CLINICAL GUIDELINES FOR MEDICAL NECESSITY

MEDICAL POLICY

Filgrastim and Biosimilars

Neupogen®

Nivestym™

Nypozi™

Releuko®

Zarxio®

Sargramostim (Leukine®)

Tbo-Filgrastim (Granix®)

Version: 1.0

EFFECTIVE DATE: 2/1/2025

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Filgrastim (Neupogen®); Filgrastim-aafi (Nivestym™); Filgrastim-txid (Nypozi™); Filgrastim-ayow (Releuko®); Filgrastim-sndz (Zarxio®); Sargramostim (Leukine®); Tbo-Filgrastim (Granix®)

Note: For Medicare members/enrollees, to ensure consistency with the Medicare National Coverage Determinations (NCD) and Local Coverage Determinations (LCD), all applicable NCDs, LCDs, and Medicare Coverage Articles should be reviewed prior to applying the criteria set forth in this clinical policy. Please refer to the CMS website at http://www.cms.gov for additional information.

Note: For Medicaid members/enrollees, circumstances when state Medicaid coverage provisions conflict with the coverage provisions within 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.

Filgrastim (Neupogen); Filgrastim-aafi (Nivestym); Filgrastim-txid (Nypozi); Filgrastim-ayow (Releuko); Filgrastim-sndz (Zarxio); Sargramostim (Leukine); Tbo-Filgrastim (Granix): Discussion

Granulocyte colony-stimulating factors (G-CSF), recombinant human granulocyte-macrophage colony stimulating factor (rhu GM-CSF), recombinant methionyl human granulocyte colony-stimulating growth factor (r-metHuG-CSF), also known as white blood cell growth factors are used to treat myelosuppression which can be caused by cancer chemotherapy. Myelosuppression is when the bone marrows' ability to produce blood cells is greatly reduced. Neutrophils are an important part of the body's immune system and assists with combating infection. Abnormally low number of neutrophils (neutropenia) increases the risk of infection. Neutropenic infections can occur during chemotherapy and can result in increased costs, delays in treatment, and/or a reduction in chemotherapy dose, which may negatively impact disease control, patient's health, and treatment outcomes.

Filgrastim, its biosimilars, and tbo-filgrastim, are granulocyte colony-stimulating factors (G-CSF). These are proteins involved in the production and regulation of neutrophils. Sargramostim is a granulocyte-macrophage colony stimulating factor (GM-CSF). These proteins increase neutrophil, eosinophil, megakaryocyte, macrophage, and dendritic cell production. The administration of G-CSF or GM-CSF are used to stimulate the bone marrow to increase the production of neutrophils. These are often given as part of a myelosuppressive chemotherapy treatment to reduce the risk of febrile neutropenia.

Filgrastim and its biosimilars, sargramostim, and tbo-filgrastim can be given 24 hours after myelosuppressive chemotherapy and should not be administered within 24 hours of the next dose of chemotherapy. Multiple doses can be given 24 hours apart. Same day administration of filgrastim or it biosimilars, sargramostim or tbo-filgrastim with chemotherapy is not recommended per FDA or NCCN.[1,2,3,4,5,6,7,8,9]

Febrile neutropenia is having an absolute neutrophil count (ANC) of less than 500 neutrophils/mcL, or an anticipated decline in the ANC to ≤500 within the next 48 hours, accompanied by a single oral temperature of ≥38.3°C/101°F or a temperature ≥38.0°C/100.4°F for a duration of over 1 hour.[10]

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Filgrastim; Filgrastim-aafi; Filgrastim-txid; Filgrastim-ayow; Filgrastim-sndz; Sargramostim; Tbo-Filgrastim: Definitions

