Clinical Policy Title:	filgrastim, filgrastim-sndz, tbo- filgrastim, filgrastim-aafi, filgrastim-ayow
Policy Number:	RxA.157
Drug(s) Applied:	Neupogen®, Zarxio®, Nivestym™, Granix® and Releuko®
Original Policy Date:	02/07/2020
Last Review Date:	04/18/2022
Line of Business Policy Applies to:	All lines of business

Background

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

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™, Zarxio® and Releuko® are indicated to:

- Decrease the incidence of infection, as manifested by FN, in patients with non-myeloid 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 non-myeloid 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.
- Only for Neupogen®, Nivestym™, Zarxio®: Mobilize autologous hematopoietic progenitor cells into the peripheral blood for collection by leukapheresis.

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

Dosing Information

Drug Name	Indication	Dosing Regimen	Maximum Dose
filgrastim (Neupogen®), filgrastim-sndz (Zarxio®), filgrastim-aafi (Nivestym™) and filgrastim-ayow (Releuko®)	Chemotherapy- Induced Neutropenia	Recommended starting dose: 5 mcg/kg subcutaneously or intravenously once daily Dose may be increased in increments of 5 mcg/kg for each chemotherapy cycle,	30 mcg/kg/day [intravenously] or 24 mcg/kg/day [subcutaneously]

Dosing Information

Drug Name	Indication	Dosing Regimen	Maximum Dose
		according to the duration and severity of the absolute neutrophil count (ANC) nadir. Stop therapy if the ANC increases beyond 10,000/mm^3 Do not administer 24 hours before and after chemotherapy	
	Chronic neutropenia	Congenital: 6 mcg/kg subcutaneously twice daily Idiopathic or cyclic: 5 mcg/kg subcutaneously once daily	30 mcg/kg/day [intravenously] or 24 mcg/kg/day [subcutaneously]
	Bone marrow transplantation	10 mcg/kg intravenously or subcutaneously infusion once daily	10 mcg/kg/day
filgrastim (Neupogen®)	Patients acutely exposed to myelosuppressive doses of radiation	10 mcg/kg subcutaneously once daily	10 mcg/kg/day
tbo-filgrastim (Granix®)	Severe neutropenia	5 mcg/kg subcutaneously or intravenously once daily	5 mcg/kg/day
filgrastim (Neupogen®), filgrastim-sndz (Zarxio®), filgrastim-aafi (Nivestym™)	Peripheral blood progenitor cell collection	10 mcg/kg subcutaneously bolus or continuous infusion once daily	10 mcg/kg/day

Dosage Forms

- 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
- 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

Clinical Policy

Provider must submit documentation (such as office chart notes, lab results or other clinical information) supporting that member has met all approval criteria. The provision of provider samples does not guarantee coverage under the terms of the pharmacy benefit administered by RxAdvance. All criteria for initial approval must be met in order to obtain coverage.

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®, Granix®, Releuko® requests, member has had a failure with Nivestym™ or Zarxio®*, unless contraindicated or clinically significant adverse effects are experienced;
   *Prior authorization may be required for Zarxio® and Nivestym™.
4. Dose does not exceed 30 mcg/kg per day [intravenously] or 24 mcg/kg per day [subcutaneously].

Approval Duration
Commercial: 6 months
Medicaid: 6 months

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

1. Diagnosis of non-myeloid malignancy;
2. Member is undergoing myeloablative chemotherapy following BMT;
3. For Neupogen®, Granix®, Releuko® requests, member has had a failure with Nivestym™, Zarxio®, unless contraindicated or clinically significant adverse effects are experienced;
   *Prior authorization may be required for Zarxio® and Nivestym™.
4. Dose does not exceed 10 mcg/kg per day [intravenously or subcutaneously].

Approval Duration
Commercial: 6 months
Medicaid: 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. Request is for Neupogen®, Zarxio®, Nivestym™, Granix®;
3. The prescribed drug will be initiated before leukapheresis (e.g., prescribed for 6 to 7 days with leukapheresis on days 5, 6 and 7);
4. Neupogen®, Granix® requests, member has had a failure with Nivestym™, or Zarxio®*, unless contraindicated or clinically significant adverse effects are experienced;
   *Prior authorization may be required for Zarxio® and Nivestym™,.
5. Dose does not exceed 10 mcg/kg per day [intravenously or subcutaneously].

Approval Duration
Commercial: 6 months
Medicaid: 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. For Neupogen®, Releuko® or Granix® requests, member has had a failure with Nivestym™ or Zarxio®*, unless contraindicated or clinically significant adverse effects are experienced;
   *Prior authorization may be required for Zarxio® and Nivestym™.

3. Dose does not exceed: 30 mcg/kg per day [intravenously] or 24 mcg/kg per day [subcutaneously].

Approval Duration
Commercial: 6 months
Medicaid: 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. Request is for Neupogen®, Zarxio®, Nivestym™, Granix®;
3. For Neupogen®, Granix® requests, member has had a failure with Nivestym™ or Zarxio®*, unless contraindicated or clinically significant adverse effects are experienced;
   *Prior authorization may be required for Zarxio® and Nivestym™.
4. Dose does not exceed 10 mcg/kg per day [subcutaneously].

