Original Effective Date: 06/2012
Current Effective Date: 11/17/2022
Last P&T Approval/Version: 07/27/2022
Next Review Due By: 07/2023
Policy Number: C2437-A

Filgrastim

PRODUCTS AFFECTED

Neupogen (filgrastim); Zarxio (filgrastim-sndz); Nivestym (filgrastim-aafi); Granix (tbo-filgrastim), Releuko (filgrastim-ayow)

COVERAGE POLICY

Coverage for services, procedures, medical devices, and drugs are dependent upon benefit eligibility as outlined in the member's specific benefit plan. This Coverage Guideline must be read in its entirety to determine coverage eligibility, if any.
This Coverage Guideline provides information related to coverage determinations only and does not imply that a service or treatment is clinically appropriate or inappropriate. The provider and the member are responsible for all decisions regarding the appropriateness of care. Providers should provide Molina Healthcare complete medical rationale when requesting any exceptions to these guidelines.

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, patient 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.

DIAGNOSIS:
see FDA-approved uses above

REQUIRED MEDICAL INFORMATION:
This clinical policy is consistent with standards of medical practice current at the time that this clinical policy was approved. If a drug within this policy receives an updated FDA label within the last 180 days, medical necessity for the member will be reviewed using the updated FDA label information along with state and federal requirements, benefit being administered and formulary preferencing. Coverage will be determined on a case-by case basis until the criteria can be updated through Molina Healthcare, Inc. clinical governance. Additional information may be required on a case-by-case basis to allow for adequate review.

FOR ALL INDICATIONS:

1. IF THIS IS A NON-FORMULARY/NON-PREFERRED PRODUCT FOR INITIAL OR CONTINUATION OF THERAPY REQUEST: Documentation of trial/failure of or intolerance to a majority (not more than 3) of the preferred formulary alternatives for the given diagnosis. Submit documentation including medication(s) tried, dates of trial(s) and reason for treatment failure(s).
   OR
   IF THIS IS FOR A MEDICAL BENEFIT REQUEST: 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 data demonstrating clinical superiority of reference drugs over the FDA approved biosimilar drugs. A reference medication is approved under the following conditions:
(a) 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 (b) an adverse reaction to a specific inactive ingredient in the preferred biologic product or biosimilar OR (c) 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 filgrastim is being used following myelosuppressive chemotherapy [Documentation of current chemotherapy regimen, any previous chemotherapy regimens, and anticipated treatment plan] [DOCUMENTATION REQUIRED]
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 is receiving either induction chemotherapy OR consolidation chemotherapy [DOCUMENTATION REQUIRED]

C. FEBRILE NEUTROPENIA PROPHYLAXIS FOLLOWING HEMATOPOETIC STEM CELL 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) for a non-myeloid malignancy [DOCUMENTATION REQUIRED]

D. PERIPHERAL BLOOD PROGENITOR CELL COLLECTION:
1. Prescriber attests that member is in need of filgrastim 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. FEBRILE NEUTROPENIA PROPHYLAXIS DURING RADIATION THERAPY:
1. Documentation member is receiving radiation therapy alone or caution will be used if member is receiving concomitant chemotherapy [DOCUMENTATION REQUIRED of current radiation therapy, any previous or current chemotherapy regimens, and anticipated treatment plan]
NOTE: ASCO guidelines state that CSFs should be avoided in patients receiving concomitant chemotherapy and radiation therapy, particularly involving the mediastinum. The NCCN guidelines for myeloid growth factors (version 1.2022) state that caution should be exercised when administering prophylactic G-CSF in patients given concurrent chemotherapy and radiation.

F. CHRONIC NEUTROPENIA:
1. Documentation of a diagnosis of congenital, cyclic, or idiopathic neutropenia [DOCUMENTATION REQUIRED]
AND
2. Prescriber attests that member is symptomatic (e.g., fever, infections, oropharyngeal ulcers)

G. TREATMENT OF FEBRILE NEUTROPENIA:
1. Documentation member has a diagnosis of febrile neutropenia [DOCUMENTATION REQUIRED]
AND
2. Prescriber attests that member is concurrently receiving appropriate antibiotics, if member is at high-risk for developing infection-associated complications

H. HEPATITIS C TREATMENT RELATED NEUTROPENIA:
1. Documented diagnosis of Hepatitis C
AND
2. Prescriber attests or clinical reviewer has found member is undergoing treatment with peginterferon
AND
3. Documentation of neutropenia (ANC ≤ 500 cells/mm3 after dose reduction of peginterferon) [DOCUMENTATION REQUIRED]

I. HIV RELATED NEUTROPENIA:
1. Documented diagnosis of HIV infection
AND
2. Documentation member has an ANC ≤ 1,000 (cells/mm3) [DOCUMENTATION REQUIRED]

