Clinical Policy: Filgrastim (Neupogen), Filgrastim-sndz (Zarxio), Tbo-filgrastim (Granix), Filgrastim-aafi (Nivestym), Filgrastim-ayow (Releuko)

Reference Number: NH.PHAR.297
Effective Date: 09.01.24
Last Review Date: 04.25 Coding Implications
Line of Business: Medicaid Revision Log

See Important Reminder **at the end of this policy for important regulatory and legal information.**

Description

Filgrastim (Neupogen®) and its biosimilars, filgrastim-sndz (Zarxio®), filgrastim-aafi (Nivestym™), filgrastim-ayow (Releuko®), and tbo-filgrastim (Granix®), are human granulocyte colony-stimulating factors.

FDA Approved Indication(s)

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 (FN).

Neupogen, Nivestym, and Zarxio are indicated to mobilize autologous hematopoietic progenitor cells into the peripheral blood for collection by leukapheresis.

Neupogen, Nivestym, Releuko, and Zarxio are indicated to:

- Decrease the incidence of infection, as manifested by FN, in patients with nonmyeloid malignancies receiving myelosuppressive anti-cancer drugs associated with a significant incidence of severe neutropenia with fever.
- Reduce the time to neutrophil recovery and the duration of fever, following induction or consolidation chemotherapy treatment of patients with acute myeloid leukemia (AML).
- Reduce the duration of neutropenia and neutropenia-related clinical sequelae, e.g., FN, in patients with nonmyeloid malignancies undergoing myeloablative chemotherapy followed by bone marrow transplantation (BMT).
- Reduce the incidence and duration of sequelae of severe neutropenia (e.g., fever, infections, oropharyngeal ulcers) in symptomatic patients with congenital neutropenia, cyclic neutropenia, or idiopathic neutropenia.

Neupogen is also indicated to increase survival in patients acutely exposed to myelosuppressive doses of radiation (hematopoietic syndrome of acute radiation syndrome).

Policy/Criteria

Provider must submit documentation (such as office chart notes, lab results or other clinical information) supporting that member has met all approval criteria.

It is the policy of health plans affiliated with Centene Corporation® that Granix, Neupogen, Nivestym, Releuko, and Zarxio are **medically necessary** when the following criteria are met:

CLINICAL POLICY
Filgrastim, Filgrastim-sndz, Filgrastim-aafi, Filgrastim-ayow, Tbo-filgrastim

I. Initial Approval Criteria

A. Chemotherapy-Induced Neutropenia (must meet all)**:**

1. Diagnosis of non-myeloid malignancy (i.e., solid tumor and lymphoid malignancies) or AML;
0. Prescribed for use following myelosuppressive chemotherapy;
1. Member must try and fail at least one preferred product unless contraindicated or clinically significant adverse effects are experienced;
2. The requested medication will not be prescribed concurrently with other colony stimulating factors (e.g., pegfilgrastim, Leukine®) within any chemotherapy cycle;
3. For members receiving palliative chemotherapy, provider attestation that chemotherapy dose reduction has been considered;
4. Documentation of member's current weight (in kg);
5. Dose does not exceed 30 mcg/kg per day [IV] or 24 mcg/kg per day [SC] (*see Appendix F for dose rounding guidelines*).

Approval duration: 6 months

B. Bone Marrow Transplantation (must meet all)**:**

1. Diagnosis of non-myeloid malignancy (i.e., solid tumor and lymphoid malignancies);
6. Member is undergoing myeloablative chemotherapy followed by BMT;
7. Member must try and fail at least one preferred product unless contraindicated or clinically significant adverse effects are experienced;
8. The requested medication will not be prescribed concurrently with other colony stimulating factors (e.g., pegfilgrastim, Leukine®) within any chemotherapy cycle;
9. Documentation of member's current weight (in kg);
2. Dose does not exceed 10 mcg/kg per day [IV] (*see Appendix F for dose rounding guidelines*).