Approval Duration
Commercial: 6 months
Medicaid: 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. For Neupogen®, Releuko® requests, member has had a failure with Nivestym™ or Zarxio®*, unless contraindicated or clinically significant adverse effects are experienced;
   *Prior authorization is may be required for Zarxio® and Nivestym™.
4. Request meets one of the following (a or b):
   a. Dose does not exceed 2 mcg/kg twice a week [subcutaneously];
   b. Dose is supported by practice guidelines or peer-reviewed literature for the relevant off-label use (prescriber must submit supporting evidence).

Approval Duration
Commercial: 6 months
Medicaid: 6 months

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

1. Request is for Neupogen®, Nivestym™ or Releuko®;
2. Diagnosis of Wilms Tumor (Nephroblastoma);
3. Member has had a failure with Zarxio® or Nivestym™, unless contraindicated or clinically significant adverse effects are experienced;
4. Dose is within FDA maximum limit for any FDA-approved indication or is supported by practice guidelines or peer-reviewed literature for the relevant off-label use (prescriber must submit supporting evidence).

Approval Duration
Commercial: 6 months
Medicaid: 6 months

II. Continued Therapy Approval

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

1. Member is currently receiving medication that has been authorized by RxAdvance or the member has met initial approval criteria listed in this policy;
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
   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
Commercial: 6 months
Medicaid: 6 months

III. Appendices

APPENDIX A: Abbreviation/Acronym Key
MDS: Myelodysplastic Syndrome
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
NCCN: National Comprehensive Cancer Network

APPENDIX B: Therapeutic Alternatives
Not applicable.

APPENDIX C: Contraindications/Boxed Warnings
- Contraindication(s):
  - History of serious allergic reactions to filgrastim products or pegfilgrastim products.
    *Contraindications listed reflect direct statements made in the manufacturer's package insert; for additional uses, warnings, and precautions, please refer to clinical guidelines.

- 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° Cover 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) 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.

References

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2. Neupogen® Prescribing Information. Thousand Oaks, CA: Amgen, Inc.; February 2021. Available at: www.neupogen.com. Accessed March 15, 2022.
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4. Zarxio® Prescribing Information. Princeton, NJ: Sandoz, Inc.; March 2021. Available at: www.zarxio.com. Accessed March 15, 2022.
5. Nivestym™ Prescribing Information. Lake Forest, IL: Hospira, Inc.; November 2021. Available at: https://www.nivestym.com/. Accessed March 15, 2022.
6. National Comprehensive Cancer Network. Myeloid Growth Factors Version 2.2018. Available at: http://www.nccn.org/professionals/physician_gls/pdf/myeloid_growth.pdf. Accessed: March 15, 2022.
7. National Comprehensive Cancer Network Drugs and Biologics Compendium. Available at: http://www.nccn.org/professionals/drug_compendium. Accessed March 15, 2022.
8. Clinical Pharmacology [database online]. Tampa, FL: Gold Standard, Inc.; 2020. Available at: http://www.clinicalpharmacology-ip.com/. Accessed March 15, 2022.
9. National Comprehensive Cancer Network. Myelodysplastic Syndromes version 3.2022 Available at: https://www.nccn.org/professionals/physician_gls/pdf/mds.pdf. Accessed March 15, 2022.

Review/Revision History	Review/Revised Date	P&T Approval Date
Policy established.	01/2020	02/07/2020
Policy was reviewed: 1) Policy description table updated 2) Dosing Regimen was updated to replace QD with "once daily" and BID with “twice daily” 3) Dosing regimen for chemotherapy-induced neutropenia was updated 4) Continuation therapy criteria II.A.1. rephrased to “Member is currently receiving medication that has been authorized by RxAdvance or the member has met initial approval criteria listed in this policy” 5) Initial therapy and continued therapy approval duration updated 6) Appendix A, Abbreviation/Acronym Key was updated to include SC and IV 7) References were updated	07/31/2020	09/14/2020
Policy was reviewed: 1) References were updated. 2) Updated dosing information: Separated ‘acutely exposed to myelosuppressive doses of radiation’ from other drugs as it is only applicable for Neupogen®. 3) Initial approval criteria I.E.1 was added “Request is for Neupogen®”. 4) Appendix C was updated: added “filgrastim products or pegfilgrastim products” to Contraindications.	02/19/2021	06/10/2021
Policy was reviewed: 1) Clinical Policy Title, Drug(s) Applied: Updated to include new drug Releuko®. 2) Background: Updated to include new drug Releuko®. 3) Dosing Information, Drug Name: Updated to include new drug Releuko®. 4) Dosage Forms: Updated to include new brand dosage form, filgrastim-ayow (Releuko®): Single-dose prefilled syringes for injection: 300 mcg/0.5 mL, 480 mcg/0.8 mL and Single-dose vials for injection: 300 mcg/mL, 480 mcg/1.6 mL. 5) Initial Approval Criteria, I.A.3, I.B.3, I.D.2, I.F.3: Updated to include trial and failure criteria For Releuko® member has had a failure with Zarxio® or Nivestym™, unless contraindicated or clinically significant adverse effects are	03/14/2022	04/18/2022

experienced. 6) Initial Approval Criteria, I.C.2, I.E.3: Updated to include new drug criteria Request is for Neupogen®, Zarxio®, Nivestym™, Granix®. 7) Initial Approval Criteria, I.H: Updated to include approval criteria for indication, Wilms Tumor (Nephroblastoma). 8) Appendix A: Updated to include abbreviations NCCN and MDS. 9) Appendix A: Updated to remove abbreviations IV and SC. 10) Disclaimer about contraindications "Contraindications listed reflect statements made in the manufacturer's package insert..." was added to Appendix C. 11) References were reviewed and updated.		