OBJECTIVE
The intent of the colony stimulating factor (CSF) medical drug criteria is to ensure appropriate selection of patients for treatment according to product labeling and/or clinical studies and/or guidelines and according to dosing recommended in product labeling. The policy will consider CSF agents appropriate for patients with FDA labeled indication(s) or indications supported in clinical studies and/or clinical guidelines. Dosing will be limited to the FDA labeled or compendia supported dosage for the specific indication.

AGENTS
Granix® (tbo-filgrastim)
Leukine® (sargramostim)
Neulasta® (pegfilgrastim)
Neupogen® (filgrastim)
Zarxio™ (filgrastim-sndz)

PRIOR AUTHORIZATION CRITERIA FOR APPROVAL
ONE of the agents listed above will be approved when the following are met:
1. The patient does not have any contraindications to therapy with the requested agent AND
2. The patient has a diagnosis of ONE of the following:
   a. If Neupogen, Granix, or Zarxio, the patient has a diagnosis of ONE of the following:
      i. Acute myeloid leukemia receiving induction or consolidation chemotherapy OR
      ii. Primary prophylaxis after induction or consolidation chemotherapy in patients with acute myeloid leukemia (AML) OR
      iii. Myelodysplastic syndrome AND ONE of the following:
         1. ANC ≤500/mm³ AND a history of recurrent or resistant bacterial infections OR
         2. Enhancement of erythropoietic activity for the treatment of refractory anemia and ALL of the following:
            a. Concurrent use with erythropoietin (Epogen, Procrit) AND
            b. Serum erythropoietin level ≤500 mU/mL AND
            c. Confirmation of adequate iron stores (i.e. 20% transferrin, ferritin 100 ng/ml or iron stain on bone marrow aspirate or biopsy)
      iv. Non-myeloid malignancy undergoing myeloablative chemotherapy followed by autologous or allogeneic bone marrow transplantation (BMT) OR
      v. Mobilization and engraftment of peripheral blood progenitor cells (PBPC) for leukapheresis OR
vi. Delayed or failed BMT engraftment

OR

vii. HIV AND ONE of the following:
   1. ANC ≤750/mm$^3$
      OR
   2. Drug-induced neutropenia (e.g. zidovudine or ganciclovir)

OR

viii. Aplastic anemia

OR

ix. Receiving myelosuppressive chemotherapy associated with neutropenia (ANC ≤500/mm$^3$) AND ONE of the following:
   1. Patient has febrile neutropenia
      OR
   2. Patient has a history of FN during previous course of chemotherapy

OR

x. Severe chronic neutropenia AND BOTH of the following:
   1. The patient has at least one symptom (e.g. fever, infections, oropharyngeal ulcers)
   2. Diagnostic labs have been evaluated (e.g. CBC with differential, platelet counts, and bone marrow morphology and karyotype)

OR

xi. Primary prophylaxis for the prevention of febrile neutropenia (FN) in patients receiving a chemotherapy regimen with a ≥ 20% risk

OR

xii. Primary prophylaxis for prevention of FN where the chemotherapy regimen risk is <20% but the patient has at least ONE of the following risk factors:
   1. Age > 65
   2. Previous chemotherapy and/or radiation
   3. Previous episodes of FN
   4. Current infection(s) or open wounds
   5. Recent surgery
   6. Poor performance status
   7. Bone marrow involvement by tumor producing cytopenias
   8. Poor nutritional status
   9. Decreased renal or hepatic function

OR

xiii. Secondary prophylaxis in patients who had a neutropenic episode from a prior chemotherapy cycle for which primary prophylaxis was not received AND in which a reduced dose may compromise disease or overall survival or treatment outcomes

OR

b. If Leukine, the patient has a diagnosis of ONE of the following:
   i. Acute myeloid leukemia receiving induction or consolidation chemotherapy

OR

   ii. Primary prophylaxis after induction or consolidation chemotherapy in patients with acute myeloid leukemia (AML)