Approval duration: 6 months

C. Peripheral Blood Progenitor Cell Collection (must meet all)**:**

1. Prescribed for the mobilization of autologous hematopoietic progenitor cells into the peripheral blood for collection by leukapheresis;
2. The prescribed drug will be initiated before leukapheresis (e.g., prescribed for 6 to 7 days with leukapheresis on days 5, 6 and 7);
3. Member must try and fail at least one preferred product unless contraindicated or clinically significant adverse effects are experienced;
4. The requested medication will not be prescribed concurrently with other colony stimulating factors (e.g., pegfilgrastim, Leukine®) within any chemotherapy cycle;
5. Documentation of member's current weight (in kg);
3. Request meets one of the following (a or b):*
   a. Dose does not exceed 10 mcg/kg per day [IV or SC] (*see Appendix F for dose rounding guidelines*);
   b. Dose is supported by practice guidelines or peer-reviewed literature for the relevant off-label use (*prescriber must submit supporting evidence*).

   **Prescribed regimen must be FDA-approved or recommended by NCCN.*

Approved duration: 1 month

D. Chronic Neutropenia (must meet all)**:**

1. Prescribed for use in symptomatic (e.g., fever, infections, oropharyngeal ulcers) severe chronic neutropenia caused by congenital neutropenia, cyclic neutropenia, or idiopathic neutropenia;
2. Member must try and fail at least one preferred product unless contraindicated or clinically significant adverse effects are experienced;
3. The requested medication will not be prescribed concurrently with other colony stimulating factors (e.g., pegfilgrastim, Leukine®) within any chemotherapy cycle;
4. Documentation of member's current weight (in kg);
5. Dose does not exceed: 30 mcg/kg per day [IV] or 24 mcg/kg per day [SC] (*see Appendix F for dose rounding guidelines*).

Approved duration: 6 months

E. Acute Radiation Syndrome (must meet all)**:**

1. Prescribed for use following suspected or confirmed acute exposure to myelosuppressive doses of radiation;
2. Member must try and fail at least one preferred product unless contraindicated or clinically significant adverse effects are experienced**;**
3. The requested medication will not be prescribed concurrently with other colony stimulating factors (e.g., pegfilgrastim, Leukine®) within any chemotherapy cycle;
4. Documentation of member's current weight (in kg);
6. Dose does not exceed 10 mcg/kg per day [SC] (*see Appendix F for dose rounding guidelines*).

Approved duration: 6 months

F. Myelodysplastic Syndrome (off-label) (must meet all)**:**

1. Diagnosis of myelodysplastic syndrome with symptomatic anemia without del (5q) abnormality;
2. Current (within the past 30 days) serum erythropoietin level ≤ 500 mU/mL;
3. Member previously has no response to either an erythropoiesis-stimulating agent (e.g., epoetin alfa, darbepoetin) or Reblozyl®;
4. Prescribed in combination with an erythropoiesis-stimulating agent (e.g., epoetin alfa);
5. Member must try and fail at least one preferred product unless contraindicated or clinically significant adverse effects are experienced;
6. The requested medication will not be prescribed concurrently with other colony stimulating factors (e.g., pegfilgrastim, Leukine®) within any chemotherapy cycle;
7. Documentation of member's current weight (in kg);
8. Request meets one of the following (a or b):
    a. Dose does not exceed 2 mcg/kg twice a week [SC] (*see Appendix F for dose rounding guidelines*);
    b. Dose is supported by practice guidelines or peer-reviewed literature for the relevant off-label use (*prescriber must submit supporting evidence*).
    Approved duration: 6 months

G. Wilms Tumor (off-label) (must meet all)**:**

1. Diagnosis of Wilms tumor (nephroblastoma);
5. Request is for supportive care for member receiving a regimen of cyclophosphamide and etoposide, or cyclophosphamide, doxorubicin, and vincristine in Regimen M and Regimen I (*see Appendix D*);
6. Member must try and fail at least one preferred product unless contraindicated or clinically significant adverse effects are experienced;
7. The requested medication will not be prescribed concurrently with other colony stimulating factors (e.g., pegfilgrastim, Leukine®) within any chemotherapy cycle;
8. Documentation of member's current weight (in kg);
2. Request meets one of the following (a or b):
   a. Dose does not exceed 30 mcg/kg per day [IV] or 24 mcg/kg per day [SC] (*see Appendix F for dose rounding guidelines*);
   b. Dose is supported by practice guidelines or peer-reviewed literature for the relevant off-label use (*prescriber must submit supporting evidence*).
   Approved duration: 6 months

