POLICY Document for
LEUKINE (sargramostim)

The overall objective of this policy is to support the appropriate and cost effective use of the medication, specific to use of preferred medication options, and overall clinically appropriate use. This document provides specific information to both sections of the overall policy.

Section 1: Preferred Product
- Policy information specific to preferred medications

Section 2: Clinical Criteria
- Policy information specific to the clinical appropriateness for the medication

Section 1: Preferred Product

EXCEPTIONS CRITERIA
Colony Stimulating Factors – Short Acting

PREFERRED PRODUCT: ZARXIO and NIVESTYM

POLICY
This policy informs prescribers of preferred products and provides an exception process for targeted products through prior authorization.

I. PLAN DESIGN SUMMARY

This program applies to the short acting colony stimulating factor products specified in this policy. Coverage for targeted products is provided based on clinical circumstances that would exclude the use of the preferred product and may be based on previous use of a product. The coverage review process will ascertain situations where a clinical exception can be made. This program applies to all members requesting treatment with a targeted product.

Each referral is reviewed based on all utilization management (UM) programs implemented for the client.

Table. Colony Stimulating Factors – Short Acting

	Product(s)
Preferred	• **Zarxio** (filgrastim-sndz) • **Nivestym** (filgrastim-aafi)
Targeted	• **Granix** (TBO-filgrastim) • **Leukine** (sargramostim) • **Neupogen** (filgrastim)

II. EXCEPTION CRITERIA
This program applies to members requesting treatment for an indication that is FDA-approved for the preferred product.

A. Coverage for the targeted products, Neupogen or Granix, is provided when the member meets one of the following criteria:
   1. Member has failed treatment with all of the preferred products due to a documented intolerable adverse event (e.g., rash, nausea, vomiting) and the adverse event was not an expected adverse event attributed to the active ingredient as described in the prescribing information (i.e., known adverse reaction for both the brand and biosimilar medication)
   2. Member has a documented latex allergy and the prescriber states that the member must use latex-free vials and the member had an inadequate response or an intolerable adverse effect to Nivestym.
   3. Neupogen or Granix are requested for doses less than 180 mcg and the member had an inadequate response or an intolerable adverse effect to Nivestym.

B. Coverage for the targeted product, Leukine, is provided when the member has had a documented inadequate response or an intolerable adverse effect to any of the preferred products.

Section 2: Clinical Criteria

SPECIALTY GUIDELINE MANAGEMENT

LEUKINE (sargramostim)

POLICY

I. INDICATIONS

The indications below including FDA-approved indications and compendial uses are considered a covered benefit provided that all the approval criteria are met and the member has no exclusions to the prescribed therapy.

A. FDA-Approved Indications[1]
   1. Acute Myeloid Leukemia Following Induction Chemotherapy
      Leukine is indicated to shorten time to neutrophil recovery and to reduce the incidence of severe, life-threatening, or fatal infections following induction chemotherapy in adult patients 55 years and older with acute myeloid leukemia (AML).
   2. Autologous Peripheral Blood Progenitor Cells Mobilization and Collection
      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.
   3. Autologous Peripheral Blood Progenitor Cell and Bone Marrow Transplantation
      Leukine is indicated for acceleration of myeloid reconstitution following autologous peripheral blood progenitor cell (PBPC) or bone marrow transplantation in adult and pediatric patients 2 years of age and older with non-Hodgkin's lymphoma (NHL), acute lymphoblastic leukemia (ALL) and Hodgkin's lymphoma (HL).
   4. Allogeneic Bone Marrow Transplantation (BMT)
      Leukine is indicated for acceleration of myeloid reconstitution in adult and pediatric patients 2 years of age and older undergoing allogeneic BMT from human leukocyte antigens (HLA)-matched related donors.
   5. Allogenic or Autologous Bone Marrow Transplantation: Treatment of Delayed Neutrophil Recovery or Graft Failure

Leukine is indicated for the treatment of adult and pediatric patients 2 years and older who have undergone allogeneic or autologous BMT in whom neutrophil recovery is delayed or failed.

6. Acute Exposure to Myelosuppressive Doses of Radiation (H-ARS)
   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 [H-ARS]).

B. Compendial Uses[2-10]
1. Prophylaxis and treatment of chemotherapy-induced febrile neutropenia in non-myeloid malignancies
2. Treatment of neutropenia and anemia in patients with myelodysplastic syndromes (MDS)
3. Acute myeloid leukemia
4. Agranulocytosis (non-chemotherapy drug induced)
5. Aplastic anemia
6. Neutropenia related to HIV/AIDS
7. Stem cell transplantation-related indications
8. Neuroblastoma
9. Severe chronic neutropenia (congenital, cyclic, or idiopathic)

All other indications are considered experimental/investigational and not medically necessary.

