VENTURA COUNTY
HEALTH CARE PLAN

UTILIZATION MANAGEMENT MEDICAL POLICY

POLICY: Colony Stimulating Factors – Filgrastim Products Utilization Management Medical Policy
- Neupogen® (filgrastim intravenous or subcutaneous injection – Amgen)
- Nivestym™ (filgrastim intravenous or subcutaneous injection – Hospira/Pfizer)
- Releuko® (filgrastim-ayow intravenous or subcutaneous injection – Amneal)
- Zarxio® (filgrastim-sndz intravenous or subcutaneous injection – Sandoz)

REVIEW DATE: 09/20/2023

OVERVIEW

Filgrastim, a leukocyte growth factor, is indicated for the following uses:[1-4]

- **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.
- **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.

Nivestym, Releuko, and Zarxio are biosimilars to Neupogen.[2-4] Releuko indication labeling does not include mobilization of autologous hematopoietic progenitor cells into the peripheral blood for collection by leukapheresis.[4] Neupogen is additionally indicated to increase survival in patients acutely exposed to myelosuppressive doses of radiation (Hematopoietic Syndrome of Acute Radiation Syndrome).[1]

Guidelines

The National Comprehensive Cancer Network (NCCN) addresses the use of filgrastim products in several guidelines.

- **Acute Lymphoblastic Leukemia (ALL):** Guidelines (version 2.2023 – July 28, 2023) recommend granulocyte colony stimulating factors (CSFs) as supportive care for myelosuppressive blocks of therapy or as directed by treatment protocol.[5]
- **Hematopoietic Cell Transplantation:** Guidelines (version 1.2023 – March 31, 2023) recommend filgrastim for hematopoietic cell mobilization for allogeneic or autologous donors as a single agent or in combination with other treatments.[6]
- **Hematopoietic Growth Factors:** Guidelines (version 2.2023 – March 6, 2023) 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.[7] 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. Filgrastim products are also recommended for mobilization and following hematopoietic cell transplant.

- **Management of Immunotherapy-Related Toxicities:** Guidelines (version 2.2023 – May 9, 2023) recommend granulocyte CSFs as supportive care for neutropenic patients with Grade 1 cytokine release syndrome resulting from chimeric antigen receptor T-cell therapy.[8]
- **Myelodysplastic Syndromes (MDS):** Guidelines (version 1.2023 – September 12, 2022) 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).[9]

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.[10] 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.[11-14]

Filgrastim has been used for agranulocytosis caused by non-cytotoxic medications, primarily described in case series, case reports and literature reviews.[15-21]

POLICY STATEMENT

Prior Authorization is recommended for medical benefit coverage of filgrastim products. Approval is recommended for those who meet the **Criteria** and **Dosing** for the listed indications. Extended approvals are allowed if the patient continues to meet the Criteria and Dosing. Requests for doses outside of the established dosing documented in this policy will be considered on a case-by-case basis by a clinician (i.e., Medical Director or Pharmacist). 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 as well as the monitoring required for adverse events and long-term efficacy, approval for some conditions requires filgrastim 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.

   Dosing. Approve up to 10 mcg/kg per day by intravenous or subcutaneous injection.

2. **Bone Marrow Transplant 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.

   Dosing. Approve up to 30 mcg/kg per day by intravenous or subcutaneous injection.

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3. **Cancer in a Patient Receiving Myelosuppressive Chemotherapy.** Approve for 6 months if the patient meets 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; prior chemotherapy or radiation therapy; persistent neutropenia; bone marrow involvement by tumor; recent surgery and/or open wounds; liver and/or renal dysfunction; poor performance status; or human immunodeficiency virus (HIV) infection.
     - **iii.** Patient meets both of the following (a and b):
       - **a)** Patient has had a neutropenic complication from prior chemotherapy and did not receive prophylaxis with a colony stimulating factor; AND
         Note: Examples of colony stimulating factors include filgrastim products, pegfilgrastim products, and sargramostim products (e.g., Leukine).
       - **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; invasive fungal infection; or other clinically documented infections.
   - **B)** The medication is prescribed by or in consultation with an oncologist or hematologist.

   Dosing. Approve up to 10 mcg/kg per day by intravenous or subcutaneous injection for up to 14 days per month.

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4. **Peripheral Blood Progenitor Cell 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.

   Dosing. Approve up to 32 mcg/kg per day by intravenous or subcutaneous injection.

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5. **Radiation Syndrome (Hematopoietic Syndrome of Acute Radiation Syndrome).** Approve for 1 month if prescribed by or in consultation with a physician who has expertise in treating acute radiation syndrome.
   Dosing. Approve up to 10 mcg/kg per day as a subcutaneous injection.

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.

   Dosing. Approve up to 12 mcg/kg per day by subcutaneous injection.

Other Uses with Supportive Evidence

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

   Dosing. Approve up to 10 mcg/kg per day as a subcutaneous injection.

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 Kymriah (tisagenlecleucel intravenous infusion) and Yescarta (axicabtagene ciloleucel intravenous infusion).

   Dosing. Approve up to 10 mcg/kg per day by intravenous or subcutaneous injection.

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

   Dosing. Approve up to 10 mcg/kg per day as a subcutaneous injection.

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

    Dosing. Approve up to 5 mcg/kg per day as a subcutaneous or intravenous injection.

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 that specializes in infectious diseases, a hematologist, or a physician who specializes in the management of HIV/AIDS.

    Dosing. Approve up to 10 mcg/kg per day as a subcutaneous injection.

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; March 2021.
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.
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6. The NCCN Hematopoietic Cell Transplantation Clinical Practice Guidelines in Oncology (version 1.2023 – March 31, 2023). © 2023 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed on September 7, 2023.
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8. The NCCN Management of Immunotherapy-Related Toxicities Clinical Practice Guidelines in Oncology (version 2.2023 – May 9, 2023). © 2023 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed on September 7, 2023.
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14. Mitsuyasu R. Prevention of bacterial infections in patients with advanced HIV infection. *AIDS*. 1999;13(Suppl 2):S19-S23.
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18. Bhatt V, Saleem A. Review: Drug-induced neutropenia-pathophysiology, clinical features, and management. *Ann Clin Lab Sci*. 2004;34(2):131-136.
19. Curtis BR. Drug-induced immune neutropenia/agranulocytosis. *Immunohematology*. 2014;30(2):95-101.
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21. Andres E, Mourot-Cottet R, Maloisel F, et al. Idiosyncratic drug-induced neutropenia and agranulocytosis. *QJM*. 2017 May;110(5):299-305.

HISTORY

Type of Revision	Summary of Changes	Review Date
Annual Revision	No criteria changes.	08/31/2022
Update	03/21/2023: **Bone Marrow Transplant in a Patient with Cancer Who Received Chemotherapy** diagnosis was updated to remove eviCore routing.	-
Annual Revision	**Other Uses with Supportive Evidence**: **Radiation-Induced Neutropenia** was removed from the policy.	09/20/2023