J. FELTYS SYNDROME:
1. Documented diagnosis for Felty's syndrome [DOCUMENTATION REQUIRED]
AND
2. Documentation of a history of recurrent or severe infections
AND
3. Member has tried and failed (A) or (B):
   a. methotrexate (at maximum tolerated dose of up to 25mg weekly)
   OR
   b. leflunomide if unable to tolerate methotrexate AND concurrent use of another DMARD for at least two months

K. ACUTE RADIATION SYNDROME:

1. Documentation that member has had suspected or confirmed acute exposure to myelosuppressive doses of radiation [greater than 2 Grays (Gy)] [DOCUMENTATION REQUIRED]

CONTINUATION OF THERAPY:

A. FOR ALL INDICATIONS:

1. Member is compliant with filgrastim therapy as verified by prescriber and fill 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), low disease activity and/or improvements in the condition's signs and symptoms [DOCUMENTATION REQUIRED]
   AND
3. Prescriber attests to ~~of~~ regular lab monitoring (i.e., CBC) as clinically appropriate and rationale for medical necessity for continuation of therapy

DURATION OF APPROVAL:

Initial Authorization: 12 weeks; For oncology/chemotherapy related indications: Up to 12 weeks or up to length of chemotherapy approval date- whichever is shorter,
Continuation of Therapy: 12 weeks; For oncology/chemotherapy related indications: Up to 12 weeks or up to length of chemotherapy approval date-whichever is shorter

PRESCRIBER REQUIREMENTS:

Prescribed by or in consultation with a board-certified hematologist, oncologist, rheumatologist (Felty's Syndrome), infectious disease (HIV or Hep C treatment related neutropenia), or transplant specialist. [If prescribed in consultation, consultation notes must be submitted with initial request and reauthorization requests]

AGE RESTRICTIONS:

One month of age and older

QUANTITY:

Neupogen: 300 mcg vial: 14 doses per 28 days
Neupogen/Zarxio/Nivestym/Releuko 300 mcg prefilled syringes: 14 doses per 28 days
Neupogen 480 mcg vial: 14 doses per 28 days
Neupogen/Zarxio/Nivestym/Releuko 480 mcg prefilled syringes: 14 doses per 28 days

Maximum Quantity Limits – based on FDA label

PLACE OF ADMINISTRATION:

The recommendation is that injectable medications in this policy will be for pharmacy or medical benefit coverage and the subcutaneous injectable products administered in a place of service that is a non-hospital facility-based location.

The recommendation is that infused medications in this policy will be for pharmacy or medical benefit coverage administered in a place of service that is a non-inpatient hospital facility-based location.

DRUG INFORMATION

ROUTE OF ADMINISTRATION:

Intravenous or Subcutaneous

DRUG CLASS:

Granulocyte Colony-Stimulating Factors (G-CSF)

FDA-APPROVED USES:

ALL PRODUCTS: Myelosuppressive chemotherapy recipients with non-myeloid malignancies: To decrease the incidence of infection (neutropenic fever) in members with non-myeloid malignancies receiving myelosuppressive chemotherapy associated with a significant incidence of severe neutropenia with fever

NEUPOGEN ONLY:
Increase survival in members acutely exposed to myelosuppressive doses of radiation (Hematopoietic Syndrome of Acute Radiation Syndrome)

NEUPOGEN/ZARXIO/NIVESTYM/RELEUKO ONLY:
Acute myeloid leukemia following induction or consolidation chemotherapy: To reduce the time to neutrophil recovery and the duration of fever, following induction or consolidation chemotherapy in adults with acute myeloid leukemia (AML)

Bone marrow transplantation: To reduce the duration of neutropenia and neutropenia-related events (e.g., neutropenic fever) in members with non-myeloid malignancies receiving myeloablative chemotherapy followed by bone marrow transplantation.

Severe chronic neutropenia: Long-term administration to reduce the incidence and duration of neutropenic complications (e.g., fever, infections, oropharyngeal ulcers) in symptomatic members with congenital neutropenia, cyclic neutropenia, or idiopathic neutropenia.