OR

   iii. Myelodysplastic syndrome AND ONE of the following:
      1. ANC ≤500/mm$^3$ AND a history of recurrent or resistant bacterial infections
2. Enhancement of erythropoietic activity for the treatment of refractory anemia and ALL of the following:
   a. Concurrent use with erythropoietin (Epogen, Procrit) AND
   b. Serum erythropoietin level ≤500 mU/mL AND
   c. Confirmation of adequate iron stores (i.e. 20% transferrin, ferritin 100 ng/ml or iron stain on bone marrow aspirate or biopsy)

OR

iv. Non-myeloid malignancy undergoing myeloablative chemotherapy followed by autologous or allogeneic bone marrow transplantation (BMT)

OR

v. Mobilization and engraftment of peripheral blood progenitor cells (PBPC) for leukapheresis

OR

vi. Delayed or failed BMT engraftment

OR

vii. HIV AND ONE of the following:
   1. ANC ≤750/mm³ OR
   2. Drug-induced neutropenia (e.g. zidovudine or ganciclovir)

OR

viii. Aplastic anemia

OR

ix. Receiving myelosuppressive chemotherapy associated with neutropenia (ANC ≤500/mm³) AND ONE of the following:
   1. Patient has febrile neutropenia OR
   2. Patient has history of FN during previous course of chemotherapy

OR

x. Severe chronic neutropenia AND BOTH of the following:
   1. The patient has at least one symptom (e.g. fever, infections, oropharyngeal ulcers) AND
   2. Diagnostic labs have been evaluated (e.g. CBC with differential, platelet counts, and bone marrow morphology and karyotype)

OR

xi. Primary prophylaxis for the prevention of febrile neutropenia (FN) in patients receiving a chemotherapy regimen with a ≥ 20% risk

OR

xii. Primary prophylaxis for prevention of FN where the chemotherapy regimen risk is <20% but the patient has at least ONE of the following risk factors:
   1. Age > 65
   2. Previous chemotherapy and/or radiation
   3. Previous episodes of FN
   4. Current infection(s) or open wounds
   5. Recent surgery
   6. Poor performance status
   7. Bone marrow involvement by tumor producing cytopenias
   8. Poor nutritional status
   9. Decreased renal or hepatic function
OR

xiii. Secondary prophylaxis in patients who had a neutropenic episode from a prior chemotherapy cycle for which primary prophylaxis was not received AND in which a reduced dose may compromise disease or overall survival or treatment outcomes

OR

taxiv. Crohn’s disease

OR

xv. Malignant melanoma (adjuvant)

OR

c. If Neulasta, the patient has a diagnosis of ONE of the following:

i. Primary prophylaxis for the prevention of febrile neutropenia (FN) in patients receiving a chemotherapy regimen with a ≥ 20% risk

OR

ii. Primary prophylaxis for prevention of FN where the chemotherapy regimen risk is <20% but the patient has at least ONE of the following risk factors:

1. Age > 65
2. Previous chemotherapy and/or radiation
3. Previous episodes of FN
4. Current infection(s) or open wounds
5. Recent surgery
6. Poor performance status
7. Bone marrow involvement by tumor producing cytopenias
8. Poor nutritional status
9. Decreased renal or hepatic function

OR

iii. Receiving myelosuppressive chemotherapy associated with neutropenia (ANC ≤500/mm^3) AND ONE of the following:

1. Patient has febrile neutropenia

OR

2. Patient has history of FN during previous course of chemotherapy

OR

ii. Secondary prophylaxis in patients who had a neutropenic episode from a prior chemotherapy cycle for which primary prophylaxis was not received AND in which a reduced dose may compromise disease or overall survival or treatment outcomes

