      AND
   3. (a) Member has a risk of febrile neutropenia (FN) of greater than 20% based on current chemotherapy regimen (as listed in current ASCO and NCCN guidelines for myeloid growth factors [See Appendix]
      OR
      (b) Member has a risk of febrile neutropenia of 10-20% based on chemotherapy regimen, and at least ONE of the following risk factors apply:
         (i) Prior chemotherapy or radiation therapy
         (ii) Persistent neutropenia (defined as neutrophil count less than 500 neutrophils/mcL or less than 1,000 neutrophils/mcL and a predicted decline to less than or equal to 500 neutrophils/mcL over next 48 hours)
         (iii) Bone marrow involvement by tumor
         (iv) Recent surgery and/or open wounds
         (v) Liver dysfunction (bilirubin greater than 2.0 mg/dL)
         (vi) Renal dysfunction (creatinine clearance less than 50 mL/min)
         (vii) Age greater than 65 receiving full chemotherapy dose intensity
      OR
      (c) Previous neutropenic fever complication from a prior cycle of similar chemotherapy
      OR

(d) The member is receiving a dose-dense chemotherapy regimen

B. FEBRILE NEUTROPENIA PROPHYLAXIS IN ACUTE MYELOID LEUKEMIA (AML):
1. Documentation that Member must is receiving either induction chemotherapy OR consolidation chemotherapy

C. FEBRILE NEUTROPENIA PROPHYLAXIS FOLLOWING HEMATOPOETIC STEMCELL TRANSPLANT (HSCT):
1. Documented diagnosis of non-myeloid malignancy
AND
2. Documentation member is undergoing or must have had a hematopoietic stem cell transplant (HSCT) (e.g. bone marrow transplant, peripheral-blood progenitor cell (PBPC) transplant) fora non- myeloid malignancy

D. PERIPHERAL BLOOD PROGENITOR CELL COLLECTION:
1. Prescriber attests that member is in need of sargramostim therapy for the mobilization of autologous hematopoietic progenitor cells into the peripheral blood for collection by leukapheresis and will be initiated before leukapheresis (e.g., prescribed for 6 to 7 days with leukapheresis on days 5, 6 and 7)

E. DRUG OR HIV INDUCED NEUTROPENIA:
1. Documentation patient is immunosuppressed of has a diagnosis of HIV disease
AND
2. Documentation member is concurrently taking ganciclovir or zidovudine

F. NEUROBLASTOMA:
1. Documentation member has a diagnosis of relapsed or refractory high-risk neuroblastoma in the bone or bone marrow
AND
2. Prescriber attests sargramostim will be used concurrently with naxitamab

G. ACUTE RADIATION SYNDROME:
1. Documentation that member has had suspected or confirmed acute exposure to myelosuppressive doses of radiation [greater than 2 Grays (Gy)]

DURATION OF APPROVAL:
Initial Authorization: Up to 12 weeks or up to length of chemotherapy approval date- whichever is shorter,
Continuation of Therapy: Up to 6 months

QUANTITY:
Must be prescribed within FDA labeled or compendia supported dosing maximums

PRESCRIBER REQUIREMENTS:
Prescribed by or in consultation with a board-certified hematologist, oncologist, infectious disease specialist or transplant specialist

AGE RESTRICTIONS:
One month of age and older

CONTINUATION OF THERAPY:
A. FOR ALL INDICATIONS:
1. Member is compliant with sargramostim therapy as verified by prescriber and fill/claim history
AND

