

Reference number(s)
1930-A

SPECIALTY GUIDELINE MANAGEMENT

NEUPOGEN (filgrastim)
GRANIX (tbo-filgrastim)
NIVESTYM (filgrastim-aafi)
RELEUKO (filgrastim-ayow)
ZARXIO (filgrastim-sndz)

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

Neupogen

1. Patients with Cancer Receiving Myelosuppressive Chemotherapy
Neupogen is indicated to decrease the incidence of infection, as manifested by febrile neutropenia, in patients with non-myeloid malignancies receiving myelosuppressive anti-cancer drugs associated with a significant incidence of severe neutropenia with fever.
2. Patients With Acute Myeloid Leukemia Receiving Induction or Consolidation Chemotherapy
Neupogen is indicated for reducing the time to neutrophil recovery and the duration of fever, following induction or consolidation chemotherapy treatment of patients with acute myeloid leukemia (AML).
3. Patients with Cancer Undergoing Bone Marrow Transplantation
Neupogen is indicated to reduce the duration of neutropenia and neutropenia-related clinical sequelae, (e.g., febrile neutropenia) in patients with non-myeloid malignancies undergoing myeloablative chemotherapy followed by marrow transplantation.
4. Patients Undergoing Autologous Peripheral Blood Progenitor Cell Collection and Therapy
Neupogen is indicated for the mobilization of autologous hematopoietic progenitor cells into the peripheral blood for collection by leukapheresis.
5. Patients With Severe Chronic Neutropenia
Neupogen is indicated for chronic administration to reduce the incidence and duration of sequelae of neutropenia (e.g., fever, infections, oropharyngeal ulcers) in symptomatic patients with congenital neutropenia, cyclic neutropenia, or idiopathic neutropenia.
6. Patients Acutely Exposed to Myelosuppressive Doses of Radiation (Hematopoietic Syndrome of Acute Radiation Syndrome)
Neupogen is indicated to increase survival in patients acutely exposed to myelosuppressive doses of radiation (Hematopoietic Syndrome of Acute Radiation Syndrome).

Nivestym

Reference number(s)
1930-A

1. **Patients with Cancer Receiving Myelosuppressive Chemotherapy**
Nivestym is indicated to decrease the incidence of infection, as manifested by febrile neutropenia, in patients with non-myeloid malignancies receiving myelosuppressive anti-cancer drugs associated with a significant incidence of severe neutropenia with fever.
2. **Patients With Acute Myeloid Leukemia Receiving Induction or Consolidation Chemotherapy**
Nivestym is indicated for reducing the time to neutrophil recovery and the duration of fever, following induction or consolidation chemotherapy treatment of patients with acute myeloid leukemia (AML).
3. **Patients with Cancer Undergoing Bone Marrow Transplantation (BMT)**
Nivestym is indicated to reduce the duration of neutropenia and neutropenia-related clinical sequelae, (e.g., febrile neutropenia) in patients with non-myeloid malignancies undergoing myeloablative chemotherapy followed by bone marrow transplantation.
4. **Patients Undergoing Autologous Peripheral Blood Progenitor Cell Collection and Therapy**
Nivestym is indicated for the mobilization of autologous hematopoietic progenitor cells into the peripheral blood for collection by leukapheresis.
5. **Patients With Severe Chronic Neutropenia**
Nivestym is indicated for chronic administration to reduce the incidence and duration of sequelae of neutropenia (e.g., fever, infections, oropharyngeal ulcers) in symptomatic patients with congenital neutropenia, cyclic neutropenia, or idiopathic neutropenia.

Granix

Granix is indicated to reduce the duration of severe neutropenia in adult and pediatric patients 1 month and older with non-myeloid malignancies receiving myelosuppressive anti-cancer drugs associated with a clinically significant incidence of febrile neutropenia.

Zarxio

1. **Patients with Cancer Receiving Myelosuppressive Chemotherapy**
Zarxio is indicated to decrease the incidence of infection, as manifested by febrile neutropenia, in patients with non-myeloid malignancies receiving myelosuppressive anti-cancer drugs associated with a significant incidence of severe neutropenia with fever.
2. **Patients With Acute Myeloid Leukemia Receiving Induction or Consolidation Chemotherapy**
Zarxio is indicated for reducing the time to neutrophil recovery and the duration of fever, following induction or consolidation chemotherapy treatment of patients with acute myeloid leukemia (AML).
3. **Patients with Cancer Undergoing Bone Marrow Transplantation**
Zarxio is indicated to reduce the duration of neutropenia and neutropenia-related clinical sequelae, (e.g., febrile neutropenia) in patients with non-myeloid malignancies undergoing myeloablative chemotherapy followed by bone marrow transplantation.
4. **Patients Undergoing Autologous Peripheral Blood Progenitor Cell Collection and Therapy**
Zarxio is indicated for the mobilization of autologous hematopoietic progenitor cells into the peripheral blood for collection by leukapheresis.
5. **Patients With Severe Chronic Neutropenia**
Zarxio is indicated for chronic administration to reduce the incidence and duration of sequelae of neutropenia (e.g., fever, infections, oropharyngeal ulcers) in symptomatic patients with congenital neutropenia, cyclic neutropenia, or idiopathic neutropenia.

