EXPRESS SCRIPTS®

PRIOR AUTHORIZATION POLICY

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)

TAC APPROVAL DATE: 08/01/2018

OVERVIEW

Neupogen, a granulocyte colony stimulating factor (G-CSF), is indicated for the following: 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 bone marrow transplantation; 4) for the mobilization of hematopoietic progenitor cells into the peripheral blood for collection by leukapheresis; and 5) for chronic administration 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; and 6) to increase survival in patients acutely exposed to myelosuppressive doses of radiation (Hematopoietic Syndrome of Acute Radiation Syndrome).[1] Nivestym and Zarxio are two products that are biosimilars to Neupogen.[8,9] These have the same indications except do not have an indication regarding hematopoietic syndrome of acute radiation syndrome. Depending upon the indication, filgrastim is given by subcutaneously (SC) bolus injection, by short intravenous (IV) infusion or by continuous IV infusion. Data support the use of filgrastim in many other conditions.

POLICY STATEMENT

Prior authorization is recommended for prescription benefit coverage of filgrastim products. Due to the specialized skills required for evaluation and diagnosis of patients treated with filgrastim as well as the monitoring required for adverse events and efficacy, initial approval in most instances requires filgrastim to be prescribed by or in consultation with a physician who specializes in the condition being treated. 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.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

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

FDA-Approved Indications

1. **Patients with Cancer Receiving Myelosuppressive Chemotherapy.** Approve for 6 months if the patient meets the following (A and B):
   A) The agent is prescribed by, or in consultation with, an oncologist or hematologist; AND
   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 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 one or more risk factors for febrile neutropenia according to the prescribing physician (e.g., aged ≥ 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 (e.g., filgrastim products [Neupogen, Zarxio, Granix, Nivestym], pegfilgrastim products [Neulasta, Fulphila], Leukine® [sargramostim injection]), and a reduced dose or frequency of chemotherapy may compromise treatment outcome; OR
      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 prescribing physician (e.g., 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; other clinically documented infections).

   Filgrastim is indicated for this condition 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 and fever.[1-3] The National Comprehensive Cancer Network (NCCN) guidelines for myeloid growth factors[2] (version 1.2018) 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.[2] 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 CSF in other scenarios in those given myelosuppressive chemotherapy.

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

   Filgrastim is indicated to reduce the time to neutrophil recovery and the duration of fever, following induction or consolidation chemotherapy treatment of adults with AML.[1]

3. **Patients with Cancer Receiving Bone Marrow Transplant (BMT).** Approve for 1 month if prescribed by, or in consultation with, a hematologist, an oncologist, or a physician that specializes in transplantation.

   Filgrastim is indicated to 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 BMT.[1]

4. **Patients (Adults and Children) Undergoing 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 that specializes in transplantation.

   Filgrastim is indicated for the mobilization of hematopoietic progenitor cells into the peripheral blood for collection by leukapheresis. Mobilization allows for the collection of increased numbers of progenitor cells capable of engraftment compared with collection by leukapheresis without mobilization or bone marrow harvest. After myeloablative chemotherapy, the transplantation of an increased number of progenitor cells can lead to a more rapid engraftment, which may result in a decreased need for supportive care. The scenarios that filgrastim is utilized include patients with cancer or healthy donors undergoing mobilization of PBPC, as well as patients with cancer post autologous PBPC transplantation.[1-2,4-5] This criterion is recommended based on the professional opinion of specialized and other physicians.

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

   Filgrastim is indicated for chronic administration 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.[1-2,6-7] This criterion is recommended based on the professional opinion of specialized and other physicians.

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.

   Neupogen is indicated to increase survival in patients acutely exposed to myelosuppressive doses of radiation (Hematopoietic Syndrome of Acute Radiation Syndrome).[1] Approval of Neupogen for this use was based on efficacy studies performed in in animals and data supporting the use of Neupogen for other approved indications.[1] Other sources also cite filgrastim being used for this scenario.[17]

Other Uses with Supportive Evidence

7. **Neutropenia Associated with Human Immunodeficiency Virus (HIV) or Acquired Immunodeficiency Syndrome (AIDS) in Adults.** 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 that specializes in the management of HIV/AIDS.