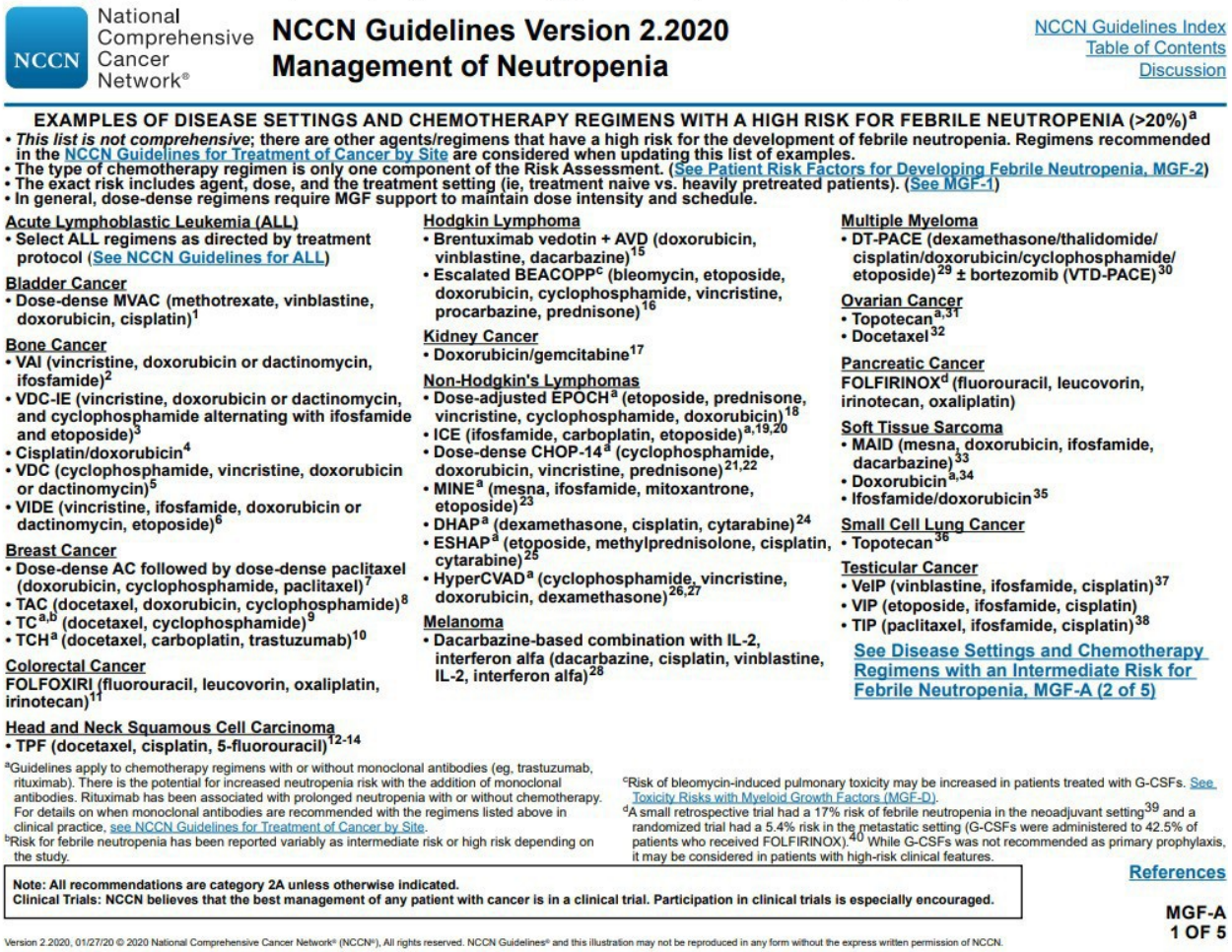
2. Documentation of clinical benefits to support continuation of treatment including positive response to therapy (i.e. member did not become neutropenic mid-cycle requiring G-CFS)
   AND
3. Documentation of regular lab monitoring (i.e. CBC and ANC)

CONTRAINDICATIONS/EXCLUSIONS/DISCONTINUATION:
All other uses of sargramostim are considered experimental/investigational and therefore, will follow Molina's Off-Label policy. Use in routine infection prophylaxis (e.g. adjunctive therapy to antibiotics in a member with uncomplicated febrile neutropenia, afebrile neutropenia). Continued use beyond 42 days with no response.
Concurrent use with other CSF agents (filgrstim and pegfilgrastim). Known hypersensitivity to GM-CSF, sargramostim, yeast derived products or any component of Leukine. Member is a neonate. For ANC >20,000 cells/mm3 or platelet >500,000/mm3 administration will be interrupted or the dose reduced by half AND twice weekly monitoring of CBC with dif will be performed. Receiving chemotherapy with a risk of febrile neutropenia <20% and no significant high risk for complications. Sargramostim will be administered in the period between 24 hours before and 24 hours after administration of cytotoxic chemotherapy. Used concurrently with myelosuppressive chemotherapy or radiation. Administered prior to or concurrent with chemotherapy for AML. Used to increase the dose-intensity of cytotoxic chemotherapy beyond established dosing range for these regimens. Used before and/or concurrently with chemotherapy for a "priming" effect.
Use in acute promyelocytic leukemia (APL). For diagnosis of AML ONLY: excessive (≥10%) leukemic myeloid blasts in the bone marrow or peripheral blood