H. Other diagnoses/indications (must meet all)**:**

1. Member must try and fail at least one preferred product unless contraindicated or clinically significant adverse effects are experienced;
2. Member must meet one of the following (a or b):
   a. If this drug has recently (within the last 6 months) undergone a label change (e.g., newly approved indication, age expansion, new dosing regimen) that is not yet reflected in this policy, refer to one of the following policies (i or ii):
      i. For drugs on the PDL, the no coverage criteria policy: CP.PMN.255; or
      ii. For drugs NOT on the PDL, the non-formulary policy: CP.PMN.16; or
   b. If the requested use (e.g., diagnosis, age, dosing regimen) is NOT specifically listed under section III (Diagnoses/Indications for which coverage is NOT authorized) AND criterion 2a above does not apply, refer to the off-label use policy CP.PMN.53.

II. Continued Therapy

A. All Indications in Section I (must meet all)**:**

1. Member meets one of the following (a or b):
   a. Currently receiving medication via Centene benefit or member has previously met initial approval criteria;
   b. Member is currently receiving medication and is enrolled in a state and product with continuity of care regulations (*refer to state specific addendums for CC.PHARM.03A and CC.PHARM.03B);*
2. Member is responding positively to therapy;
3. Member must try and fail at least one preferred product unless contraindicated or clinically significant adverse effects are experienced;
4. The requested medication will not be prescribed concurrently with other colony stimulating factors (e.g., pegfilgrastim, Leukine®) within any chemotherapy cycle;
5. Documentation of member's current weight (in kg);

6. If request is for a dose increase, request meets one of the following (a or b):
   a. New dose does not exceed the FDA-approved maximum recommended dose for the relevant indication in Section V (*see Appendix F for dose rounding guidelines*);
   b. New dose is supported by practice guidelines or peer-reviewed literature for the relevant off-label use (*prescriber must submit supporting evidence*).

Approval duration: 6 months

B. Other diagnoses/indications (must meet 1 and 2)**:**

1. Member must try and fail at least one preferred product unless contraindicated or clinically significant adverse effects are experienced;
2. Member must meet one of the following (a or b):
   a. If this drug has recently (within the last 6 months) undergone a label change (e.g., newly approved indication, age expansion, new dosing regimen) that is not yet reflected in this policy, refer to one of the following policies (i or ii):
      i. For drugs on the PDL, the no coverage criteria policy: CP.PMN.255; or
      ii. For drugs NOT on the PDL, the non-formulary policy: CP.PMN.16; or
   b. If the requested use (e.g., diagnosis, age, dosing regimen) is NOT specifically listed under section III (Diagnoses/Indications for which coverage is NOT authorized) AND criterion 2a above does not apply, refer to the off-label use policy CP.PMN.53.

III. Diagnoses/Indications for which coverage is NOT authorized:

A. Non-FDA approved indications, which are not addressed in this policy, unless there is sufficient documentation of efficacy and safety according to the off label use policies – CP.PMN.53, or evidence of coverage documents.

IV. Appendices/General Information *Appendix*

A. Abbreviation/Acronym Key

AML: acute myeloid leukemia
ANC: absolute neutrophil count
BMT: bone marrow transplantation
FDA: Food and Drug Administration
FN: febrile neutropenia
G-CSF: granulocyte colony-stimulating factor

Appendix B. Therapeutic Alternatives

Not applicable

Appendix C. Contraindications/Boxed Warnings

- Contraindication(s): history of serious allergic reactions to human granulocyte colony-stimulating factors such as filgrastim products or pegfilgrastim products
- Boxed warning(s): none reported

Appendix D. General Information

- Zarxio is not recommended in patients requiring direct administration of less than 0.3 mL due to the potential for dosing errors. The spring-mechanism of the needle guard apparatus affixed to the prefilled syringe interferes with the visibility of the graduation markings on the syringe barrel corresponding to 0.1 mL and 0.2 mL. The visibility of these markings is necessary to accurately measure doses of Zarxio less than 0.3 mL (180 mcg).