Reference number(s)
1930-A

Releuko

1. Patients with Cancer Receiving Myelosuppressive Chemotherapy
Releuko is indicated to decrease the incidence of infection, as manifested by febrile neutropenia, in patients with non-myeloid malignancies receiving myelosuppressive anti-cancer drugs associated with a significant incidence of severe neutropenia with fever.
2. Patients With Acute Myeloid Leukemia Receiving Induction or Consolidation Chemotherapy
Releuko is indicated for reducing the time to neutrophil recovery and the duration of fever, following induction or consolidation chemotherapy treatment of patients with acute myeloid leukemia (AML).
3. Patients with Cancer Undergoing Bone Marrow Transplantation
Releuko is indicated to reduce the duration of neutropenia and neutropenia-related clinical sequelae, (e.g., febrile neutropenia) in patients with non-myeloid malignancies undergoing myeloablative chemotherapy followed by bone marrow transplantation.
4. Patients With Severe Chronic Neutropenia
Releuko is indicated for chronic administration to reduce the incidence and duration of sequelae of neutropenia (e.g., fever, infections, oropharyngeal ulcers) in symptomatic patients with congenital neutropenia, cyclic neutropenia, or idiopathic neutropenia.

B. Compendial Uses

1. Treatment of chemotherapy-induced febrile neutropenia
2. Prophylaxis for chemotherapy-induced febrile neutropenia in patients with solid tumors
3. Treatment of anemia and neutropenia in patients with myelodysplastic syndromes (MDS)
4. Stem cell transplantation-related indications
5. Agranulocytosis (non-chemotherapy drug induced)
6. Aplastic anemia
7. Neutropenia related to HIV/AIDS
8. Neutropenia related to renal transplantation¹⁰
9. Acute myeloid leukemia
10. Supportive care for neutropenic patients with CAR T-cell-related toxicities
11. Hairy Cell Leukemia, neutropenic fever
12. Chronic Myeloid Leukemia, treatment of persistent neutropenia due to tyrosine kinase inhibitor therapy
13. Glycogen Storage Disease (GSD) Type 1

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

II. DOCUMENTATION

Primary Prophylaxis of Febrile Neutropenia

- A. Documentation must be provided of the member's diagnosis and chemotherapeutic regimen.
- B. If chemotherapeutic regimen has a low or intermediate risk of febrile neutropenia (less than 20%), 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

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):

Reference number(s)
1930-A

1. The requested medication will not be used in combination with other colony stimulating factors within any chemotherapy cycle.
2. The member will not receive chemotherapy at the same time as they receive radiation therapy.
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 any of the following:
 - a. Myelosuppressive anti-cancer therapy that is expected to result in 20% or higher incidence of FN (febrile neutropenia) (FN) (*See Appendix A*)
 - b. Myelosuppressive anti-cancer therapy that is expected to result in 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-morbidities, or other patient specific risk factors (*See Appendix C*).
 - c. Myelosuppressive anti-cancer therapy that is expected to result in less than 10% risk of FN and who have at least 2 patient-related risk factors (*See Appendix C*).
 - 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 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 $1 \times 10^9/L$) neutropenia
 - g. Prior episodes of febrile neutropenia

B. Other indications

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

1. Myelodysplastic syndrome (anemia or neutropenia)
2. Stem cell transplantation-related indications (including applicable gene therapy protocols)
3. Agranulocytosis (non-chemotherapy drug induced)
4. Aplastic anemia
5. Neutropenia related to HIV/AIDS
6. Neutropenia related to renal transplantation
7. Acute myeloid leukemia
8. Severe chronic neutropenia (congenital, cyclic, or idiopathic)
9. Hematopoietic Syndrome of Acute Radiation Syndrome
Treatment for radiation-induced myelosuppression following a radiological/nuclear incident
10. CAR T-cell-related toxicities
Supportive care for neutropenic patients with CAR T-cell-related toxicities
11. Hairy Cell Leukemia
Members with hairy cell leukemia with neutropenic fever following chemotherapy
12. Chronic Myeloid Leukemia
Members with chronic myeloid leukemia (CML) for treatment of persistent neutropenia due to tyrosine kinase inhibitor therapy
13. Glycogen Storage Disease (GSD) Type 1
Individuals with GSD Type 1 for treatment of low neutrophil counts

Reference number(s)
1930-A

IV. CONTINUATION OF THERAPY

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

V. APPENDIX

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)