OTHER SPECIAL CONSIDERATIONS:
None

BACKGROUND:
None

APPENDIX:
A biosimilar is highly similar version of a brand name biological drug that meets strict controls for structural, pharmaceutical, and clinical consistency. A biosimilar manufacturer must demonstrate that there are no meaningful clinical differences (i.e., safety and efficacy) between the biosimilar and the reference product. Clinical performance is demonstrated through human pharmacokinetic (exposure) and pharmacodynamic (response) studies, an assessment of clinical immunogenicity, and, if needed, additional clinical studies.1
As costs for biological specialty drugs continue to rise, the growing biosimilar market will benefit providers and patients by broadening biological treatment options and expanding access to these medications at lower costs. Molina Healthcare, Inc. continues to be committed to continually reevaluating Preferred strategies and applying innovative cost-controls to ensure patients receive safe, effective and quality healthcare. This commitment includes potentially creating a preference for biosimilars when value can be added without compromising patient satisfaction and safety.
1. Food and Drug Administration. Biosimilar and Interchangeable Products. Retrieved from https://www.fda.gov/drugs/biosimilars/biosimilar-and- interchangeable-products. Accessed October 8, 2019.



National Comprehensive Cancer Network®

NCCN Guidelines Version 2.2020
Management of Neutropenia

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Discussion

EXAMPLES OF DISEASE SETTINGS AND CHEMOTHERAPY REGIMENS WITH A HIGH RISK FOR FEBRILE NEUTROPENIA (>20%)[a]

- ***This list is not comprehensive***; there are other agents/regimens that have a high risk for the development of febrile neutropenia. Regimens recommended in the NCCN Guidelines for Treatment of Cancer by Site are considered when updating this list of examples.
- The type of chemotherapy regimen is only one component of the Risk Assessment. (See Patient Risk Factors for Developing Febrile Neutropenia, MGF-2)
- The exact risk includes agent, dose, and the treatment setting (ie, treatment naive vs. heavily pretreated patients). (See MGF-1)
- In general, dose-dense regimens require MGF support to maintain dose intensity and schedule.

Acute Lymphoblastic Leukemia (ALL)
- Select ALL regimens as directed by treatment protocol (See NCCN Guidelines for ALL)

Bladder Cancer
- Dose-dense MVAC (methotrexate, vinblastine, doxorubicin, cisplatin)[1]

Bone Cancer
- VAI (vincristine, doxorubicin or dactinomycin, ifosfamide)[2]
- VDC-IE (vincristine, doxorubicin or dactinomycin, and cyclophosphamide alternating with ifosfamide and etoposide)[3]
- Cisplatin/doxorubicin[4]
- VDC (cyclophosphamide, vincristine, doxorubicin or dactinomycin)[5]
- VIDE (vincristine, ifosfamide, doxorubicin or dactinomycin, etoposide)[6]

Breast Cancer
- Dose-dense AC followed by dose-dense paclitaxel (doxorubicin, cyclophosphamide, paclitaxel)[7]
- TAC (docetaxel, doxorubicin, cyclophosphamide)[8]
- TC[a,b] (docetaxel, cyclophosphamide)[9]
- TCH[a] (docetaxel, carboplatin, trastuzumab)[10]

Colorectal Cancer
FOLFOXIRI (fluorouracil, leucovorin, oxaliplatin, irinotecan)[11]

Head and Neck Squamous Cell Carcinoma
- TPF (docetaxel, cisplatin, 5-fluorouracil)[12-14]

Hodgkin Lymphoma
- Brentuximab vedotin + AVD (doxorubicin, vinblastine, dacarbazine)[15]
- Escalated BEACOPP[c] (bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, prednisone)[16]

Kidney Cancer
- Doxorubicin/gemcitabine[17]

Non-Hodgkin's Lymphomas
- Dose-adjusted EPOCH[a] (etoposide, prednisone, vincristine, cyclophosphamide, doxorubicin)[18]
- ICE (ifosfamide, carboplatin, etoposide)[a,19,20]
- Dose-dense CHOP-14[a] (cyclophosphamide, doxorubicin, vincristine, prednisone)[21,22]
- MINE[a] (mesna, ifosfamide, mitoxantrone, etoposide)[23]
- DHAP[a] (dexamethasone, cisplatin, cytarabine)[24]
- ESHAP[a] (etoposide, methylprednisolone, cisplatin, cytarabine)[25]
- HyperCVAD[a] (cyclophosphamide, vincristine, doxorubicin, dexamethasone)[26,27]