AND

3. The dose is within the FDA labeled or compendia supported dose

<table>
<thead>
<tr>
<th>Indication</th>
<th>Length of Approval</th>
</tr>
</thead>
<tbody>
<tr>
<td>AML induction/consolidation</td>
<td>6 months</td>
</tr>
<tr>
<td>AML primary prophylaxis</td>
<td>6 months</td>
</tr>
<tr>
<td>Myelodysplastic syndrome</td>
<td>6 months</td>
</tr>
<tr>
<td>Autologous or allogeneic BMT</td>
<td>6 months</td>
</tr>
<tr>
<td>Peripheral blood progenitor cell mobilization</td>
<td>6 months</td>
</tr>
<tr>
<td>Delayed or failed BMT engraftment</td>
<td>6 months</td>
</tr>
<tr>
<td>HIV</td>
<td>3 months</td>
</tr>
<tr>
<td>Aplastic anemia</td>
<td>6 months</td>
</tr>
<tr>
<td>Myelosuppressive chemotherapy</td>
<td>3 months</td>
</tr>
<tr>
<td>Severe chronic neutropenia</td>
<td>6 months</td>
</tr>
<tr>
<td>Primary prophylaxis for prevention of FN</td>
<td>3 months</td>
</tr>
<tr>
<td>Secondary prophylaxis for neutropenic episode</td>
<td>3 months</td>
</tr>
<tr>
<td>Condition</td>
<td>Duration</td>
</tr>
<tr>
<td>---------------------------------</td>
<td>----------</td>
</tr>
<tr>
<td>Crohn’s disease</td>
<td>3 months</td>
</tr>
<tr>
<td>Malignant melanoma (adjuvant)</td>
<td>6 months</td>
</tr>
</tbody>
</table>

**Contraindications**

<table>
<thead>
<tr>
<th>Agent(s)</th>
<th>Contraindication(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Granix (tbo-filgrastim)</td>
<td>None</td>
</tr>
<tr>
<td>Leukine (sargramostim)</td>
<td>Hypersensitivity to GM-CSF, yeast-derived products or any component of the product; Excessive leukemic myeloid blasts in bone marrow or peripheral blood (≥10%); Concomitant use with chemotherapy and radiotherapy</td>
</tr>
<tr>
<td>Neupogen (filgrastim)</td>
<td>Hypersensitivity</td>
</tr>
<tr>
<td>Neulasta (pegfilgrastim)</td>
<td>Hypersensitivity</td>
</tr>
<tr>
<td>Zarxio (filgrastim-sndz)</td>
<td>Patients with a history of serious allergic reactions to human granulocyte colony-stimulating factors such as filgrastim or pegfilgrastim products</td>
</tr>
</tbody>
</table>

Blue Cross and Blue Shield of Alabama does not approve or deny procedures, services, testing, or equipment for our members. Our decisions concern coverage only. The decision of whether or not to have a certain test, treatment or procedure is one made between the physician and his/her patient. Blue Cross and Blue Shield of Alabama administers benefits based on the members’ contract and corporate medical policies. Physicians should always exercise their best medical judgment in providing the care they feel is most appropriate for their patients. Needed care should not be delayed or refused because of a coverage determination.

This medical policy is not an authorization, certification, explanation of benefits, or a contract. Eligibility and benefits are determined on a case-by-case basis according to the terms of the member’s plan in effect as of the date services are rendered. All medical policies are based on (i) research of current medical literature and (ii) review of common medical practices in the treatment and diagnosis of disease as of the date hereof. Physicians and other providers are solely responsible for all aspects of medical care and treatment, including the type, quality, and levels of care and treatment.

This policy is intended to be used for adjudication of claims (including pre-admission certification, predeterminations, and pre-procedure review) in Blue Cross and Blue Shield’s administration of plan contracts.

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Prime Therapeutics LLC is an independent limited liability company providing pharmacy benefit management services.
Granulocyte colony-stimulating factor (G-CSF) and granulocyte-macrophage colony-stimulating factor (GM-CSF) are naturally occurring glycoprotein cytokines. Together, G-CSF and GM-CSF exert major control over the reproduction and maturation of committed myeloid-lineage progenitor cells.

