PRIOR AUTHORIZATION POLICY

POLICY: Colony Stimulating Factors – Filgrastim Products Prior Authorization Policy
- Neupogen® (filgrastim intravenous or subcutaneous injection – Amgen)
- Nivestym® (filgrastim-aafi intravenous or subcutaneous injection – Hospira/Pfizer)
- Nypozi™ (filgrastim-txid intravenous or subcutaneous injection – Tanvex)
- Releuko® (filgrastim-ayow intravenous or subcutaneous injection – Amneal)
- Zarxio® (filgrastim-sndz intravenous or subcutaneous injection – Sandoz)

REVIEW DATE: 10/09/2024; selected revision 12/04/2024

OVERVIEW

Filgrastim, a granulocyte colony stimulating factor (G-CSF), is indicated for the following uses:[1-5]

- **Decrease the incidence of infection as manifested by febrile neutropenia**, in patients with nonmyeloid malignancies receiving myelosuppressive anti-cancer drugs associated with a significant incidence of severe neutropenia with fever.
- **Mobilization of hematopoietic progenitor cells,** into the peripheral blood for collection by leukapheresis.
- **Reduce the time to neutrophil recovery and the duration of fever,** following induction or consolidation chemotherapy treatment of adults with acute myeloid leukemia (AML).
- **Reduce the duration of neutropenia and neutropenia-related clinical sequelae (e.g., febrile neutropenia),** in patients with nonmyeloid malignancies undergoing myeloablative chemotherapy followed by bone marrow transplantation (BMT).
- **Reduce the incidence and duration of sequelae of neutropenia (e.g., fever, infections, oropharyngeal ulcers),** in symptomatic patients with congenital neutropenia, cyclic neutropenia, or idiopathic neutropenia
- **Increase survival in patients acutely exposed to myelosuppressive doses of radiation** (Hematopoietic Syndrome of Acute Radiation Syndrome [H-ARS])

Nivestym, Nypozi, Releuko, and Zarxio are biosimilars to Neupogen.[1-5] Releuko indication labeling does not include mobilization of autologous hematopoietic progenitor cells into the peripheral blood for collection by leukapheresis.[4] Neupogen, Nypozi, and Zarxio labeling include the indication for treatment of H-ARS.[1,2,5]

Guidelines

The National Comprehensive Cancer Network (NCCN) addresses the use of filgrastim products in several guidelines. Of note, throughout the recommendations, it is acknowledged that an FDA-approved biosimilar is an appropriate substitute for filgrastim.

- **Acute Lymphoblastic Leukemia (ALL):** Guidelines (version 2.2024 – July 19, 2024) recommend granulocyte colony stimulating factors (CSFs) as supportive care for myelosuppressive blocks of therapy or as directed by treatment protocol.[6]
- **Acute Myeloid Leukemia (AML):** Guidelines (version 3.2024 – May 17, 2024) recommend granulocyte colony stimulating factors (CSFs) as supportive care for myelosuppressive blocks of therapy or as directed by treatment protocol.[23]
- **Hematopoietic Cell Transplantation:** Guidelines (version 2.2024 – August 30, 2024) recommend filgrastim for hematopoietic cell mobilization for allogeneic or autologous donors as a single agent or in combination with other treatments.[7]

- **Hematopoietic Growth Factors:** Guidelines (version 3.2024 – January 30, 2024) recommend filgrastim, along with other CSFs, for prophylactic use if the patient is receiving anti-cancer medications that are associated with a high (> 20%) incidence of severe neutropenia with fever.[8] Consider CSF therapy for patients with an intermediate (10% to 20%) probability of developing febrile neutropenia based on risk factors. The NCCN guidelines also recommend therapy with CSFs in other scenarios in those given myelosuppressive chemotherapy.
- **Management of Immunotherapy-Related Toxicities:** Guidelines (version 1.2024 – December 7, 2023) recommend granulocyte CSFs as supportive care for neutropenic patients with Grade 1 cytokine release syndrome resulting from chimeric antigen receptor T-cell therapy.[9]
- **Myelodysplastic Syndromes (MDS):** Guidelines (version 3.2024 – July 25, 2024) consider filgrastim for use in certain patients (e.g., neutropenic patients with recurrent or resistant infections, combination use with epoetin alfa or Aranesp® [darbepoetin alfa injection] in patients with anemia).[10]

The American Society of Clinical Oncology clinical practice guidelines for the use of white blood cell growth factors (2015) recommend CSFs to reduce the risk of febrile neutropenia in patients receiving cancer chemotherapy.[11] CSFs may be considered in patients receiving radiation therapy alone if prolonged delays secondary to neutropenia are expected. The guidelines state CSFs should be avoided in patients receiving concomitant chemotherapy and radiation therapy, particularly involving the mediastinum.