Reference number(s)
1930-A

- 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. Soft Tissue Sarcoma:
 - i. MAID (mesna, doxorubicin, ifosfamide, dacarbazine)
 - ii. Doxorubicin
 - iii. Ifosfamide/doxorubicin
- 15. Small Cell Lung Cancer:
 - i. Top (topotecan)
 - ii. CAV (cyclophosphamide, doxorubicin, vincristine)
- 16. Testicular Cancer:
 - i. VeIP (vinblastine, ifosfamide, cisplatin)
 - ii. VIP (etoposide, ifosfamide, cisplatin)
 - iii. TIP (paclitaxel, ifosfamide, cisplatin)
- 17. Gestational Trophoblastic Neoplasia:
 - i. EMA/CO (etoposide, methotrexate, dactinomycin/cyclophosphamide, vincristine)
 - ii. EMA/EP (etoposide, methotrexate, dactinomycin/etoposide, cisplatin)
 - iii. EP/EMA (etoposide, cisplatin/etoposide, methotrexate, dactinomycin)
 - iv. TP/TE (paclitaxel, cisplatin/paclitaxel, etoposide)
 - v. BEP (bleomycin, etoposide, cisplatin)
 - vi. VIP (etoposide, ifosfamide, cisplatin)
 - vii. ICE (ifosfamide, carboplatin, etoposide)
- 18. Wilms Tumor:
 - i. Regimen M (vincristine, dactinomycin, doxorubicin, cyclophosphamide, etoposide)
 - ii. Regimen I (vincristine, doxorubicin, cyclophosphamide, etoposide)

*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)

Reference number(s)
1930-A

- 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)
 - iv. FOLFIRINOX (fluorouracil, leucovorin, oxaliplatin, irinotecan)
- 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. Pancreatic Cancer:
 - FOLFIRINOX (fluorouracil, leucovorin, oxaliplatin, irinotecan)
- 10. Prostate Cancer:
 - Cabazitaxel
- 11. Small Cell Lung Cancer:
 - Etoposide/carboplatin
- 12. Testicular Cancer:
 - i. BEP (bleomycin, etoposide, cisplatin)
 - ii. Etoposide/cisplatin
- 13. 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.

C. APPENDIX C: Patient Risk Factors*

1. Active infections, open wounds, or recent surgery

Reference number(s)
1930-A

2. Age greater than or equal to 65 years
3. Bone marrow involvement by tumor producing cytopenias
4. Previous chemotherapy or radiation therapy
5. Poor nutritional status
6. Poor performance status
7. Previous episodes of FN
8. Other serious co-morbidities, including renal dysfunction, liver dysfunction, HIV infection, cardiovascular disease
9. Persistent neutropenia

*This list is not all-inclusive.

VI. REFERENCES

1. Neupogen [package insert]. Thousand Oaks, CA: Amgen Inc.; April 2023.
2. Nivestym [package insert]. Lake Forest, IL: Hospira Inc.; March 2023.
3. Granix [package insert]. North Wales, PA: Teva Pharmaceuticals USA, Inc.; November 2019.
4. Zarxio [package insert]. Princeton, NJ: Sandoz Inc.; September 2022.
5. Releuko [package insert]. Piscataway, NJ: Kashiv BioSciences, LLC; April 2022.
6. The NCCN Drugs & Biologics Compendium® © 2023 National Comprehensive Cancer Network, Inc. Available at: <https://www.nccn.org>. Accessed June 19, 2023.
7. National Comprehensive Cancer Network. NCCN Clinical Practice Guidelines in Oncology: Hematopoietic Growth Factors. Version 2.2023. https://www.nccn.org/professionals/physician_gls/pdf/growthfactors.pdf. Accessed: June 12, 2023.
8. IBM Micromedex® DRUGDEX® (electronic version). IBM Watson Health, Greenwood Village, Colorado, USA. Available at <https://www.micromedexsolutions.com>. (Accessed: June 19, 2023).
9. Lexicomp Online, AHFS DI (Adult and Pediatric) [database online]. Hudson, OH: Wolters Kluwer Clinical Drug Information, Inc.; Accessed June 19, 2023.
10. 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.
11. National Comprehensive Cancer Network. NCCN Clinical Practice Guidelines in Oncology: Hairy Cell Leukemia. Version 1.2023. https://www.nccn.org/professionals/physician_gls/pdf/hairy_cell.pdf Accessed June 19, 2023.
12. National Comprehensive Cancer Network. NCCN Clinical Practice Guidelines in Oncology: Chronic Myeloid Leukemia. Version 2.2023. https://www.nccn.org/professionals/physician_gls/pdf/cml.pdf Accessed June 23, 2023.
13. 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.
14. National Comprehensive Cancer Network. NCCN Clinical Practice Guidelines in Oncology: Gestational Trophoblastic Neoplasia. Version 1.2023. https://www.nccn.org/professionals/physician_gls/pdf/gtn.pdf Accessed June 19, 2023.
15. National Comprehensive Cancer Network. NCCN Clinical Practice Guidelines in Oncology: Wilms Tumor (Nephroblastoma). Version 1.2023. https://www.nccn.org/professionals/physician_gls/pdf/wilms_tumor.pdf Accessed June 19, 2023.
16. Kishnani PS, Austin SL, Abdenur JE, et al. Diagnosis and management of glycogen storage disease type I: a practice guideline of the American College of Medical Genetics and Genomics. *Genet Med*. 2014;16(11):e1.