

POLICY: Colony Stimulating Factors – Filgrastim Products

- 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)

APPROVAL DATE: 08/21/2019**OVERVIEW**

Filgrastim products include Neupogen, Nivestym, and Zarxio; Nivestym and Zarxio are two products that are biosimilars to Neupogen.¹⁻³ These products are leukocyte growth factors indicated for the following uses: 1) to 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; 2) to reduce the time to neutrophil recovery and the duration of fever following induction or consolidation chemotherapy treatment of adults with acute myeloid leukemia (AML); 3) to 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; 4) for the mobilization of hematopoietic progenitor cells into the peripheral blood for collection by leukapheresis; and 5) to 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. 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 Depending on the indication, filgrastim is given subcutaneously or intravenously. Granix (tbo-filgrastim injection for subcutaneous use) is another filgrastim product.⁴

Guidelines

The National Comprehensive Cancer Network (NCCN) guidelines for hematopoietic growth factors (version 2.2019 – March 27, 2019) recommend filgrastim, along with other granulocyte colony-stimulating factors (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 (category 1).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. The American Society of Clinical Oncology (ASCO) also has clinical practice guidelines for the use of white blood cell growth factors (2015) that also recommends CSFs to reduce the risk of febrile neutropenia in patients receiving cancer chemotherapy.⁶ The NCCN guidelines for hematopoietic growth factors (version 2.2019 – March 27, 2019) recommend filgrastim products for mobilization and following hematopoietic cell transplant.⁵

The NCCN guidelines for myelodysplastic syndromes (MDS) [version 2.2019 – October 18, 2018] 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).¹¹ Data are also available.¹¹⁻¹³

The NCCN guidelines for acute lymphoblastic leukemia (ALL) [version 2.2019 – May 15, 2019] recommend granulocyte CSF for myelosuppressive blocks of therapy or as directed by treatment protocol.¹⁴

ASCO guidelines, updated in 2015, state that CSFs may be considered in patients receiving radiation therapy alone if prolonged delays secondary to neutropenia are expected.⁶ However, the filgrastim

prescribing information notes that the safety and efficacy of filgrastim have not been evaluated in patients receiving concurrent radiation therapy.¹⁻³ Simultaneous use of filgrastim with chemotherapy and radiation therapy should be avoided. The ASCO guidelines state that CSFs should be avoided in patients receiving concomitant chemotherapy and radiation therapy, particularly involving the mediastinum.⁶ The NCCN guidelines for Hematopoietic Growth Factors (version 2.2019 – March 27, 2019) state the prophylactic use of CSFs in patients given concurrent chemotherapy and radiation is not recommended.⁵

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 assessed use of filgrastim for the treatment of neutropenia in this patient population.⁷⁻¹⁰ In one open-label, non-comparative, multicenter study involving 200 HIV-positive patients filgrastim reversed neutropenia in 98% of patients with a median reversal time of 2 days.⁸ In another multicenter, randomized, controlled, open-label trial, use of daily filgrastim or intermittent filgrastim reduced the incidence of severe neutropenia or death compared with control patients who had advanced HIV infection.⁷ Additionally, those receiving filgrastim developed fewer bacterial infections.

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

Dosing Information

The NCCN guidelines for hematopoietic growth factors (version 2.2019 – March 27, 2019) recommend filgrastim products for the mobilization and following hematopoietic cell transplant.⁵ Doses for mobilization of hematopoietic progenitor cells in the autologous setting are up to 32 mcg/kg per day of SC injection, in daily or twice-daily dosing.

The prescribing information for filgrastim products notes that in rare circumstances, patients with congenital neutropenia have required doses exceeding 100 mcg/kg per day.¹⁻³

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 indication(s). 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.

RECOMMENDED AUTHORIZATION CRITERIA

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

FDA-Approved Indications

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- 1. Cancer in Patients Receiving Myelosuppressive Chemotherapy.** Approve for 6 months if the patient meets the following criteria (A and B):
 - A)** The agent is prescribed by, or in consultation with, an oncologist or hematologist; AND
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- B)** The patient meets ONE of the following conditions (i, ii, iii, or iv):
- i.** The patient is receiving myelosuppressive anti-cancer medications that are associated with a high risk of febrile neutropenia (the risk of febrile neutropenia is at least 20% based on the chemotherapy regimen); OR
 - ii.** The 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 \geq 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.** The 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.** The 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. Note: Examples of risk factors include sepsis syndrome; age $>$ 65 years; severe neutropenia (absolute neutrophil count [ANC] $<$ 100 cells/mm³); neutropenia expected to be $>$ 10 days in duration; invasive fungal infection; or other clinically-documented infections.

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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- 2. Acute Myeloid Leukemia (AML) in Patients 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.

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- 3. Bone Marrow Transplant (BMT) in Patients 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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- 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.

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

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

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- 6. Radiation Syndrome (Hematopoietic Syndrome of Acute Radiation Syndrome).** Approve for 1 month if prescribed by or in consultation with a physician with expertise in treating acute radiation syndrome.

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

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.

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

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- 8. Myelodysplastic Syndrome.** 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.

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- 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.

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- 10. 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.

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- 11. Radiation-Induced Neutropenia.** Approve for 6 months if the patient meets the following criteria (A and B):

- A) Filgrastim is prescribed by or in consultation with an oncologist, radiologist, or radiation oncologist; AND
- B) The patient is not concurrently receiving chemotherapy.

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

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Filgrastim has not been shown to be effective, or there are limited or preliminary data or potential safety concerns that are not supportive of general approval for the following conditions. Rationale for non-

coverage for these specific conditions is provided below. (Note: This is not an exhaustive list of Conditions Not Recommended for Approval.)

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; April 2018.
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.
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HISTORY

Type of Revision	Summary of Changes	Approval Date
Annual revision	Nivestym was added to the policy. When the criteria stated Neupogen or Zarxio, it was changed to filgrastim products to also include Nivestym. For the criteria regarding patients with cancer receiving myelosuppressive therapy in the criteria that reference a colony stimulating factor, the terminology of filgrastim and pegfilgrastim products were added, along with the listing of the individual products, which included adding Nivestym and Fulphila.	08/01/2018

selected revision	For the indication regarding patients with cancer (adults and children) receiving myelosuppressive chemotherapy, removed “adults and children”. Also, for this indication removed this notation in other sections regarding this use.	08/08/2018
Annual revision	<p>For all conditions, the Dosing sections were revised to provide for the maximum range of dosing (see Policy). Additionally, the following sections were removed: initial/extended approval, duration of therapy, and labs/diagnostics. The waste management section was also deleted. Additional changes per the specific indications were as follows:</p> <ol style="list-style-type: none"> 1. Cancer in Patients Receiving Myelosuppressive Chemotherapy: CSFs are now provided as examples in a Note rather than as part of the criterion. Also, risk factors are now listed as Notes rather than as part of the criterion. The wording in reference to “according to the prescribing physician” was changed to “according to the prescriber”. 2. Acute Myeloid Leukemia in Patients Receiving Chemotherapy: The qualifier of “adults” was removed from the indication. 3. Peripheral Blood Progenitor Cell Collection and Therapy: The qualifier of “adults and children” was removed from the indication. 4. Severe Chronic Neutropenia: The qualifier of “adults and children” was removed from the indication. 5. Neutropenia Associated with HIV or AIDS: The qualifier of “adults” was removed from the indication. 6. MDS: The qualifier of “adults” was removed from the indication. 7. Aplastic Anemia: The criteria for approval were eliminated for this condition. 	08/21/2019