With the advent of recombinant molecular biology techniques, biologically active synthetic copies of G-CSF and GM-CSF have become available in clinically useful quantities and have been approved by the FDA for clinical use. Recombinant CSFs are administered to enhance recovery of hematopoietic functions in neutropenic individuals, or to decrease the incidence and severity of infections associated with drug-related myelosuppression.

The most common adverse event attributed to the use of colony stimulating factors (CSF) is mild to moderate bone pain reported in approximately 10-30% of patients. Most patients can be controlled on a non-opiate analgesic. The use of CSFs has also been associated with heightened risk for musculoskeletal pain. There have been fatal cases of splenic rupture reported with the use of G-CSF.

GM-CSF has a higher incidence of fever compared to the other CSF agents. Mild to moderate anemia is a common adverse event associated with these agents in patients receiving CSF for peripheral blood stem cell mobilization (65% for filgrastim). Guidelines recommend the use of epoetin for the treatment of anemia when appropriate. Other adverse reactions occurring in up to 65% of patients are generally not severe and are reversible. Such adverse reactions observed with GM-CSF administration include low-grade fever, facial flushing, mild myalgias, headache, nausea, and dyspnea. Approximately 1% of patients develop blood clots with GM-CSF administration, which could result in life-threatening pulmonary embolus or stroke.

In clinical studies with filgrastim, the incidence of antibodies binding to filgrastim was 3% (11/333). In these patients no evidence of a neutralizing response was seen. The overall incidence of antibody development has not been adequately studied.

The FDA approved indications for these agents are listed in the table below.