- **Biosimilar drug** - An FDA-approved biological drug that is like another biological drug (called the reference drug), which is made from living organisms, but may be made in a different way from the reference drug and of slightly different substances. A biosimilar drug must be shown to be as safe, same dose, work as well, works in the same way, and for the same condition as the reference drug.
- **Food and Drug Administration (FDA)** - The FDA is responsible for protecting the public health by assuring the safety, efficacy, and security of human and veterinary drugs, biological products, medical devices, our nation's food supply, cosmetics, and products that emit radiation.
- **National Comprehensive Cancer Network (NCCN)** - An alliance of more than 30 leading cancer centers devoted to patient care, research, and education. The NCCN guidelines are utilized for Radiation Therapy and Medical Oncology standards. NCCN consensus clinical standards are periodically updated and NantHealth, Inc. reviews these and updates its policies within a timely manner.
- **Primary Prophylaxis** - The recommended administration of G-CSF is within the first 5 days of starting chemotherapy to reduce the risk of febrile neutropenia. The prophylactic use of G-CSF can result in a reduction in infection-related mortality. Primary prophylaxis is based on the percentage of febrile neutropenia risk for chemotherapy regimens and/or the following risk factors:
  - Prior chemotherapy or radiation therapy
  - Persistent neutropenia
  - Bone marrow involvement by tumor
  - Recent surgery and/or open wounds
  - Liver dysfunction (bilirubin greater than 2.0)
  - Renal dysfunction (creatinine clearance less than 50)
  - Age >65 years receiving full chemotherapy dose intensity
  - Poor performance status
  - Human immunodeficiency virus (HIV) infection (low CD4 counts)
  - Chronic immunosuppression in the post-transplant setting[10]
- **Secondary Prophylaxis** - NCCN recommends evaluating patients prior to each subsequent cycle of chemotherapy to determine the febrile neutropenia risk. Secondary prophylaxis is allowed for intermediate or low-risk individuals with solid tumors and non-myeloid malignancies receiving treatment in the curative/adjuvant, or palliative settings, and is permitted based on both of the following criteria:
  - An episode of febrile neutropenia or a dose-limiting neutropenic event, (a nadir count or a day-of-treatment count impacting the planned dose of chemotherapy immunodeficiency virus (HIV) infection (low CD4 counts)
  - Intermediate risk of febrile neutropenia and the patient did not receive primary prophylaxis with G-CSF immunosuppression in the post-transplant setting.[10]

Filgrastim and Biosimilars, Sargramostim, and Tbo-filgrastim: Policy

Note: Coverage of filgrastim and biosimilars, sargramostim, and Tbo-filgrastim will be provided for an FDA-approved indication or National Comprehensive Cancer Network (NCCN) guidelines when it is a Category 1, 2A, or 2B recommendation or when all criteria are met.

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Filgrastim and biosimilars, Sargramostim, and Tbo-filgrastim will be considered for coverage when the following criteria are met:

Filgrastim; Filgrastim-aafi; Filgrastim-txid; Filgrastim-ayow; Filgrastim-sndz

1. Prescribed by or in consultation with an oncologist; AND

For **FDA** criteria coverage:

2. Pediatric or adult patients; AND
3. Decrease the incidence of infection, as manifested by febrile neutropenia, in patients with non-myeloid malignancies receiving myelosuppressive anti-cancer drugs associated with a significant incidence of severe neutropenia with fever; OR
4. Reduce the time to neutrophil recovery and the duration of fever, following induction or consolidation chemotherapy treatment of patients with acute myeloid leukemia (AML); OR
5. Reduce the duration of neutropenia and neutropenia-related clinical sequelae, (e.g., febrile neutropenia, in patients with non-myeloid malignancies undergoing myeloablative chemotherapy followed by bone marrow transplant); OR
6. Mobilize autologous hematopoietic progenitor cells into the peripheral blood by collection by leukapheresis[1,2,3,5]

   Note: The above excludes the biosimilar drug filgrastim-ayow; OR

7. Used to increase survival in patients acutely exposed to myelosuppressive doses of radiation (hematopoietic syndrome of acute radiation syndrome)[1,2,5]

   Note: The above excludes the following biosimilar drugs: filgrastim-aafi and filgrastim-ayow; OR

For **NCCN** required criteria coverage:

