SPECIALTY GUIDELINE MANAGEMENT

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

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. 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 adults with acute myeloid leukemia.

3. Patients with Cancer Receiving Bone Marrow Transplant

   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 adults with acute myeloid leukemia (AML).

3. **Patients with Cancer Receiving 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 adults 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.

B. Compendial Uses (Neupogen/Granix/Zarxio/Nivestym)
   1. Treatment of chemotherapy-induced febrile neutropenia in patients with non-myeloid malignancies
   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
   14. Chronic Myeloid Leukemia
   15. Glycogen Storage Disease (GSD) Type 1

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

II. REQUIRED DOCUMENTATION
   Primary Prophylaxis of Febrile Neutropenia
   Documentation must be provided of the member’s diagnosis and chemotherapeutic regimen.

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):
   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 concurrent chemotherapy and 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 myelosuppressive anti-cancer therapy that is expected to result in 20% or higher incidence of FN (febrile neutropenia) (FN) (See Appendix A) OR 10 – 19% risk of FN (See Appendix B).
      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.

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

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. Dose-adjusted EPOCH (etoposide, prednisone, vincristine, cyclophosphamide, doxorubicin)
    ii. ICE (ifosfamide, carboplatin, etoposide)
    iii. Dose-dense CHOP-14 (cyclophosphamide, doxorubicin, vincristine, prednisone) ± rituximab
    iv. MINE (mesna, ifosfamide, mitoxantrone, etoposide)
    v. DHAP (dexamethasone, cisplatin, cytarabine)
    vi. ESHAP (etoposide, methylprednisolone, cisplatin, cytarabine (Ara-C))
    vii. HyperCVAD ± rituximab (cyclophosphamide, vincristine, doxorubicin, dexamethasone ± rituximab)
    viii. 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

Neupogen and filgrastim biosimilars 1930-A SGM P2020 © 2020 CVS Caremark. All rights reserved.

This document contains confidential and proprietary information of CVS Caremark and cannot be reproduced, distributed or printed without written permission from CVS Caremark. This document contains prescription brand name drugs that are trademarks or registered trademarks of pharmaceutical manufacturers that are not affiliated with CVS Caremark.
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)

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. CHP (cyclophosphamide, doxorubicin, prednisone) + brentuximab vedotin
viii. 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)

VI. REFERENCES