NEUPOGEN/ZARXIO/NIVESTYM ONLY:
Peripheral blood progenitor cell collection and therapy: Mobilization of autologous hematopoietic progenitor cells into the peripheral blood for apheresis collection

COMPENDIAL APPROVED OFF-LABELED USES:
None

APPENDIX

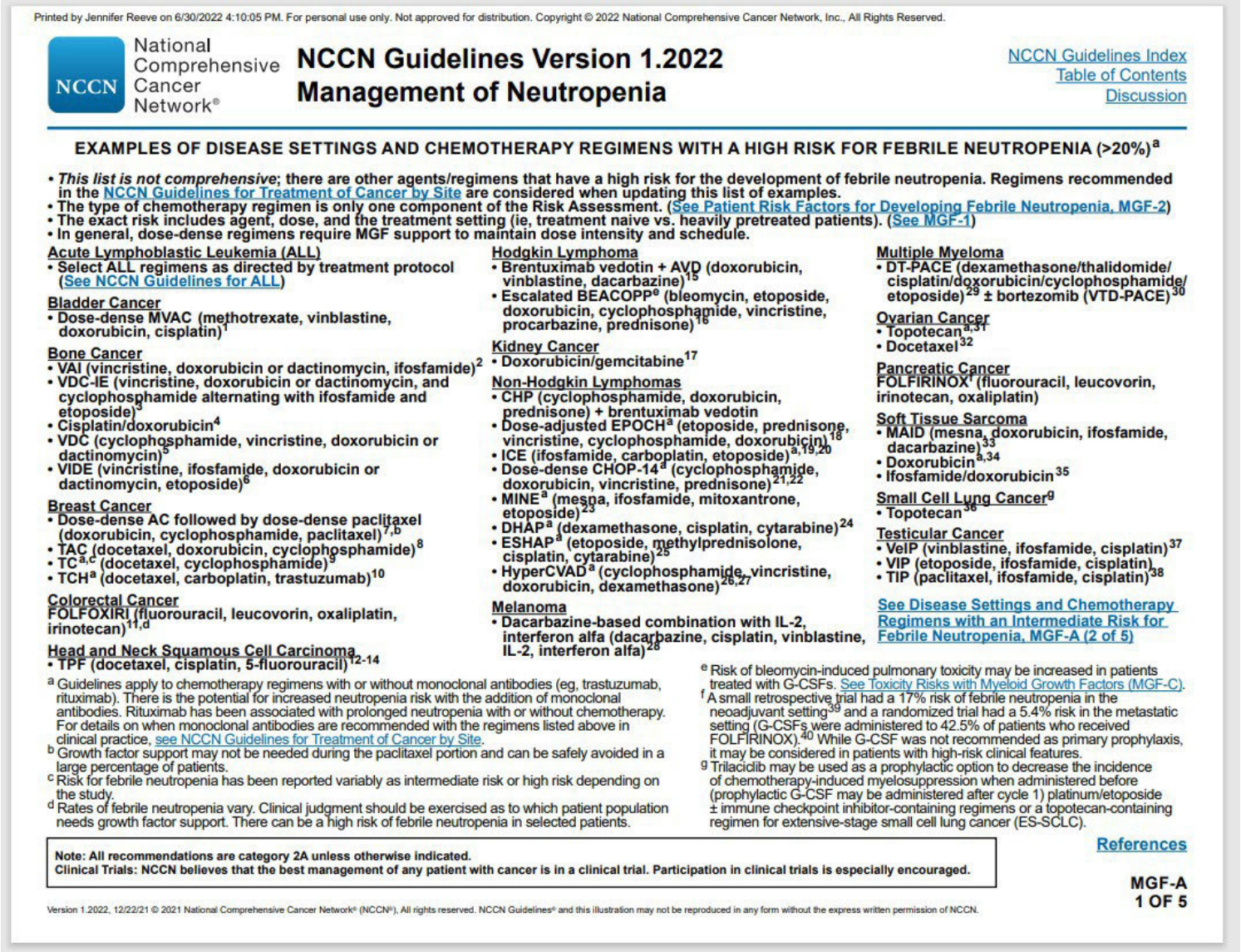
APPENDIX:
A biosimilar is highly similar version of a brand name biological drug that meets strict controls for structural, pharmaceutical, and clinical consistency. A biosimilar manufacturer must demonstrate that there are no meaningful clinical differences (i.e., safety and efficacy) between the biosimilar 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.

High risk for chemotherapy induced FN infectious complications because of bone marrow compromise OR co-morbidity with any of the following risk factors (not an all-inclusive list):

Age >65 years
Poor performance

Drug and Biologic Coverage Criteria
status Previous
episodes of FN
History of previous chemotherapy or radiation therapy
Completion of combined chemoradiotherapy
Bone marrow involvement by tumor producing
cytopenia Pre-existing neutropenia
Poor nutritional status
Poor renal function
Liver dysfunction (i.e. elevated bilirubin)
Presence of open wound(s) or active
infection Recent surgery (within the past 12
weeks) More advanced cancer
Other serious co-morbidities



National Comprehensive Cancer Network®

NCCN Guidelines Version 1.2022
Management of Neutropenia

NCCN Guidelines Index
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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,b]
- TAC (docetaxel, doxorubicin, cyclophosphamide)[8]
- TC[a,c] (docetaxel, cyclophosphamide)[9]
- TCH[a] (docetaxel, carboplatin, trastuzumab)[10]