8. Adult patients 18 years or older; AND
9. Prophylaxis of chemotherapy-induced febrile neutropenia or other dose-limiting neutropenic events in high-risk (>20% overall risk of febrile neutropenia) patients with solid tumors and non-myeloid malignancies receiving treatment in the curative/adjuvant or palliative settings; OR
10. Consider for prophylaxis of chemotherapy-induced febrile neutropenia or other dose-limiting neutropenic events in intermediate-risk (10% to 20% overall risk of febrile neutropenia) patients with solid tumors and non-myeloid malignancies receiving treatment in the curative/adjuvant or palliative settings who have one or more patient risk factors; OR
11. Consider for prophylaxis of chemotherapy-induced febrile neutropenia or other dose-limiting neutropenic events in low-risk (<10% overall risk of febrile neutropenia) patients with solid tumors and non-myeloid malignancies receiving treatment in the curative/adjuvant or palliative settings and who have 2 or more patient-related risk factors. The use of granulocyte colony-stimulating factors in this setting is based on clinical judgment; OR
12. Treatment of chemotherapy-induced febrile neutropenia for one of the following:
    a) Patients who have been receiving prophylactic tbo-filgrastim

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b) Patients who have not received prophylactic granulocyte colony-stimulating factors but who have risk factors for an infection-associated complication; OR

13. Treatment for patients with radiation-induced myelosuppression following a radiologic/nuclear incident (hematopoietic acute radiation syndrome [H-ARS]).

Sargramostim

1. Prescribed by or in consultation with an oncologist; AND

For **FDA** required criteria coverage:

2. To shorten time to neutrophil recovery and to reduce the incidence of severe and life-threatening infections and infections resulting in death following induction chemotherapy in adult patients 55 years and older with acute myeloid leukemia (AML); OR
3. For the mobilization of hematopoietic progenitor cells into peripheral blood for collection by leukapheresis and autologous transplantation in adult patients; OR
4. For the acceleration of myeloid reconstitution following autologous bone marrow or peripheral blood progenitor cell transplantation in adult and pediatric patients 2 years of age and older; OR
5. For the acceleration of myeloid reconstitution following allogeneic bone marrow transplantation in adult and pediatric patients 2 years of age and older; OR
6. For treatment of delayed neutrophil recovery or graft failure after autologous or allogeneic bone marrow transplantation in adult and pediatric patients 2 years of age and older; OR
7. To increase survival in adult and pediatric patients from birth to 17 years of age acutely exposed to myelosuppressive doses of radiation (hematopoietic syndrome of acute radiation syndrome [H-ARS])[6]; OR

For **NCCN** required criteria coverage:

8. At least 18 years of age; AND
9. Consider for treatment of chemotherapy-induced febrile neutropenia in patients who have not received prophylactic granulocyte colony-stimulating factors but who have risk factors for an infection-associated complication; OR
10. Treatment for patients with radiation-induced myelosuppression following a radiologic/nuclear incident (hematopoietic acute radiation syndrome [H-ARS]).[10]

Tbo-filgrastim

1. Prescribed by or in consultation with an oncologist; AND

For **FDA** criteria coverage:

2. Pediatric and adult patients; AND
3. For reduction in the duration of severe neutropenia in adults and pediatric patients 1 month of age and older with non-myeloid malignancies receiving myelosuppressive anticancer drugs associated with a clinically significant incidence of febrile neutropenia[7]; OR

For **NCCN** required criteria coverage:

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4. At least 18 years of age; AND
5. Prophylaxis of chemotherapy-induced febrile neutropenia or other dose-limiting neutropenic events in high-risk (>20% overall risk of febrile neutropenia) patients with solid tumors and non-myeloid malignancies receiving treatment in the curative/adjuvant or palliative settings; OR
6. Consider for prophylaxis of chemotherapy-induced febrile neutropenia or other dose-limiting neutropenic events in intermediate-risk (10% to 20% overall risk of febrile neutropenia) patients with solid tumors and non-myeloid malignancies receiving treatment in the curative/adjuvant or palliative settings who have one or more patient risk factors; OR
7. Consider for prophylaxis of chemotherapy-induced febrile neutropenia or other dose-limiting neutropenic events in low-risk (<10% overall risk of febrile neutropenia) patients with solid tumors and non-myeloid malignancies receiving treatment in the curative/adjuvant or palliative settings who have 2 or more patient-related risk factors. Use of granulocyte colony-stimulating factors in this setting is based on clinical judgment; OR
8. Treatment of chemotherapy-induced febrile neutropenia for one of the following:
   a) Patients who have been receiving prophylactic tbo-filgrastim
   b) Patients who have not received prophylactic granulocyte colony-stimulating factors but who have risk factors for an infection-associated complication; OR
9. Treatment for patients with radiation-induced myelosuppression following a radiologic/nuclear incident (hematopoietic acute radiation syndrome [H-ARS]).[10]