<table>
<thead>
<tr>
<th>Agent(s)</th>
<th>Indication(s)</th>
<th>Dosing</th>
<th>FDA Labeled Indications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neupogen®</td>
<td>Decrease the incidence of infection in patients with nonmyeloid malignancies receiving myelosuppressive chemotherapy associated with a significant incidence of severe neutropenia with fever.</td>
<td>5 mcg/kg/day by SC injection, short IV infusion, or continuous IV infusion. Adjust dose based on ANC nadir. Use should be discontinued if ANC surpasses 10,000/mm³</td>
<td>Category A, B, or C</td>
</tr>
<tr>
<td><em>(filgrastim)</em></td>
<td>Reduce the time to neutrophil recovery and the duration of fever, following induction or consolidation chemotherapy in adults with acute myeloid leukemia (AML).</td>
<td>5 mcg/kg/day by SC injection, short IV infusion, or continuous IV infusion. Adjust dose based on ANC nadir. Use should be discontinued if ANC surpasses 10,000/mm³</td>
<td>Category A, B, or C</td>
</tr>
<tr>
<td></td>
<td>Reduce the duration of neutropenia and related clinical sequelae in patients with nonmyeloid malignancies undergoing myeloablative chemotherapy followed by bone marrow transplantation.</td>
<td>10 mcg/kg/day after BMT as IV infusion for no longer than 24 hours. First dose should be given at least 24 hours after cytotoxic chemotherapy and marrow infusion. Dose titration recommended based on labeling</td>
<td>Category A, B, or C</td>
</tr>
<tr>
<td>Agent(s)</td>
<td>Indication(s)</td>
<td>Dosing</td>
<td></td>
</tr>
<tr>
<td>--------------------------</td>
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<td>--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------</td>
<td></td>
</tr>
<tr>
<td><strong>Neulasta®</strong> (pegfilgrastim)</td>
<td>Decrease the incidence of infection in patients with nonmyeloid malignancies receiving myelosuppressive chemotherapy associated with a significant incidence of febrile neutropenia</td>
<td>6 mg SC once per chemotherapy cycle. Do not administered 14 days before and 24 hours after cytotoxic chemotherapy</td>
<td></td>
</tr>
<tr>
<td>Leukine (sargramostim)</td>
<td>Following induction chemotherapy in patients with AML. Efficacy not assessed in patients &lt;55 years of age.</td>
<td>250 mcg/m²/day IV starting approximately on day 11 or 4 days after completion of induction chemotherapy if day 10 bone marrow is hypoplastic with &lt;5% blasts. Continue until ANC &gt;1500 cells/mm³ for 3 consecutive days or max of 42 days. Reduce dose by 50% if ANC &gt;20,000 cells/mm³.</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Mobilization of hematopoietic progenitor cells into peripheral blood (PBPC) for collection by leukapheresis</td>
<td>250 mcg/m²/day IV over 24 hours or SC once daily. Continue through period of PBPC collection. Reduce dose by 50% if WBC &gt;50,000 cells/mm³.</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Acceleration of myeloid recovery in patients with NHL, ALL and HD undergoing autologous BMT</td>
<td>250 mcg/m²/day IV over 24 hours or SC once daily immediately following infusion of PBPC continuing until an ANC &gt;1500 cells/mm³ for 3 consecutive days.</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Acceleration of myeloid recovery in patients undergoing allogeneic BMT from HLA-matched related donors</td>
<td>250 mcg/m²/day IV over 2 hours beginning 2-4 hours BMT and not less than 24 hours after last dose of chemotherapy or radiation. Do not administer until post marrow infusion ANC is &lt;500 cells/mm³, continue until ANC &gt;1500 cells/mm³ for 3 consecutive days.</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Patients who have undergone allogeneic or autologous BMT who have delayed or failed engraftment.</td>
<td>250 mcg/m²/day for 14 days as 2 hour IV infusion. Dose can be repeated after 7 days off therapy if engraftment has not occurred. If still not occurred, a third course of 500 mcg/m²/day for 14 days may be tried after another 7 days off therapy.</td>
<td></td>
</tr>
<tr>
<td>Granix^ (tbo-filgrastim)</td>
<td>Reduction in the duration of severe neutropenia in patients with non-myeloid malignancies receiving myelosuppressive anti-cancer drugs associated with a clinically significant incidence of febrile neutropenia</td>
<td>5 mcg/kg/day as SC injection. Give the first dose no earlier than 24 hours following myelosuppressive chemotherapy. Continue dosing until expected neutrophil nadir is passed and count has recovered to normal range.</td>
<td></td>
</tr>
<tr>
<td>*Zarxio™ (filgrastim-sndz)</td>
<td>Decrease the incidence of infection, as manifested by febrile neutropenia, in patients with nonmyeloid malignancies receiving myelosuppressive anticancer drugs associated with a significant incidence of severe neutropenia with fever</td>
<td>5 mcg/kg/day by SC injection, short IV infusion, or continuous IV infusion. Adjust dose based on ANC nadir. Use should be discontinued if ANC surpasses 10,000/mm³.</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Reduce the time to neutrophil recovery and the duration of fever, following induction or consolidation chemotherapy treatment of</td>
<td>5 mcg/kg/day by SC injection, short IV infusion, or continuous IV infusion. Adjust dose based on ANC nadir. Use</td>
<td></td>
</tr>
</tbody>
</table>

*Zarxio™ is approved for the treatment of neutropenia in adult and pediatric patients with non-myeloid malignancies and neutropenia following myelosuppressive chemotherapy.
Agent(s) | Indication(s) | Dosing
--- | --- | ---
patients with acute myeloid leukemia (AML) | should be discontinued if ANC surpasses 10,000/mm³ | 
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 (BMT) | 10 mcg/kg/day after BMT as IV infusion for no longer than 24 hours. First dose should be given at least 24 hours after cytotoxic chemotherapy and marrow infusion. Dose titration recommended based on labeling | 
Mobilize autologous hematopoietic progenitor cells into the peripheral blood for collection by leukapheresis | 10 mcg/kg/day SC injection. Give at least 4 days before first leukapheresis and continue to last. Dose modifications based on WBC >100,000/mm³ | 
Reduce the incidence and duration of sequelae of severe neutropenia (e.g., fever, infections, oropharyngeal ulcers) in symptomatic patients with congenital neutropenia, cyclic neutropenia, or idiopathic neutropenia | 