- Neutropenia is defined as an absolute neutrophil count (ANC) of < 500 neutrophils/mcL or an ANC of < 1,000 neutrophils/mcL and a predicted decline to ≤ 500 neutrophils/mcL over the next 48 hours. Neutropenia can progress to FN, defined as a single temperature of ≥ 38.8°C orally or ≥ 38.0°C over 1 hour.
- The development of febrile neutropenia is a common dose-limiting toxicity of many chemotherapy regimens. This risk is directly related to the intensity of the chemotherapy regimen. Chemotherapy regimens that have an incidence of febrile neutropenia greater than 20% in clinical trials in chemotherapy naïve patients are considered by the National Comprehensive Cancer Network (NCCN) panel at high risk. Prophylaxis with myeloid growth factors is recommended at this level of risk (Category 1 recommendation). NCCN Compendium recommend prophylaxis be considered in intermediate-risk (10-20% overall risk of FN) patients (Category 2A recommendation). In addition to chemotherapy regimens, other risk factors such as: treatment-related, patient related, cancer-related, and co-morbidities have also been associated with an increased risk of febrile neutropenia. Therefore, the type of chemotherapy regimen is only one component of the risk assessment.
- For chemotherapy patients, continuing filgrastim until the ANC has reached 10,000/mm^3 following the expected chemotherapy-induced neutrophil nadir (as specified in the G-CSF package insert), is known to be safe and effective. However, a shorter duration of administration that is sufficient to achieve clinically adequate neutrophil recovery is a reasonable alternative, considering issues of patient convenience and cost.[5]
- Evidence supports dose reduction of pegylated interferon according to FDA approved labeling as treatment for neutropenia occurring in hepatitis C patients treated with combination therapy (pegylated interferon + ribavirin). Treatment with filgrastim is not

  FDA approved or recommended by current hepatitis C treatment guidelines except in patients with decompensated cirrhosis.
- There are insufficient data to support the use of filgrastim to treat febrile neutropenia in patients who have received prophylactic Neulasta.
- In a randomized, double-blind, multi-center safety and efficacy study of 218 breast cancer patients receiving chemotherapy with a high risk of neutropenia, Zarxio was non-inferior to Neupogen on the primary endpoint of duration of severe neutropenia (1.17 days for Zarxio and 1.20 days for Neupogen).
- NCCN guidelines for myelodysplastic syndrome list filgrastim with a category 2A recommendation for use as initial treatment of symptomatic anemia in lower risk disease with no del (5q), serum erythropoietin levels ≤500 mU/mL, and ring sideroblasts ≥15%. Filgrastim may also be considered for the treatment of symptomatic anemia in lower risk disease with serum erythropoietin levels ≤500 mU/mL, and ring sideroblasts <15% when these is no response or erythroid response followed by loss of response to epoetin or darbepoetin alone (category 2A recommendation).
- For patients with a latex allergy, Granix (tbo-filgrastim) and Nivestym (filgrastim-aafi) are considered to be latex free. For Neupogen (filgrastim), and Zarxio (filgrastim-sndz), the presence of latex definitively be ruled out.
- According to the ASCO, 2006 Clinical Practice Guideline for the Use of White Blood Cell Growth Factors, dose reduction or delay remains an appropriate strategy for the palliative treatment of cancer, as there is no evidence that dose maintenance or escalation

improves clinically important outcomes in this setting. The 2015 updates to this guideline found no new data supporting the use of colony-stimulating factors (CSFs) to maintain dose-intensity in the treatment of metastatic disease, and the review found no demonstrable benefit in the use of myeloid growth factors to in patients with metastatic lung, small-cell lung, colorectal, hormone-refractory prostate, or breast cancer. To date, there have been no improvements in disease-free or OS reported for any common cancer with the use of CSFs to maintain dose-intensity, instead of dose reduction. The ASCO Panel recognizes that there may be individual patients who will not tolerate effective doses of chemotherapy without CSFs. Medical Oncologists making the decision to use prophylactic MGFs, or not, may need to consider not only the optimal chemotherapy regimen, but also the individual member risk factors and the intention of treatment; that is, curative, prolongation of life, or symptom control and palliation.