Authorization Period and Renewal Criteria

1. Initial Authorization Period: 12 months
2. Renewal Criteria: No evidence of disease progression or unacceptable toxicity
3. Renewal Authorization Period: 12 months

Filgrastim; Filgrastim-aafi; Filgrastim-txid; Filgrastim-ayow; Filgrastim-sndz; Sargramostim; Tbo-filgrastim: References

1. Filgrastim (Neupogen) Package Insert. https://www.accessdata.fda.gov/drugsatfda_docs/label/2023/103353s5198lbl.pdf. Accessed January 29, 2025.
2. Filgrastim-sndz (Zarxio) Package Insert. https://www.accessdata.fda.gov/drugsatfda_docs/label/2024/125553s038lbl.pdf. Accessed January 29, 2025.
3. Filgrastim-aafi (Nivestym) Package Insert. https://www.accessdata.fda.gov/drugsatfda_docs/label/2024/761080s014lbl.pdf. Accessed January 29, 2025.
4. Filgrastim-ayow (Releuko) Package Insert. https://www.accessdata.fda.gov/drugsatfda_docs/label/2023/761082s010lbl.pdf. Accessed January 29, 2025.
5. Filgrastim-txid (Nypozi) Package Insert. https://www.accessdata.fda.gov/drugsatfda_docs/label/2024/761126s000lbl.pdf. Accessed January 29, 2025.

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6. Sargramostim (Leukine) Package Insert. https://www.accessdata.fda.gov/drugsatfda_docs/label/2022/103362s5249lbl.pdf. Accessed January 22, 2025.
7. Tbo-filgrastim (Granix) Package Insert. https://www.accessdata.fda.gov/drugsatfda_docs/label/2023/125294s058lbl.pdf. Accessed January 22, 2025.
8. Lyman GH, Kuderer NM. Epidemiology of febrile neutropenia. Supportive Cancer Therapy. 1:23-35;2003. https://pubmed.ncbi.nlm.nih.gov/18628128. Accessed January 22, 2025.
9. Lalami Y, Klastersky J. Impact of chemotherapy-induced neutropenia (CIN) and febrile neutropenia (FN) on cancer treatment outcomes: An overview about well-established and recently emerging clinical data. Crit Rev Oncol Hematol. 120:163-179;2017. https://pubmed.ncbi.nlm.nih.gov/29198330. Accessed January 22, 2025.
10. National Comprehensive Cancer Network. Hematopoietic Growth Factors. https://www.nccn.org/professionals/physician_gls/pdf/growthfactors.pdf. Accessed January 29, 2025.

Filgrastim; Filgrastim-aafi; Filgrastim-txid; Filgrastim-ayow; Filgrastim-sndz; Sargramostim; Tbo-Filgrastim: Coding (CPT®, ICD-10, and HCPCS) *

*Procedure codes appearing in medical policy documents are only included as a general reference. This list may not be all-inclusive and is subject to updates. In addition, the codes listed are not a guarantee of payment. CPT codes are available through the AMA.

Code	Description
C00.0 - C41.9, C43.0 - C43.9, C4A.0 – C4A.9, C44.00 - C75.9, C7A.1 - C7A.8, C76.0 - C91.32, C91.50 - C91.92	Malignant neoplasms
D70.9	Neutropenia, unspecified
J1442	Filgrastim (Neupogen®)
J1447	Tbo-filgrastim (Granix®)
J2820	Sargramostim (Leukine®)
J3590, C9173	Filgrastim-txid (Nypozi)

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Q5101	Filgrastim-sndz (Zarxio)
Q5110	Filgrastim-aafi (Nivestym™)
Q5125	Filgrastim-ayow (Releuko®)

Filgrastim; Filgrastim-aafi; Filgrastim-txid; Filgrastim-ayow; Filgrastim-sndz; Sargramostim; Tbo-Filgrastim: Revision and Review History

No.	Description	Date(s)
1	Original Effective Date:	2/1/2025
2	Policy Review Dates:	
3	Policy Revision Dates:	
4	Department Owner:	Medical Affairs
5	NH Advisory Committee:	3/5/2025
6	Revision Changes:	

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