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

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

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

Kidney Cancer
- Doxorubicin/gemcitabine[17]

Non-Hodgkin Lymphomas
- CHP (cyclophosphamide, doxorubicin, prednisone) + brentuximab vedotin
- 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[f] (fluorouracil, leucovorin, irinotecan, oxaliplatin)

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

Small Cell Lung Cancer[g]
- 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] Growth factor support may not be needed during the paclitaxel portion and can be safely avoided in a large percentage of patients.
[c] Risk for febrile neutropenia has been reported variably as intermediate risk or high risk depending on the study.
[d] Rates of febrile neutropenia vary. Clinical judgment should be exercised as to which patient population needs growth factor support. There can be a high risk of febrile neutropenia in selected patients.
[e] Risk of bleomycin-induced pulmonary toxicity may be increased in patients treated with G-CSFs. See Toxicity Risks with Myeloid Growth Factors (MGF-C).
[f] 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-CSF was not recommended as primary prophylaxis, it may be considered in patients with high-risk clinical features.
[g] Trilaciclib may be used as a prophylactic option to decrease the incidence of chemotherapy-induced myelosuppression when administered before (prophylactic G-CSF may be administered after cycle 1) platinum/etoposide ± immune checkpoint inhibitor-containing regimens or a topotecan-containing regimen for extensive-stage small cell lung cancer (ES-SCLC).

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

BACKGROUND AND OTHER CONSIDERATIONS

BACKGROUND:
None

CONTRAINDICATIONS/EXCLUSIONS/DISCONTINUATION:
All other uses of filgrastim and its biosimilars 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 (Neulasta). Known hypersensitivity to filgrastim or any ingredient in the requested formulation. E. coli protein hypersensitivity. Receiving chemotherapy with a risk of febrile neutropenia <20% and no significant high risk for complications. Filgrastim will be administered in the period between 24 hours before and24 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).

OTHER SPECIAL CONSIDERATIONS:
None

CODING/BILLING INFORMATION

Note: 1) This list of codes may not be all-inclusive. 2) Deleted codes and codes which are not effective at the time the service is rendered may not be eligible for reimbursement

HCPCS CODE	DESCRIPTION
J1442	Inj, filgrastim (g-csf), excludes biosimilars, 1 mcg
Q5101	Inj, filgrastim-sndz, biosimilar, (zarxio), 1 mcg
J1447	Inj, tbo-filgrastim, 1 mcg
Q5110	Inj, filgrastim-aafi, biosimilar, (nivestym), 1 mcg
J3590	Injection, filgrastim-ayow, biosimilar, (releuko), 1 microgram

AVAILABLE DOSAGE FORMS:
Neupogen SOLN 300MCG/ML
Neupogen SOLN 480MCG/1.6ML
Neupogen SOSY 300MCG/0.5ML
Neupogen SOSY 480MCG/0.8ML
Nivestym SOLN 300MCG/ML
Nivestym SOLN 480MCG/1.6ML
Nivestym SOSY300MCG/0.5ML
Nivestym SOSY 480MCG/0.8ML
Zarxio SOSY 300MCG/0.5ML
Zarxio SOSY 480MCG/0.8ML
Granix SOLN 300MCG/ML
Granix SOLN 480MCG/1.6ML
Granix SOSY 300MCG/0.5ML
Granix SOSY 480MCG/0.8ML
Releuko SOLN 300MCG/ML
Releuko SOLN 480MCG/1.6ML

REFERENCES

1. Neupogen [package insert]. Thousand Oaks, CA; Amgen Inc; February 2021.
2. Zarxio [prescribing information]. Princeton, NJ: Sandoz, Inc.; March 2021
3. Granix [prescribing information]. Sunnyvale, CA; Pharmacyclics, Inc.; November ~~2013~~ 2019
4. Nivestym [prescribing information]. Lake Forest, IL; Pfizer; April 2021.
5. Releuko (filgrastim-ayow) [package insert]. Bridgewater, NY: Amneal Pharmaceuticals LLC; March 2022.
6. National Comprehensive Cancer Network. 2022. Hematopoietic Growth Factors (Version 1.2022). [online] Available at: < growthfactors.pdf (nccn.org)> [Accessed 30 June 2022]

SUMMARY OF REVIEW/REVISIONS	DATE
REVISION- Notable revisions: Products Affected Required Medical Information Continuation of Therapy Duration of Approval Prescriber Requirements Quantity FDA-Approved Uses Coding/Billing Information Available Dosage Forms References	Q3 2022
Q2 2022 Established tracking in new format	Historical changes on file