SC=subcutaneous; BMT=bone marrow transplant; ANC=absolute neutrophil count; AML; acute myelogenous leukemia; NHL=non-Hodgkin’s lymphoma; ALL=acute lymphoblastic leukemia; HD=Hodgkin’s disease; WBC=white blood cells
*Should not be administered 24 hours before or after administration of cytotoxic chemotherapy
**Neulasta is not indicated for the mobilization of peripheral blood progenitor cells or hematopoietic stem cell transplantation.
^Can be administered by either a health care professional, patient, or caregiver. If a patient (or caregiver) is not an appropriate candidate for self-administration for any reason, tbo-filgrastim should be administered by a health care professional.

There are numerous causes of neutropenia. In general, although there is an incomplete understanding of the causes of neutropenia, it can be bucketed into two groups, mechanism or etiologic. Mechanisms that cause neutropenia include prolonged drug or other direct stem cell toxic exposure (e.g. immune mediated). Chemotherapy induced neutropenia is discussed in further sections of this document. Etiologic causes are either congenital or acquired. Acquired causes are not addressed herein. Some congenital neutropenia conditions require regular treatment with G-CSF (e.g. severe congenital neutropenia (SCN) and cyclic neutropenia (CN)).

For patients with neutropenia, the risk of serious infection increases as the ANC decreases. Research has shown a direct correlation between total incidence of life threatening infections and the duration and severity of neutropenia.⁵

Febrile neutropenia (FN) (defined as neutropenia [<500 neutrophils/mcl or < 1,000 neutrophils/mcl and a predicted decline to ≤500/mcl over the next 48 hours] AND a fever of ≥38.3°C orally or ≥38.0 over 1 hour) is a major dose limiting toxicity of chemotherapy which can result in hospital stay and/or chemotherapy dose reductions or treatment delays for subsequent cycles. Reducing chemotherapy doses or delaying subsequent chemotherapy cycles can affect patient outcomes.⁵ The use of prophylactic CSFs has been shown to decrease the risk of neutropenia as well as rates of infection.⁶ CSFs have also been shown to improve the delivery of full dose-intensity chemotherapy at the planned schedule, although in most studies this has not been shown to result in higher overall survival. The use of CSFs has reduced the incidence, length, and severity of chemotherapy-related neutropenia in several different cancers.⁶ There is less evidence to support the use of CSFs as an adjunct to antibiotics.⁶

The 2014 National Comprehensive Cancer Network (NCCN) guidelines are based on the risk of febrile neutropenia associated with chemotherapy. When considering prophylactic use of CSFs, patients should be placed into one of three risk categories based on chemotherapy regimen and other patient risk factors: overall high-risk group (>20% risk of FN), intermediate-risk group (10-20% risk), or low-risk group (<10% risk).⁶ The risk of
developing FN is directly related to the intensity of the chemotherapy regimen. Risk for developing FN should be assessed prior to the first chemotherapy cycle and before each subsequent cycle.

In addition to the chemotherapy regimen risk factors, there are also patient risk factors that are evaluated when considering the overall risk for FN. These include age (>65), previous chemotherapy or radiotherapy, any preexisting conditions [previous neutropenia, current infection, recent surgery], tumor involvement in the bone marrow, poor performance status, decreased renal or hepatic function, and HIV-infected patients.6

For chemotherapy regimens associated with an intermediate risk, patient specific risk factors should be evaluated which may elevate a regimen into the high risk category where CSF prophylaxis is recommended.6

Efficacy of these agents is supported in clinical trials and treatment guidelines. While FDA labeled indications for these agents vary, filgrastim and sargramostim are used for all FDA labeled or indications determined to be medically necessary and are often referred to collectively in guidelines. Pegfilgrastim has more limited data and is supported in labeling and guidelines for fewer indications.

