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

Reference Number: CP.PHAR.297
Effective Date: 12.01.16
Last Review Date: 05.20
Line of Business: Commercial, HIM, Medicaid

Coding Implications
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™), 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:

- 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)
- Mobilize autologous hematopoietic progenitor cells into the peripheral blood for collection by leukapheresis
- 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 Neupogen, Zarxio, Nivestym, and Granix are **medically necessary** when the following criteria are met:

I. Initial Approval Criteria

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

1. Diagnosis of non-myeloid malignancy or AML;
2. Prescribed for use following myelosuppressive chemotherapy;
3. For Neupogen, Nivestym or Granix requests, member meets one of the following (a or b):
   a. Medical justification supports inability to use Zarxio (e.g., contraindications to the excipients);
      **Prior authorization may be required for Zarxio.*
   b. Request is for the treatment associated with Stage IV or metastatic cancer for a State with regulations against step therapy in advanced oncology settings *(see Appendix E)*;
4. Dose does not exceed 30 mcg/kg per day [IV] or 24 mcg/kg per day [SC].

Approval duration:
Medicaid/HIM – 6 months
Commercial – 6 months or to the member's renewal date, whichever is longer

B. Bone Marrow Transplantation (must meet all)**:**
1. Diagnosis of non-myeloid malignancy;
2. Member is undergoing myeloablative chemotherapy following BMT;
3. For Neupogen, Nivestym or Granix requests, medical justification supports inability to use Zarxio (e.g., contraindications to the excipients);
   **Prior authorization may be required for Zarxio.*
4. Dose does not exceed 10 mcg/kg per day [IV or SC].

Approval duration:
Medicaid/HIM – 6 months
Commercial – 6 months or to the member's renewal date, whichever is longer

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. For Neupogen, Nivestym or Granix requests, medical justification supports inability to use Zarxio (e.g., contraindications to the excipients);
   **Prior authorization may be required for Zarxio*
4. Dose does not exceed 10 mcg/kg per day [IV or SC].

Approved duration:
Medicaid/HIM – 1 month
Commercial – 6 months or to the member's renewal date, whichever is longer

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. For Neupogen, Nivestym or Granix requests, medical justification supports inability to use Zarxio (e.g., contraindications to the excipients);
   **Prior authorization is (or may be) required for Zarxio.*
3. Dose does not exceed: 30 mcg/kg per day [IV] or 24 mcg/kg per day [SC].

Approved duration:
Medicaid/HIM – 6 months
Commercial – 6 months or to the member's renewal date, whichever is longer

E. Acute Radiation Syndrome (must meet all)**:**
1. Prescribed for use following suspected or confirmed acute exposure to myelosuppressive doses of radiation;
2. For Neupogen, Nivestym or Granix requests, medical justification supports inability to use Zarxio (e.g., contraindications to the excipients);
   **Prior authorization may be required for Zarxio.*
3. Dose does not exceed 10 mcg/kg per day [SC].

Approved duration:
Medicaid/HIM – 6 months
Commercial – 6 months or to the member's renewal date, whichever is longer

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. For Neupogen, Nivestym or Granix requests, medical justification supports inability to use Zarxio (e.g., contraindications to the excipients);
   **Prior authorization is (or may be) required for Zarxio*
4. Request meets one of the following (a or b):
   a. Dose does not exceed 2 mcg/kg twice a week [SC];
   b. Dose is supported by practice guidelines or peer-reviewed literature for the relevant off-label use (*prescriber must submit supporting evidence*).

Approved duration:
Medicaid/HIM – 6 months
Commercial – 6 months or to the member's renewal date, whichever is longer

G. Other diagnoses/indications
1. Refer to the off-label use policy for the relevant line of business if diagnosis is NOT specifically listed under section III (Diagnoses/Indications for which coverage is NOT authorized): CP.CPA.09 for commercial, HIM.PHAR.21 for health insurance marketplace, and CP.PMN.53 for Medicaid.

II. Continued Therapy

A. All Indications in Section I (must meet all)**:**
1. Currently receiving medication via Centene benefit or member has previously met initial approval criteria;
2. Member is responding positively to therapy;
3. For Neupogen, Nivestym or Granix requests, member meets one of the following (a or b):
   a. Medical justification supports inability to use Zarxio (e.g., contraindications to the excipients);
      **Prior authorization may be required for Zarxio.*

b. Request is for the treatment associated with Stage IV or metastatic cancer for a State with regulations against step therapy in advanced oncology settings *(see Appendix E*);

4. 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
   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:
Medicaid/HIM – 6 months
Commercial – 6 months or to the member's renewal date, whichever is longer

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

1. Currently receiving medication via Centene benefit and documentation supports positive response to therapy.
   Approval duration: Duration of request or 6 months (whichever is less); or
2. Refer to the off-label use policy for the relevant line of business if diagnosis is NOT specifically listed under section III (Diagnoses/Indications for which coverage is NOT authorized): CP.CPA.09 for commercial, HIM.PHAR.21 for health insurance marketplace, and CP.PMN.53 for Medicaid.

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.CPA.09 for commercial, HIM.PHAR.21 for health insurance marketplace, and CP.PMN.53 for Medicaid 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
- 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 ≥ 38.8ºC orally or ≥ 38.0ºC 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 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.

