AETNA BETTER HEALTH®
Coverage Policy/Guideline

Name:	Neupogen and filgrastim biosimilars	Page:	1 of 12
Effective Date:	1/29/2024	Last Review Date:	12/2023

Applies to:	☒Illinois	☐Florida	☐Florida Kids
	☐New Jersey	☐Maryland	☐Michigan
	☐Pennsylvania Kids	☐Virginia	☐Arizona

Intent:

The intent of this policy/guideline is to provide information to the prescribing practitioner outlining the coverage criteria for Neupogen and filgrastim biosimilars under the patient's prescription drug benefit.

Description:

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

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.

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 transplantation
   9. Acute myeloid leukemia
   10. Severe chronic neutropenia (congenital, cyclic, or idiopathic)
   11. Hematopoietic Syndrome of Acute Radiation Syndrome
   12. Supportive care for neutropenic patients with CAR T-cell-related toxicities
   13. Hairy Cell Leukemia, neutropenic fever
   14. Chronic Myeloid Leukemia, treatment of persistent neutropenia due to tyrosine kinase inhibitor therapy
   15. Glycogen Storage Disease (GSD) Type 1

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

Applicable Drug List:

Granix
Nivestym
Releuko
Zarxio

Policy/Guideline:

Documentation:
Primary Prophylaxis of Febrile Neutropenia

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

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):

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 x 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
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

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

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)
    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)
18. Gestational Trophoblastic Neoplasia:
    i. EMA/EP (etoposide, methotrexate, dactinomycin/etoposide, cisplatin)
    ii. EP/EMA (etoposide, cisplatin/etoposide, methotrexate, dactinomycin)
    iii. TP/TE (paclitaxel, cisplatin/paclitaxel, etoposide)
    iv. BEP (bleomycin, etoposide, cisplatin)
    v. VIP (etoposide, ifosfamide, cisplatin)
    vi. ICE (ifosfamide, carboplatin, etoposide)
19. 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. <u>APPENDIX B: Selected Chemotherapy Regimens with an Incidence of Febrile Neutropenia of 10% to 19%</u>*†
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.

Approval Duration and Quantity Restrictions:

Approval: 6 months

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.