PRIOR AUTHORIZATION POLICY

POLICY:  Colony Stimulating Factors – Neupogen® (filgrastim injection for subcutaneous or intravenous use – Amgen)

TAC APPROVAL DATE:  07/12/2017

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). Depending upon the indication, Neupogen is given by subcutaneously (SC) bolus injection, by short intravenous (IV) infusion or by continuous IV infusion. Data support the use of Neupogen in many other conditions.

POLICY STATEMENT
Prior authorization is recommended for prescription benefit coverage of Neupogen. Because of the specialized skills required for evaluation and diagnosis of patients treated with Neupogen as well as the monitoring required for adverse events and efficacy, initial approval in most instances requires Neupogen 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 Neupogen is recommended in those who meet the following criteria:

FDA-Approved Indications

1. Patients with Cancer (Adults and Children) 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):


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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., Granix™ [tbo-filgrastim], Leukine® [sargramostim injection], Neulasta® [pegfilgratim injection], Neupogen or Zarxio™ [filgrastim-sndz 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/mm³]; neutropenia expected to be > 10 days in duration; invasive fungal infection; other clinically documented infections).

Neupogen 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 factors2 (version 1.2017) recommend Neupogen, 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.

Neupogen 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.

Neupogen 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.
Neupogen 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 Neupogen is utilized include patients with cancer or healthy donors undergoing mobilization of PBPC, as well as patients with cancer post autologous PBPC transplantation. This criterion is recommended based on the professional opinion of specialized 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.

Neupogen 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. 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). The recommended dose of Neupogen is 10 mcg/kg as a single daily SC injection for patients exposed to myelosuppressive radiation doses. Administer Neupogen as soon as possible after suspected or confirmed exposure to radiation doses greater than 2 gray. Continue Neupogen therapy until the absolute neutrophil count remains greater than 1,000/mm³ for 3 consecutive days. It is notable that due to ethical and feasibility reasons, studies investigating the efficacy of Neupogen could not be done in humans with acute radiation syndrome. Approval of Neupogen for this use was based on efficacy studies performed in animals and data supporting the use of Neupogen for other approved indications. Other sources also cite filgrastim being used for this scenario.

**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 Neupogen for the treatment of neutropenia in this patient population. In an open-label, non-comparative, multicenter study involving 200 HIV-positive patients, Neupogen reversed neutropenia in 98% of patients with a median reversal time of 2 days. In another multicenter, randomized, controlled, open-label trial, use of daily Neupogen or intermittent Neupogen reduced the incidence of severe neutropenia or death compared with control in patients who had advanced HIV infection. Additionally, patients receiving Neupogen 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.

Neupogen is recommended in guidelines published by the NCCN (version 1.2016) for use in certain patients with MDS (e.g., those with recurrent or resistant infections in neutropenic patients, combination use with Epogen®/Procrit® [epoetin alfa injection]). 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. Other data are available.

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

Neupogen has been utilized in the treatment of aplastic anemia, usually in combination with immunosuppressive therapy or with erythropoietin-stimulating products. In a multicenter, randomized, controlled study patients with anemia associated with aplastic anemia (n = 131) were treated with G-CSF alone or with Epogen/Procrit®. The response rates at 12 weeks in 110 evaluable patients were between 12.9% and 36.8%. Guidelines for aplastic anemia published by the British Committee for Standards in Haematology in 2009 state that a short course of G-CSF may be considered for severe systemic infections that are not responding to intravenous antibiotics and anti-fungal medications, but should be discontinued after 1 week if no increase in neutrophil count is noted.

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

Neupogen has been used for agranulocytosis caused by non-cytotoxic medications, primarily described in case series, case reports and literature reviews. 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. 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):

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. However, the Neupogen prescribing information notes that the safety and efficacy of Neupogen have not been evaluated in patients receiving concurrent radiation therapy. Simultaneous use of Neupogen with chemotherapy and radiation therapy should be avoided. The ASCO guidelines
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state that CSFs should be avoided in patients receiving concomitant chemotherapy and radiation therapy, particularly involving the mediastinum. The NCCN guidelines for myeloid growth factors (version 1.2016) state the prophylactic use of CSFs in patients given concurrent chemotherapy and radiation is not recommended. In one trial that that administered radiotherapy with simultaneous chemotherapy led to unexpected reduced local control.

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.

REFERENCES


**REFERENCES**


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### HISTORY

<table>
<thead>
<tr>
<th>Type of Revision</th>
<th>Summary of Changes*</th>
<th>TAC Approval Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>Annual revision</td>
<td>Added criteria regarding new FDA-approved indication for radiation syndrome (hematopoietic syndrome of acute radiation syndrome). Deleted other uses with supportive evidence criteria for radiation injury (syndrome). Added examples of Zarxio and Granix as colony stimulating factor therapy regarding criteria addressing patients with cancer (adults and children) receiving myelosuppressive chemotherapy.</td>
<td>06/10/2015</td>
</tr>
<tr>
<td>Annual revision</td>
<td>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.</td>
<td>06/29/2016</td>
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<tr>
<td>Annual revision</td>
<td>No criteria changes</td>
<td>07/12/2017</td>
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TAC – Therapeutic Assessment Committee; DEU – Drug Evaluation Unit; TAC – Therapeutic Assessment Committee; * For a further summary of criteria changes, refer to respective TAC minutes available at: http://esidepartments/sites/Dep043/Committees/TAC/Forms/AllItems.aspx.