Appendix E: States with Regulations against Redirections in Stage IV or Metastatic Cancer

State	Step Therapy Prohibited?	Notes
AR	Yes	For metastatic cancer, **unless** the preferred drug is consistent with "best practices" (1) used for treatment under (A) FDA-approved indication, or (B) National Comprehensive Cancer Network Drugs & Biologics Compendium; or (2) using evidence-based, peer-reviewed, recognized medical literature. Note – may not require step therapy a second time for same Rx drug.
FL	Yes	For stage 4 metastatic cancer and associated conditions.
GA	Yes	For stage 4 metastatic cancer
IA	Yes	For standard of care stage 4 cancer drug use, supported by peer-reviewed, evidence-based literature, and approved by FDA.
LA	Yes	For stage 4 advanced, metastatic cancer or associated conditions. Exception if "clinically equivalent therapy, contains identical active ingredient(s), and proven to have same efficacy.
PA	Yes	For stage 4 advanced, metastatic cancer
TN	Yes	For advanced metastatic cancer and associated conditions
TX	Yes	For stage 4 advanced, metastatic cancer and associated conditions

V. Dosage and Administration

Drug Name	Indication	Dosing Regimen	Maximum Dose
Filgrastim (Neupogen), filgrastim-sndz (Zarxio) , filgrastim-aafi (Nivestym)	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 or SC 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	10 mcg/kg SC QD	10 mcg/kg/day

Drug Name	Indication	Dosing Regimen	Maximum Dose
	myelosuppressive doses of radiation		
Tbo-filgrastim (Granix)	Myelosuppressive chemotherapy	5 mcg/kg SC or IV QD	5 mcg/kg/day

VI. 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
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

1. Granix Prescribing Information. North Wales, PA: Teva Pharmaceuticals USA; March 2019. Available at: http://granixhcp.com/. Accessed May 15, 2019.
2. Neupogen Prescribing Information. Thousand Oaks, CA: Amgen, Inc.; June 2018. Available at: www.neupogen.com. Accessed May 15, 2019.
3. Zarxio Prescribing Information. Princeton, NJ: Sandoz, Inc.; February 2017. Available at: www.zarxio.com. Accessed May 15, 2019.
4. Nivestym Prescribing Information. Lake Forest, IL: Hospira, Inc.; July 2018. Available at: https://www.pfizerpro.com/product/nivestym/. Accessed May 15, 2019.
5. National Comprehensive Cancer Network. Myeloid Growth Factors Version 2.2019. Available at: http://www.nccn.org/professionals/physician_gls/pdf/myeloid_growth.pdf. Accessed: May 15, 2019.
6. National Comprehensive Cancer Network Drugs and Biologics Compendium. Available at: http://www.nccn.org/professionals/drug_compendium. Accessed May 15, 2019.
7. DRUGDEX® System [Internet database]. Greenwood Village, Colo: Thomson Healthcare, Updated periodically. Accessed May 15, 2019.
8. Clinical Pharmacology [database online]. Tampa, FL: Gold Standard, Inc.; 2018. Available at: http://www.clinicalpharmacology-ip.com/. Accessed May 15, 2019.
9. National Comprehensive Cancer Network. Myelodysplastic Syndromes 2.2019. Available at: https://www.nccn.org/professionals/physician_gls/pdf/mds.pdf. Accessed May 15, 2019.

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-

todate 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 (G-CSF), biosimilar, 1 microgram
Q5110	Injection, filgrastim-aafi, biosimilar, 1 microgram

Reviews, Revisions, and Approvals	Date	P&T Approval Date
Granix, Neupogen, Zarxio are split from CP.PHAR.26.Colony Stimulating Factors 2015, and converted to a new template. Contraindications added per PIs. Under the labeled indication, "BMT," added "and bone marrow infusion." "PBPC collection" (section I.D), removed approval for use in subsequent transplant after collection; however, subsequent transplant will fall under off-label use, "supportive care in the post-hematopoietic cell transplant setting". Under sections I.A, B and C, 24-hour use restriction before and after chemotherapy is removed. Added oncology off-label uses per NCCN.	10.01.16	12.16
Updated template and references. Added continued therapy criteria for severe chronic neutropenia. For AML: changed wording from myelosuppressive chemotherapy from non-myeloid leukemia to induction or consolidation chemotherapy for acute myeloid leukemia per indication.	08.16.17	11.17
3Q 2018 annual review: added HIM line of business; revised max dosing for chemotherapy-induced neutropenia and chronic neutropenia per Clinical Pharmacology; removed radiation exposure requirement; added off-label use in myelodysplastic syndrome per NCCN Compendium; references reviewed and updated.	05.02.18	08.18
No significant changes: revised FDA Approved Indication(s) section for Granix-indication expanded to include pediatric patients ≥ 1 month old per updated FDA labeling.	09.26.18	
No significant changes; revised maximum dosing from 10 mg to 10 mcg for bone marrow transplant criteria set, consistent with prescribing information.	03.04.19	
3Q 2019 annual review: added Nivestym to criteria; added HIM-Medical Benefit line of business, references reviewed and updated.	05.15.19	08.19
Added latex allergy information to appendix	07.17.19	
Added Commercial line of business per SDC and prior clinical guidance; retire CP.CPA.129.	09.18.19	
Added requirement for redirection to Zarxio to Section II for continued therapy requests; clarified medical justification (rather than failure) why Zarxio cannot be used is required; removed HIM-	04.20.20	05.20

Reviews, Revisions, and Approvals	Date	P&T Approval Date
Medical Benefit line of business and references to HIM.PA.103 for Granix requests; allowed by-passing of redirection if state regulations do not allow step therapy in Stage IV or metastatic cancer settings..		

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.