- For mobilization of hematopoietic progenitor cells in the autologous setting, NCCN myeloid growth factor treatment guidelines include a dosing range from 10 to 32 mcg/kg/day by subcutaneous injection, in daily or twice-daily dosing, when used as a single-agent growth factor.
- Chemotherapy regimens used in the treatment of Wilms Tumor for which filgrastim supportive care may be considered:
  - Regimen M: 9 doses of vincristine, 5 doses of dactinomycin, 5 doses of doxorubicin (cumulative dose 150 mg/m2), 4 courses of 5 daily doses of cyclophosphamide, and 4 courses of 5 daily doses of etoposide over 24 weeks. Dactinomycin and doxorubicin are given together, and cyclophosphamide and etoposide are given together.
  - Regimen I: 9 doses of vincristine, 4 doses of doxorubicin (cumulative dose 180 mg/m2), 7 courses of 3 to 5 daily doses of cyclophosphamide, and 3 courses of 5 daily doses of etoposide. Doxorubicin and 3 daily doses of cyclophosphamide are given together, and 5 daily doses of cyclophosphamide and etoposide are given together.

*Appendix F: Dose Rounding Guidelines**

Weight-based Dose Range	Vial Quantity Recommendation
≤ 314.99 mcg	1 vial of 300 mcg/1 mL
315-503.99 mcg	1 vial of 480 mcg/1.6 mL
315-629.99 mcg	2 vials of 300 mcg/1 mL
630-944.99 mcg	3 vials of 300 mcg/1 mL
945-1,007.99 mcg	2 vials of 480 mcg/1.6 mL
1,008-1,511.99 mcg	3 vials of 480 mcg/1.6 mL

**This is part of a dose rounding guideline on select drug classes as part of an initiative conducted on a larger scale with multiple references and prescriber feedback.*

V. Dosage and Administration

Drug Name	Indication	Dosing Regimen	Maximum Dose
Filgrastim (Neupogen) , filgrastim-sndz (Zarxio) , filgrastim-aafi (Nivestym) , filgrastim-ayow (Releuko)	Chemotherapy - induced neutropenia	5 mcg/kg SC or IV QD Dose may be increased in increments of 5 mcg/kg for each chemotherapy cycle, according to the duration and severity of the ANC nadir Do not administer 24 hours before and after chemotherapy	30 mcg/kg/day [IV] or 24 mcg/kg/day [SC]
	Chronic neutropenia	Congenital: 6 mcg/kg SC BID Idiopathic or cyclic: 5 mcg/kg SC QD	30 mcg/kg/day [IV] or 24 mcg/kg/day [SC]
	BMT	10 mcg/kg IV infusion QD	10 mcg/kg/day
	Peripheral blood progenitor cell collection	10 mcg/kg SC bolus or continuous infusion QD	10 mcg/kg/day
	Patients acutely exposed to myelosuppressive doses of radiation	10 mcg/kg SC QD	10 mcg/kg/day
Tbo-filgrastim (Granix)	Myelosuppressive chemotherapy	5 mcg/kg SC or IV QD	5 mcg/kg/day

. **Product Availability**

Drug	Availability
Filgrastim (Neupogen)	Single-dose prefilled syringes for injection: 300 mcg/0.5 mL, 480 mcg/0.8 mL Single-dose vials for injection: 300 mcg/mL, 480 mcg/1.6 mL
Filgrastim-sndz (Zarxio)	Single-dose prefilled syringes for injection: 300 mcg/0.5 mL, 480 mcg/0.8 mL
Filgrastim-aafi (Nivestym)	Single-dose prefilled syringes for injection: 300 mcg/0.5 mL, 480 mcg/0.8 mL Single-dose vials for injection: 300 mcg/mL, 480 mcg/1.6 mL
Filgrastim-ayow (Releuko)	Single-dose prefilled syringes for injection: 300 mcg/0.5 mL, 480 mcg/0.8 mL Single-dose vials for injection: 300 mcg/mL, 480 mcg/1.6 mL
Tbo-filgrastim (Granix)	Single-dose prefilled syringes for injection: 300 mcg/0.5 mL, 480 mcg/0.8 mL Single-dose vials for injection: 300 mcg/mL, 480 mcg/1.6 mL