II. DOCUMENTATION

Primary Prophylaxis of Febrile Neutropenia

1. Documentation must be provided of the member's diagnosis and chemotherapeutic regimen.
2. If chemotherapeutic regimen has an intermediate risk of febrile neutropenia (10-19% [See Appendix B]), documentation must be provided outlining the member's risk factors that confirm the member is at high risk for febrile neutropenia.

III. CRITERIA FOR INITIAL APPROVAL

A. Neutropenia in cancer patients receiving myelosuppressive chemotherapy[1-8]

Authorization of 6 months may be granted for prevention or treatment of febrile neutropenia when all of the following criteria are met (1, 2, and 3):

1. The requested medication will not be used in combination with other colony stimulating factors within any chemotherapy cycle.
2. The member will not be receiving chemotherapy and radiation therapy at the same time.
3. One of the following criteria is met (i, ii, or iii):

i. The requested medication will be used for primary prophylaxis in members with solid tumors or non-myeloid malignancies who have received, are currently receiving, or will be receiving myelosuppressive anti-cancer therapy that is expected to result in 20% or higher incidence of febrile neutropenia (FN) *(See Appendix A)* OR 10 – 19% risk of FN *(See Appendix B)* and who are considered to be at high risk of FN because of bone marrow compromise or co-morbidity, including any of the following (not an all-inclusive list):
   a. Active infections, open wounds, or recent surgery
   b. Age greater than or equal to 65 years
   c. Bone marrow involvement by tumor producing cytopenias
   d. Previous chemotherapy or radiation therapy
   e. Poor nutritional status
   f. Poor performance status
   g. Previous episodes of FN
   h. Other serious co-morbidities, including renal dysfunction, liver dysfunction, HIV infection, cardiovascular disease
   i. Persistent neutropenia

ii. The requested medication will be used for secondary prophylaxis in members with solid tumors or non-myeloid malignancies who experienced a febrile neutropenic complication or a dose-limiting neutropenic event (a nadir or day of treatment count impacting the planned dose of

chemotherapy) from a prior cycle of similar chemotherapy, with the same dose and schedule planned for the current cycle (for which primary prophylaxis was not received).

iii. The requested medication will be used for treatment of high risk febrile neutropenia (FN) in members who have any of the following prognostic factors that are predictive of clinical deterioration:
   a. Age greater than 65 years
   b. Being hospitalized at the time of the development of fever
   c. Sepsis syndrome
   d. Invasive fungal infection
   e. Pneumonia or other clinically documented infection
   f. Prolonged (neutropenia expected to last greater than 10 days) or profound (absolute neutrophil count less than 0.1 x 10^9/L) neutropenia
   g. Prior episodes of febrile neutropenia

B. Neuroblastoma[9,10]

Authorization of 6 months may be granted for treatment of high-risk neuroblastoma when used with either of the following:

1. Dinutuxin (Unituxin), interleukin-2 (aldesleukin (Proleukin)), and isotretinoin (13-cis-retinoic acid (RA))
2. Naxitamab-gqgk (Danyelza)

C. Other indications[2-9]

Authorization of 6 months may be granted for members with any of the following indications:

1. Myelodysplastic syndrome (anemia or neutropenia)
2. Acute myeloid leukemia
3. Agranulocytosis (non-chemotherapy drug induced)
4. Aplastic anemia
5. Neutropenia related to HIV/AIDS
6. Stem cell transplantation-related indications
7. Severe chronic neutropenia (congenital, cyclic, or idiopathic)
8. Hematopoietic Syndrome of Acute Radiation Syndrome
   Treatment for radiation-induced myelosuppression following a radiological/nuclear incident

IV. CONTINUATION OF THERAPY

All members (including new members) requesting authorization for continuation of therapy must meet all initial authorization criteria.