Other Uses with Supportive Evidence

Neutropenia occurs in patients with human immunodeficiency virus (HIV) and may be caused by medications or due to the disease process. Studies have demonstrated positive outcomes with the use of filgrastim for the treatment of neutropenia in this patient population.[12-15]

Filgrastim has been used for agranulocytosis caused by non-cytotoxic medications, primarily described in case series, case reports and literature reviews.[16-22]

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of filgrastim products. All approvals are provided for the duration noted below. In cases where the approval is authorized in months, 1 month is equal to 30 days. Because of the specialized skills required for evaluation and diagnosis of patients treated with filgrastim products as well as the monitoring required for adverse events and long-term efficacy, approval for some conditions requires filgrastim products to be prescribed by or in consultation with a physician who specializes in the condition being treated.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of filgrastim products is recommended in those who meet one of the following:

FDA-Approved Indications

1. **Acute Myeloid Leukemia (AML) in a Patient Receiving Chemotherapy.** Approve for 6 months if prescribed by or in consultation with an oncologist or hematologist.

2. **Bone Marrow Transplant (BMT) in a Patient with Cancer Who Received Chemotherapy.** Approve for 1 month if prescribed by or in consultation with a hematologist, an oncologist, or a physician who specializes in transplantation.

3. **Cancer in a Patient Receiving Myelosuppressive Chemotherapy.** Approve for 6 months if the patient meets BOTH of the following (A and B):
   A) Patient meets ONE of the following (i, ii, iii, or iv):
      i. Patient is receiving myelosuppressive anti-cancer medications that are associated with a high risk of febrile neutropenia (the risk is at least 20% based on the chemotherapy regimen); OR
      ii. Patient meets BOTH of the following (a and b):
         a) Patient is receiving myelosuppressive anti-cancer medications that are associated with a risk of febrile neutropenia, but the risk is less than 20% based on the chemotherapy regimen; AND
         b) Patient has at least one risk factor for febrile neutropenia according to the prescriber; OR
         Note: Examples of risk factors include age > 65 years of age receiving full chemotherapy dose intensity; prior chemotherapy or radiation therapy; persistent neutropenia; bone marrow involvement by tumor; recent surgery and/or open wounds; liver dysfunction (bilirubin > 2.0 mg/dL); renal dysfunction (creatine clearance < 50 mL/min); poor performance status; patients with human immunodeficiency virus (HIV) infection and low CD4 counts.
      iii. Patient meets BOTH of the following (a and b):
         a) Patient has had a neutropenic complication from a prior chemotherapy cycle and did not receive prophylaxis with a colony stimulating factor; AND
         Note: Examples of colony stimulating factors include filgrastim products, pegfilgrastim products, Ryzneuta (efbemalenograstim alfa-vuxw subcutaneous injection), Rolvedon (eflapegrastim-xnst subcutaneous injection).
         b) A reduced dose or frequency of chemotherapy may compromise treatment outcome; OR
      iv. Patient who has received chemotherapy has febrile neutropenia and has at least one risk factor for poor clinical outcomes or for developing infection-associated complications according to the prescriber; AND
      Note: Examples of risk factors include sepsis syndrome; age > 65 years; severe neutropenia (absolute neutrophil count [ANC] < 100 cells/mm^3); neutropenia expected to be > 10 days in duration; pneumonia or other clinically documented infections; invasive fungal infection; hospitalization at the time of fever; prior episode of febrile neutropenia.
   B) The medication is prescribed by or in consultation with an oncologist or hematologist.

4. **Peripheral Blood Progenitor Cell (PBPC) Collection and Therapy.** Approve for 1 month if prescribed by or in consultation with an oncologist, a hematologist, or a physician who specializes in transplantation.

5. **Radiation Syndrome (Hematopoietic Syndrome of Acute Radiation Syndrome [H-ARS]).** Approve for 1 month if prescribed by or in consultation with a physician who has expertise in treating acute radiation syndrome.

6. **Severe Chronic Neutropenia (e.g., Congenital Neutropenia, Cyclic Neutropenia, Idiopathic Neutropenia).** Approve for 6 months if prescribed by or in consultation with a hematologist.

Other Uses with Supportive Evidence

7. **Acute Lymphoblastic Leukemia (ALL) in a Patient Receiving Chemotherapy.** Approve for 1 month if prescribed by or in consultation with an oncologist or a hematologist.

8. **Cytokine Release Syndrome associated with Chimeric Antigen Receptor (CAR) T-Cell Therapy.** Approve for 1 month if prescribed for a patient who has neutropenia.
   Note: Examples of CAR T-cell therapy include Abecma (idecabtagene vicleucel), Breyanzi (lisocabtagene maraleucel), Carvykti (ciltacabtagene autoleucel), Kymriah (tisagenlecleucel), Tecartus (brexucabtagene autoleucel) and Yescarta (axicabtagene ciloleucel).

9. **Drug-Induced (Non-Chemotherapy) Agranulocytosis or Neutropenia.** Approve for 1 month.

