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

Reference Number: ERX.SPA.58
Effective Date: 09.01.17
Last Review Date: 08.21
Line of Business: Commercial, 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 for reduction in the duration of severe neutropenia in patients 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.

Health plan approved formularies should be reviewed for all coverage determinations. Requirements to use preferred alternative agents apply only when such requirements align with the health plan approved formulary.

It is the policy of health plans affiliated with Envolve Pharmacy Solutions™ that Granix, Neupogen, Nivestym, Releuko, and Zarxio 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 members receiving palliative chemotherapy, provider attestation that chemotherapy dose reduction has been considered;
4. Dose does not exceed 30 mcg/kg per day [IV] or 24 mcg/kg per day [SC] (*see Appendix E for dose rounding guidelines*).

Approval duration: 6 months

B. Bone Marrow Transplantation (must meet all)**:**
1. Diagnosis of non-myeloid malignancy;
2. Member is undergoing myeloablative chemotherapy followed by BMT;
3. Dose does not exceed 10 mcg/kg per day [IV or SC] (*see Appendix E 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. Request meets one of the following (a or b):*
   a. Dose does not exceed 10 mcg/kg per day [IV or SC] (*see Appendix E 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.*

Approval 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. Dose does not exceed: 30 mcg/kg per day [IV] or 24 mcg/kg per day [SC] (*see Appendix E for dose rounding guidelines*).

Approval 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. Dose does not exceed 10 mcg/kg per day [SC] (*see Appendix E for dose rounding guidelines*).

Approval 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. Request meets one of the following (a or b):
   a. Dose does not exceed 2 mcg/kg twice a week [SC] (*see Appendix E 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);

2. 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*);
3. 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
1. Refer to ERX.PA.01 if diagnosis is NOT specifically listed under section III (Diagnoses/Indications for which coverage is NOT authorized).

II. Continued Therapy

A. All Indications in Section I (must meet all)**:**
1. Currently receiving medication via a health plan affiliated with Envolve Pharmacy Solutions or member has previously met initial approval criteria;
2. Member is responding positively to therapy;
3. 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 (*see Appendix E 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 or 2)**:**
1. Currently receiving medication via a health plan affiliated with Envolve Pharmacy Solutions and documentation supports positive response to therapy.
   Approval duration: Duration of request or 6 months (whichever is less); or
2. Refer to ERX.PA.01 if diagnosis is NOT specifically listed under section III (Diagnoses/Indications for which coverage is NOT authorized).

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 policy – ERX.PA.01 or evidence of coverage documents.

IV. Appendices/General Information

Appendix A: Abbreviation/Acronym Key

AML: acute myeloid/myelogenous 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.
- 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) is 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 E: 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 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 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

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
Filgrastim-ayow (Releuko	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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Reviews, Revisions, and Approvals	Date	P&T Approval Date
Policy split from ERX.SPMN.07 Colony Stimulating Factors and converted to new template. Renewal criteria added. Separated criteria by indication rather than by drug. All off-label uses are referred to the off-label use policy. Changed approval duration for peripheral blood progenitor cell collection and for acute radiation syndrome to reflect actual duration of therapy for these	07.17	08.17

Reviews, Revisions, and Approvals	Date	P&T Approval Date
indications. Removed requirements to avoid administration within a certain timeframe of administering chemotherapy.		
3Q 2018 annual review: allowed Granix for all indications covered by Neupogen or Zarxio; 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
3Q 2019 annual review: added Nivestym to criteria; revised redirection to prefer Zarxio for all indications except acute radiation syndrome; added information about latex allergy to general information appendix; references reviewed and updated.	07.17.19	08.19
Added appendix E: dose rounding guidelines; added reference to appendix E within criteria.	02.21.20	05.20
3Q 2020 annual review: removed Zarxio redirection; for chemotherapy-induced neutropenia criteria set, added "For members receiving palliative chemotherapy, provider attestation that chemotherapy dose reduction has been considered."	04.30.20	08.20
For peripheral blood progenitor cell collection indication, added option for off-label dosing per guidelines or peer-reviewed literature.	09.10.20	
3Q 2021 annual review: added NCCN compendium supported off-label use in Wilms tumor; references reviewed and updated.	04.01.21	08.21
RT4: added Releuko to policy.	03.10.22	

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.

This Clinical Policy is not intended to dictate to providers how to practice medicine, nor does it constitute a contract or guarantee regarding payment or results. 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.