V. APPENDIX[6,8]

A. APPENDIX A: Selected Chemotherapy Regimens with an Incidence of Febrile Neutropenia of 20% or Higher[*†]

1. Acute Lymphoblastic Leukemia:
   Select ALL regimens as directed by treatment protocol (see NCCN guidelines ALL)
2. Bladder Cancer:
   i. Dose dense MVAC (methotrexate, vinblastine, doxorubicin, cisplatin)
   ii. CBDCa/Pac (carboplatin, paclitaxel)
3. Bone Cancer:
   i. VAI (vincristine, doxorubicin or dactinomycin, ifosfamide)
   ii. VDC-IE (vincristine, doxorubicin or dactinomycin, and cyclophosphamide alternating with ifosfamide and etoposide)
   iii. Cisplatin/doxorubicin
   iv. VDC (cyclophosphamide, vincristine, doxorubicin or dactinomycin)
   v. VIDE (vincristine, ifosfamide, doxorubicin or dactinomycin, etoposide)
4. Breast Cancer:

i. Docetaxel + trastuzumab
ii. Dose-dense AC (doxorubicin, cyclophosphamide) + paclitaxel (or dose dense paclitaxel)
iii. TAC (docetaxel, doxorubicin, cyclophosphamide)
iv. AT (doxorubicin, docetaxel)
v. Doc (docetaxel)
vi. TC (docetaxel, cyclophosphamide)
vii. TCH (docetaxel, carboplatin, trastuzumab)

5. Colorectal Cancer:
   FOLFOXIRI (fluorouracil, leucovorin, oxaliplatin, irinotecan)
6. Esophageal and Gastric Cancers:
   Docetaxel/cisplatin/fluorouracil
7. Head and Neck Squamous Cell Carcinoma
   TPF (docetaxel, cisplatin, 5-fluorouracil)
8. Hodgkin Lymphoma:
   i. Brentuximab vedotin + AVD (doxorubicin, vinblastine, dacarbazine)
   ii. Escalated BEACOPP (bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, prednisone)
9. Kidney Cancer:
   Doxorubicin/gemcitabine
10. Non-Hodgkin's Lymphoma:
    i. CHP (cyclophosphamide, doxorubicin, prednisone) + brentuximab vedotin
    ii. Dose-adjusted EPOCH (etoposide, prednisone, vincristine, cyclophosphamide, doxorubicin)
    iii. ICE (ifosfamide, carboplatin, etoposide)
    iv. Dose-dense CHOP-14 (cyclophosphamide, doxorubicin, vincristine, prednisone) ± rituximab
    v. MINE (mesna, ifosfamide, mitoxantrone, etoposide)
    vi. DHAP (dexamethasone, cisplatin, cytarabine)
    vii. ESHAP (etoposide, methylprednisolone, cisplatin, cytarabine (Ara-C))
    viii. HyperCVAD ± rituximab (cyclophosphamide, vincristine, doxorubicin, dexamethasone ± rituximab)
    ix. VAPEC-B (vincristine, doxorubicin, prednisolone, etoposide, cyclophosphamide, bleomycin)
11. Melanoma:
    Dacarbazine-based combination with IL-2, interferon alpha (dacarbazine, cisplatin, vinblastine, IL-2, interferon alfa)
12. Multiple Myeloma:
    i. VTD-PACE (dexamethasone/thalidomide/cisplatin/doxorubicin/cyclophosphamide/etoposide + bortezomib)
    ii. DT-PACE (dexamethasone/thalidomide/cisplatin/doxorubicin/cyclophosphamide/etoposide)
13. Ovarian Cancer:
    i. Topotecan
    ii. Docetaxel
14. Pancreatic Cancer:
    FOLFIRINOX (fluorouracil, leucovorin, irinotecan, oxaliplatin)
15. Soft Tissue Sarcoma:
    i. MAID (mesna, doxorubicin, ifosfamide, dacarbazine)
    ii. Doxorubicin
    iii. Ifosfamide/doxorubicin
16. Small Cell Lung Cancer:
    i. Top (topotecan)
    ii. CAV (cyclophosphamide, doxorubicin, vincristine)
17. Testicular Cancer:
    i. VelP (vinblastine, ifosfamide, cisplatin)
    ii. VIP (etoposide, ifosfamide, cisplatin)
    iii. TIP (paclitaxel, ifosfamide, cisplatin)

*Applies to chemotherapy regimens with or without monoclonal antibodies (e.g., trastuzumab, rituximab)
† This list is not comprehensive; there are other agents/regimens that have an intermediate/high risk for development of febrile neutropenia.