VII. References

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13. National Comprehensive Cancer Network. Acute Myeloid Leukemia 2.2024. Available at: https://www.nccn.org/professionals/physician_gls/pdf/aml.pdf. Accessed May 8, 2024.

Coding Implications

Codes referenced in this clinical policy are for informational purposes only. Inclusion or exclusion of any codes does not guarantee coverage. Providers should reference the most up-to-date sources of professional coding guidance prior to the submission of claims for reimbursement of covered services.

HCPCS Codes	Description
J1442	Injection, filgrastim (G-CSF), excludes biosimilars, 1 microgram
J1447	Injection, tbo-filgrastim, 1 microgram
Q5101	Injection, filgrastim-sndz, biosimilar, (Zarxio), 1 microgram
Q5110	Injection, filgrastim-aafi, biosimilar, (Nivestym), 1 microgram
Q5125	Injection, filgrastim-ayow, biosimilar, (Releuko), 1 mcg

Reviews, Revisions, and Approvals	Date	P&T Approval Date
New Policy Created	06.24	06.24
Annual review, no significant changes	04.25	04.25

Important Reminder

This clinical policy has been developed by appropriately experienced and licensed health care professionals based on a review and consideration of currently available generally accepted standards of medical practice; peer-reviewed medical literature; government agency/program approval status; evidence-based guidelines and positions of leading national health professional organizations; views of physicians practicing in relevant clinical areas affected by this clinical policy; and other available clinical information. The Health Plan makes no representations and accepts no liability with respect to the content of any external information used or relied upon in developing this clinical policy. This clinical policy is consistent with standards of medical practice current at the time that this clinical policy was approved. "Health Plan" means a health plan that has adopted this clinical policy and that is operated or administered, in whole or in part, by Centene Management Company, LLC, or any of such health plan's affiliates, as applicable.

The purpose of this clinical policy is to provide a guide to medical necessity, which is a component of the guidelines used to assist in making coverage decisions and administering benefits. It does not constitute a contract or guarantee regarding payment or results. Coverage decisions and the administration of benefits are subject to all terms, conditions, exclusions and limitations of the coverage documents (e.g., evidence of coverage, certificate of coverage, policy, contract of insurance, etc.), as well as to state and federal requirements and applicable Health Plan-level administrative policies and procedures.

This clinical policy is effective as of the date determined by the Health Plan. The date of posting may not be the effective date of this clinical policy. This clinical policy may be subject to applicable legal and regulatory requirements relating to provider notification. If there is a discrepancy between the effective date of this clinical policy and any applicable legal or

regulatory requirement, the requirements of law and regulation shall govern. The Health Plan retains the right to change, amend or withdraw this clinical policy, and additional clinical policies may be developed and adopted as needed, at any time.

This clinical policy does not constitute medical advice, medical treatment or medical care. It is not intended to dictate to providers how to practice medicine. Providers are expected to exercise professional medical judgment in providing the most appropriate care, and are solely responsible for the medical advice and treatment of members. This clinical policy is not intended to recommend treatment for members. Members should consult with their treating physician in connection with diagnosis and treatment decisions.

Providers referred to in this clinical policy are independent contractors who exercise independent judgment and over whom the Health Plan has no control or right of control. Providers are not agents or employees of the Health Plan.

Note: For Medicaid members, when state Medicaid coverage provisions conflict with the coverage provisions in this clinical policy, state Medicaid coverage provisions take precedence. Please refer to the state Medicaid manual for any coverage provisions pertaining to this clinical policy.