Melanoma
- Dacarbazine-based combination with IL-2, interferon alfa (dacarbazine, cisplatin, vinblastine, IL-2, interferon alfa)[28]

Multiple Myeloma
- DT-PACE (dexamethasone/thalidomide/cisplatin/doxorubicin/cyclophosphamide/etoposide)[29] ± bortezomib (VTD-PACE)[30]

Ovarian Cancer
- Topotecan[a,31]
- Docetaxel[32]

Pancreatic Cancer
FOLFIRINOX[d] (fluorouracil, leucovorin, irinotecan, oxaliplatin)

Soft Tissue Sarcoma
- MAID (mesna, doxorubicin, ifosfamide, dacarbazine)[33]
- Doxorubicin[a,34]
- Ifosfamide/doxorubicin[35]

Small Cell Lung Cancer
- Topotecan[36]

Testicular Cancer
- VeIP (vinblastine, ifosfamide, cisplatin)[37]
- VIP (etoposide, ifosfamide, cisplatin)
- TIP (paclitaxel, ifosfamide, cisplatin)[38]

See Disease Settings and Chemotherapy Regimens with an Intermediate Risk for Febrile Neutropenia, MGF-A (2 of 5)

[a]Guidelines apply to chemotherapy regimens with or without monoclonal antibodies (eg, trastuzumab, rituximab). There is the potential for increased neutropenia risk with the addition of monoclonal antibodies. Rituximab has been associated with prolonged neutropenia with or without chemotherapy. For details on when monoclonal antibodies are recommended with the regimens listed above in clinical practice, see NCCN Guidelines for Treatment of Cancer by Site.

[b]Risk for febrile neutropenia has been reported variably as intermediate risk or high risk depending on the study.

[c]Risk of bleomycin-induced pulmonary toxicity may be increased in patients treated with G-CSFs. See Toxicity Risks with Myeloid Growth Factors (MGF-D).

[d]A small retrospective trial had a 17% risk of febrile neutropenia in the neoadjuvant setting[39] and a randomized trial had a 5.4% risk in the metastatic setting (G-CSFs were administered to 42.5% of patients who received FOLFIRINOX).[40] While G-CSFs was not recommended as primary prophylaxis, it may be considered in patients with high-risk clinical features.

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

References

MGF-A
1 OF 5

Documentation Requirements:
Molina Healthcare reserves the right to require that additional documentation be made available as part of its coverage determination; quality improvement; and fraud; waste and abuse prevention processes. Documentation required may include, but is not limited to, member records, test results and credentials of the provider ordering or performing a drug or service. Molina Healthcare may deny reimbursement or take additional appropriate action if the documentation provided does not support the initial determination that the drugs or services were medically necessary, not investigational or experimental, and otherwise within the scope of benefits afforded to the member, and/or the documentation demonstrates a pattern of billing or other practice that is inappropriate or excessive.

REFERENCES:

1. Leukine [package insert]. Bridgewater, NJ; sanofi-aventis US LLC; February2017.
2. Referenced with permission from the NCCN Drugs & Biologics Compendium (NCCN Compendium®) sargramostim. National Comprehensive Cancer Network, 2018. The NCCN Compendium® is a derivative work of the NCCN Guidelines®. NATIONAL COMPREHENSIVE CANCER NETWORK®, NCCN®, and NCCN GUIDELINES® are trademarks owned by the National Comprehensive Cancer Network, Inc." To view the most recent and complete version of the Compendium, go online to NCCN.org.
3. Spitler LE, Grossbard ML, Ernstoff MS, et al. Adjuvant therapy of stage III and IV malignant melanoma using granulocyte-macrophage colony stimulating factor. J Clin Oncol 2000;18:1614-21.

4. US Public Health Service (USPHS) and the Infectious Diseases Society of America (IDSA). The Living Document: Guidelines for the Preventing Opportunistic Infections Among HIV-Infected Persons. Retrieved November 28, 2001. Available on the World Wide Web at www.aidsinfo.nih.gov.
5. Naxitamab-gqgk (Danyelza) injection package insert. New York, NY: Y-mAbs Therapeutics, Inc; 2020 Nov.