B. APPENDIX B: Selected Chemotherapy Regimens with an Incidence of Febrile Neutropenia of 10% to 19%*†

1. Occult Primary – Adenocarcinoma:
   Gemcitabine/docetaxel
2. Breast Cancer:
   i. Docetaxel
   ii. CMF classic (cyclophosphamide, methotrexate, fluorouracil)
   iii. CA (doxorubicin, cyclophosphamide) (60 mg/m2) (hospitalized)
   iv. AC (doxorubicin, cyclophosphamide) + sequential docetaxel (taxane portion only)
   v. AC + sequential docetaxel + trastuzumab
   vi. A (doxorubicin) (75 mg/m2)
   vii. AC (doxorubicin, cyclophosphamide)
   viii. CapDoc (capecitabine, docetaxel)
   ix. Paclitaxel every 21 days
3. Cervical Cancer:
   i. Irinotecan
   ii. Cisplatin/topotecan
   iii. Paclitaxel/cisplatin
   iv. Topotecan
4. Colorectal Cancer:
   i. FL (fluorouracil, leucovorin)
   ii. CPT-11 (irinotecan) (350 mg/m2 q 3 wk)
   iii. FOLFOX (fluorouracil, leucovorin, oxaliplatin)
5. Esophageal and Gastric Cancers:
   i. Irinotecan/cisplatin
   ii. Epirubicin/cisplatin/5-fluorouracil
   iii. Epirubicin/cisplatin/capecitabine
6. Non-Hodgkin's Lymphomas:
   i. EPOCH-IT chemotherapy
   ii. GDP (gemcitabine, dexamethasone, cisplatin/carboplatin)
   iii. GDP (gemcitabine, dexamethasone, cisplatin/carboplatin) + rituximab
   iv. FMR (fludarabine, mitoxantrone, rituximab)
   v. CHOP (cyclophosphamide, doxorubicin, vincristine, prednisone) including regimens with pegylated liposomal doxorubicin
   vi. CHOP + rituximab (cyclophosphamide, doxorubicin, vincristine, prednisone, rituximab) including regimens with pegylated liposomal doxorubicin
   vii. Bendamustine
7. Non-Small Cell Lung Cancer:
   i. Cisplatin/paclitaxel
   ii. Cisplatin/vinorelbine
   iii. Cisplatin/docetaxel
   iv. Cisplatin/etoposide
   v. Carboplatin/paclitaxel
   vi. Docetaxel
8. Ovarian Cancer:
   Carboplatin/docetaxel
9. Prostate Cancer:
   Cabazitaxel
10. Small Cell Lung Cancer:
    Etoposide/carboplatin
11. Testicular Cancer:
    i. BEP (bleomycin, etoposide, cisplatin)
    ii. Etoposide/cisplatin
12. Uterine Sarcoma:
    Docetaxel

*Applies to chemotherapy regimens with or without monoclonal antibodies (e.g., trastuzumab, rituximab)
† This list is not comprehensive; there are other agents/regimens that have an intermediate/high risk for development of febrile neutropenia.

REFERENCES:

SECTION 1

1. Zarxio [package insert]. Princeton, NJ: Sandoz; August 2019.
2. Neupogen [package insert]. Thousand Oaks, CA: Amgen; June 2018.
3. Granix [package insert]. North Wales, PA: Teva Pharmaceuticals USA; March 2019.
4. Leukine [package insert]. Lexington, MA: Partner Therapeutics, Inc.; May 2018.
5. Nivestym [package insert]. Lake Forest, IL: Hospira Inc, a Pfizer company: July 2018

SECTION 2

1. Leukine [package insert]. Lexington, MA: Partner Therapeutics, Inc.; May 2018.
2. The NCCN Drugs & Biologics Compendium® © 2021 National Comprehensive Cancer Network, Inc. Available at: http://www.nccn.org. Accessed June 03, 2021.
3. IBM Micromedex® DRUGDEX ® (electronic version). IBM Watson Health, Greenwood Village, Colorado, USA. Available at https://www.micromedexsolutions.com. (Accessed: June 03, 2021).
4. Lexicomp Online, AHFS DI (Adult and Pediatric) [database online]. Hudson, OH: Wolters Kluwer Clinical Drug Information, Inc.; Accessed June 03, 2021.
5. National Comprehensive Cancer Network. NCCN Clinical Practice Guidelines in Oncology: Hematopoietic Growth Factors. Version 4.2021. https://www.nccn.org/professionals/physician_gls/pdf/growthfactors.pdf Accessed June 03, 2021.
6. Smith TJ, Bohlke K, Lyman GH, et al. Recommendations for the use of white blood cell growth factors: American Society of Clinical Oncology Clinical Practice Guideline Update. *J Clin Oncol*. 2015;33(28):3199-3212.
7. Smith TJ, Khatcheressian J, Lyman GH, et al. 2006 update of recommendations for the use of white blood cell growth factors: an evidence-based clinical practice guideline. *J Clin Oncol.* 2006;24(19):3187-3205.
8. Danyelza [package insert]. New York, NY: Y-mAbs Therapeutics, Inc.; November 2020.
9. Unituxin [package insert]. Research Triangle Park, NC: United Therapeutics Corp.; September 2020.