PRIOR AUTHORIZATION POLICY

POLICY: Colony Stimulating Factors – Filgrastim Products Prior Authorization Policy
- Neupogen® (filgrastim injection for subcutaneous or intravenous use – Amgen)
- Nivestym™ (filgrastim injection for subcutaneous or intravenous use – Hospira/Pfizer)
- Zarxio® (filgrastim-sndz injection for subcutaneous or intravenous use – Sandoz)

REVIEW DATE: 08/19/2020

OVERVIEW

Filgrastim products leukocyte growth factors, are indicated for the following uses:[1-3]

- **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 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 and Zarxio are two products that are biosimilars to Neupogen.[2,3] Neupogen is the only agent indicated to increase survival in patients acutely exposed to myelosuppressive doses of radiation (Hematopoietic Syndrome of Acute Radiation Syndrome).[1] Granix (tbo-filgrastim injection for subcutaneous use) is another filgrastim product.[4]

Guidelines

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

- **Acute Lymphoblastic Leukemia:** Guidelines (version 2.2020 **–** January 15, 2020) recommend granulocyte colony-stimulating factors (CSFs) as supportive care for myelosuppressive blocks of therapy or as directed by treatment protocol.[7]
- **Hematopoietic Growth Factors:** Guidelines (version 2.2020 – January 27, 2020) 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.[5] 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 a 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 1.2020 – December 16, 2019) recommend granulocyte CSFs as supportive care for neutropenic patients with Grade 1 cytokine release syndrome resulting from chimeric antigen receptor (CAR) T-cell therapy.[20]

- **Myelodysplastic Syndromes (MDS):** Guidelines (version 2.2020 – February 28, 2020) recommend filgrastim for use in certain patients with MDS (e.g., neutropenic patients with recurrent or resistant infections, combination use with epoetin alfa or Aranesp® [darbepoetin alfa injection] in patients with anemia]).[6]

The American Society of Clinical Oncology clinical practice guidelines for the use of white blood cell growth factors (2015) recommends CSFs to reduce the risk of febrile neutropenia in patients receiving cancer chemotherapy.[6] 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 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.[9-12]

Filgrastim has been used for agranulocytosis caused by non-cytotoxic medications, primarily described in case series, case reports and literature reviews.[13-19]

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 the following criteria:

FDA-Approved Indications

1. **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 conditions (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 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 the patient has at least one risk factor for febrile neutropenia according to the prescriber.
       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; OR

iii. Patient has had a neutropenic complication from prior chemotherapy and did not receive prophylaxis with a colony stimulating factor and a reduced dose or frequency of chemotherapy may compromise treatment outcome; OR
Note: Examples of colony-stimulating factors include filgrastim products, pegfilgrastim products, and sargramostim products (e.g., Leukine®).

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 agent is prescribed by, or in consultation with, an oncologist or hematologist.

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

3. **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.

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.

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

6. **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.

Other Uses with Supportive Evidence

7. **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.

8. **Myelodysplastic Syndromes.** Approve for 3 months if prescribed by, or in consultation with, an oncologist or hematologist.

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

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

11. **Radiation-Induced Neutropenia.** Approve for 6 months if the patient meets the following criteria (A and B):
    A) Patient is not currently receiving chemotherapy; AND
    B) The agent is prescribed by, or in consultation with, an oncologist, radiologist or radiation oncologist.

12. 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 suspension) and Yescarta™ (axicabtagene ciloleucel intravenous suspension).

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

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2. Zarxio™ injection for subcutaneous or intravenous use [prescribing information]. Princeton, NJ: Sandoz; August 2019.
3. Nivestym™ injection for subcutaneous or intravenous use [prescribing information]. Lake Forest, IL and New York, NY: Hospira and Pfizer; July 2018.
4. Granix® injection for subcutaneous use [prescribing information]. North Wales, PA: Teva Pharmaceuticals; March 2019.
5. The NCCN Hematopoietic Growth Factors Clinical Practice Guidelines in Oncology (version 2.2020 – January 27, 2020). © 2020 National Comprehensive Cancer Network, Inc. Available at: http://www.nccn.org. Accessed on July 22, 2020.
6. The NCCN Myelodysplastic Syndromes Clinical Practice Guidelines in Oncology (version 2.2020 – February 28, 2020). © 2020 National Comprehensive Cancer Network, Inc. Available at: http://www.nccn.org. Accessed: July 22, 2020.
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15. Beaushesne MF, Shalansky SJ. Nonchemotherapy drug-induced agranulocytosis: a review of 118 patients treated with colony-stimulating factors. *Pharmacother*. 1999;19(3):299-305.
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19. Andres E, Mourot-Cottet R, Maloisel F, et al. Idiosyncratic drug-induced neutropenia and agranulocytosis. *QJM*. 2017 Jan 9. [Epub ahead of print].
20. The NCCN Management of Immunotherapy-Related Toxicities Clinical Practice Guidelines in Oncology (version 1.2020 – December 16, 2020). © 2020 National Comprehensive Cancer Network, Inc. Available at: http://www.nccn.org. Accessed on July 22, 2020.