10. **Myelodysplastic Syndromes (MDS).** Approve for 3 months if prescribed by or in consultation with an oncologist or hematologist.

11. **Neutropenia Associated with Human Immunodeficiency Virus (HIV) or Acquired Immunodeficiency Syndrome (AIDS).** Approve for 4 months if the agent is prescribed by or in consultation with a physician who specializes in infectious diseases, a hematologist, or a physician who specializes in the management of HIV/AIDS.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of filgrastim products is not recommended in the following situations:

1. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

1. Neupogen® subcutaneous or intravenous injection [prescribing information]. Thousand Oaks, CA: Amgen; April 2023.
2. Zarxio™ subcutaneous or intravenous injection [prescribing information]. Princeton, NJ: Sandoz; October 2024.
3. Nivestym™ subcutaneous or intravenous injection [prescribing information]. Lake Forest, IL and New York, NY: Hospira and Pfizer; March 2023.
4. Releuko® subcutaneous or intravenous injection [prescribing information]. Bridgewater, NJ: Amneal; June 2023.
5. Nypozi™ subcutaneous or intravenous injection [prescribing information]. San Diego, CA: Tanvex, June 2024.
6. The NCCN Acute Lymphoblastic Leukemia Clinical Practice Guidelines in Oncology (version 2.2024 – July 19, 2024). © 2024 National Comprehensive Cancer Network. Available at http://www.nccn.org. Accessed on September 18, 2024.
7. The NCCN Hematopoietic Cell Transplantation Clinical Practice Guidelines in Oncology (version 2.2024 – August 30, 2024). © 2024 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed on September 18, 2024.
8. The NCCN Hematopoietic Growth Factors Clinical Practice Guidelines in Oncology (version 3.2024 – January 30, 2024). © 2024 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed on September 18, 2024.
9. The NCCN Management of Immunotherapy-Related Toxicities Clinical Practice Guidelines in Oncology (version 1.2024 – December 7, 2023). © 2024 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed on September 18, 2024.
10. The NCCN Myelodysplastic Syndromes Clinical Practice Guidelines in Oncology (version 3.2024 – July 25, 2024). © 2024 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed on September 18, 2024.
11. Smith TJ, Bohlke K, Lyman GH, Carson KR, et al. Recommendations for the use of WBC growth factors: American Society of Clinical Oncology Clinical Practice Guideline Update. *J Clin Oncol*. 2015;33(28):3199-3212.
12. Kuritzkes DR, Parenti D, Ward DJ, et al, and the G-CSF 930101 study group. Filgrastim prevents severe neutropenia and reduces infective morbidity in patients with advanced HIV infection: Results of a randomized, multicenter controlled trial. *AIDS*. 1998;12:65-71.
13. Hermans P, Rozenbaum W, Joy A, et al, and the G-CSF 92105 Study Group. Filgrastim to treat neutropenia and support myelosuppressive medication dosing in HIV infection. *AIDS*. 1996;10:1627-1633.
14. Kurizkes DR. Neutropenia, neutrophil dysfunction, and bacterial infection in patients with human immunodeficiency virus disease: The role of granulocyte colony-stimulating factor. *Clin Infect Dis*. 2000;30:256-260.
15. Mitsuyasu R. Prevention of bacterial infections in patients with advanced HIV infection. *AIDS*. 1999;13(Suppl 2):S19-S23.
16. Tesfa D, Keisu M, Palblad J. Idiosyncratic drug-induced agranulocytosis: Possible mechanism and management. *Am J Hematol*. 2009;84:428-434.

17. Andersohn F, Konzen C, Garbe E. Systematic review: Agranulocytosis induced by nonchemotherapy drugs. *Ann Intern Med*. 2007;146:657-665.
18. Beaushesne MF, Shalansky SJ. Nonchemotherapy drug-induced agranulocytosis: A review of 118 patients treated with colony-stimulating factors. *Pharmacother*. 1999;19(3):299-305.
19. Bhatt V, Saleem A. Review: Drug-induced neutropenia-pathophysiology, clinical features, and management. *Ann Clin Lab Sci*. 2004;34(2):131-136.
20. Curtis BR. Drug-induced immune neutropenia/agranulocytosis. *Immunohematology*. 2014;30(2):95-101.
21. Andres E, Mourot-Cottet R. Non-chemotherapy drug-induced neutropenia – an update. *Expert Opin Drug Saf*. 2017;16(11):1235-1242.
22. Andres E, Mourot-Cottet R, Maloisel F, et al. Idiosyncratic drug-induced neutropenia and agranulocytosis. *QJM*. 2017 May;110(5):299-305.
23. The NCCN Acute Myeloid Leukemia Clinical Practice Guidelines in Oncology (version 3.2024 – May 17, 2024). © 2024 National Comprehensive Cancer Network. Available at http://www.nccn.org. Accessed on September 18, 2024.