   Neutropenia occurs in patients with HIV and may be caused by medications or due to the disease process. Studies have been done that assess filgrastim for the treatment of neutropenia in this patient population.[10-13] In an open-label, non-comparative, multicenter study[11] involving 200 HIV-positive patients filgrastim reversed neutropenia in 98% of patients with a median reversal time of 2 days. In another multicenter, randomized, controlled, open-label trial,[10] use of daily filgrastim or intermittent filgrastim reduced the incidence of severe neutropenia or death compared with control in patients who had advanced HIV infection. Additionally, patients receiving filgrastim developed fewer bacterial infections. This criterion is recommended based on the professional opinion of specialized and other physicians.

8. Treatment of Myelodysplastic Syndromes (MDS) in Adults. Approve for 3 months if prescribed by, or in consultation with, an oncologist or hematologist.

Filgrastim is recommended in guidelines published by the NCCN (version 1.2019) for use in certain patients with MDS (e.g., those with recurrent or resistant infections in neutropenic patients, combination use with epoetin alfa).[14] In a trial 39% of assessable patients with MDS treated with erythropoietin plus G-CSF (n = 48/123) achieved an erythroid response. Also, 29% of transfusion-dependent patients (n = 25/85) became transfusion independent.[15] Other data are available.[16]

9. Aplastic Anemia (Adults and Children). Approve for 1 month if prescribed by, or in consultation with, a hematologist.

Filgrastim has been utilized in the treatment of aplastic anemia, usually in combination with immunosuppressive therapy or with erythropoietin-stimulating products.[18-22] In a multicenter, randomized, controlled study[19] patients with anemia associated with aplastic anemia (n = 131) were treated with G-CSF alone or with epoetin alfa. The response rates at 12 weeks in 110 evaluable patients were between 12.9% and 36.8%.[19]

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

Filgrastim has been used for agranulocytosis caused by non-cytotoxic medications, primarily described in case series, case reports and literature reviews.[23-31] This criterion is recommended based on the professional opinion of specialized and other physicians.

11. Acute Lymphocytic Leukemia (ALL). Approve for 1 month if prescribed by, or in consultation with, an oncologist or a hematologist.

Data notes some benefits in ALL in some scenarios.[3,32-33] This criterion is recommended based on the professional opinion of specialized and other physicians.

12. Radiation-Induced Neutropenia. Approve for 6 months if the patient meets the following criteria (A and B):[1,3,34-36]

A) The agent is prescribed by, or in consultation with, an oncologist, radiologist or radiation oncologist; AND

B) The patient is not currently receiving chemotherapy.

American Society of Clinical Oncology (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.[3] However, the filgrastim prescribing information notes that the safety and efficacy of filgrastim have not been evaluated in patients receiving concurrent radiation therapy.[1] 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.[3] The NCCN guidelines for myeloid growth factors (version 1.2018) state the prophylactic use of CSFs in patients given concurrent chemotherapy and radiation is not recommended.[2] In one trial that administered radiotherapy with simultaneous chemotherapy unexpected reduced local control occurred.[34]

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Neupogen 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. (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.

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HISTORY

Type of Revision	Summary of Changes	TAC Approval Date
Annual revision	The wording of the examples of risk factors provided under the criteria for Patients with Cancer (Adults and Children) Receiving Myelosuppressive Chemotherapy (Criterion 1.B.ii.) were revised.	06/29/2016
Annual revision	No criteria changes.	07/12/2017
Annual revision	The name of the policy was changed from Colony Stimulating Factors – Neupogen PA to Colony Stimulating Factors – Filgrastim products PA. This includes the filgrastim biosimilars of Zarxio and Nivestym. Nivestym was just added to the policy. Zarxio was added to the policy as well and the individual PA policy for Zarxio was retired. Criteria that stated Neupogen or Zarxio was changed to state filgrastim to address all products. 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
DEU selected revision	For the indication regarding Patients with Cancer (Adults and Children) Receiving Myelosuppressive Chemotherapy, removed "(adults and children)".	08/08/2018

TAC – Therapeutic Assessment Committee; PA – Prior authorization; DEU – Drug Evaluation Unit.