NCCN Guidelines recommend prophylaxis with colony stimulating factors (CSF) for chemotherapy regimens considered “high risk” (>20%) for the development of FN. NCCN guidelines recommend individualized consideration of prophylactic treatment for patients with intermediate risk (10-20%). Routine use of CSFs is not recommended in low-risk patients (<10%). Among CSFs for the prophylactic treatment of FN, filgrastim, tbo-filgrastim, and pegfilgrastim are considered category 1 recommendations, while sargramostim is considered a category 2B recommendation. The NCCN panel also recommends the therapeutic use of CSFs in certain patients with FN. Patients who are receiving prophylactic filgrastim or sargramostim should continue with CSF therapy, while those who have received prophylactic pegfilgrastim should not be treated with additional CSF because it is long-acting. There is also a lack of evidence to support the therapeutic use of tbo-filgrastim. Benefits have not been shown for the use of pegfilgrastim in chemotherapy regimens given under a two-week duration. Use of pegfilgrastim should be avoided in patients receiving weekly chemotherapy. Guidelines on the use of G-CSF and GM-CSF in myelodysplastic syndrome do not recommend the use of either of these agents as routine infection prophylaxis but can be considered for recurrent or resistant infections in neutropenic patients. These agents can also be combined with epoetin for anemia when indicated.6

European Society of Medical Oncologists clinical practice guidelines on the use of hematopoietic growth factors (hGFs) (filgrastim, sargramostim, and pegfilgrastim) recommend the following:14

- The use of hGFs in prophylaxis of chemotherapy-induced neutropenia is justified when the risk of febrile neutropenia exceeds 20%.
- The use of G-CSF or its pegylated form is not recommended for the treatment of febrile neutropenia except in settings with increased morbidity and mortality, including sepsis, tissue infection and prolonged neutropenia.

European Organization for Research and Treatment of Cancer (EORTC) guidelines for the use of G-CSF in chemotherapy induced febrile neutropenia recommend the use of G-CSF including pegfilgrastim to prevent FN and FN-related complications where indicated. Guideline supported indications include the following:15

- Evaluate patient specific risk factors before each cycle of chemotherapy regimen.
- Assess the risk of FN with individual chemotherapy regimens when determining the need for prophylactic G-CSF.
• Prophylactic use of G-CSF is recommended in situations where dose-dense or dose-intense chemotherapy has survival benefits.
• The use of G-CSF for patients with solid tumors and malignant lymphomas with FN is limited to those patients not responding to antibiotic management who are developing life-threatening infectious complications.
• Filgrastim and pegfilgrastim is recommended where the prevention of FN and FN-related complications is indicated.

American Society of Clinical Oncologist (ASCO) guidelines on the use of white blood cell growth factors recommend the use of CSF for primary prophylaxis when the risk of FN is ≥20%, and only in select patients for secondary prophylaxis. The guidelines advise no definitive conclusions can be drawn regarding the benefits of secondary prophylaxis on survival or quality of life. The use of CSF to mobilize PBPC and to shorten the period of neutropenia after cyto reduction and PBPC transplantation have been well established according to these guidelines.10

The NCCN, ASCO, and EORTC guidelines all recommend that prophylactic CSF be utilized in any patient considered high risk for FN "regardless of whether the treatment is intended to be curative, to prolong survival, or to manage symptoms."6

Compendia Supported Indications

For the purposes of the criteria, indications deemed appropriate are those that are supported by at least two compendia where one of the compendia is DrugDex with a level of evidence of 2B and strength of recommendation of B or supported in guidelines with a high level of evidence recommendation.

Aplastic Anemia
Aplastic anemia is a disorder in which the bone marrow fails to make enough blood cells.19 In most cases, red and white blood cells as well as platelets are low. CSFs are generally used in combination with erythropoietin or immunosuppressive regimens.26 A randomized study added G-CSF to the regimen of antithymocyte globulin (ATG) and cyclosporin A (CyA) and found an increase in hematologic response rate at 6 months was higher in the group with the addition of G-CSF vs the group with only ATG + CyA (77% vs 57%; P=0.03).20 A single center reported effective results in patients with acquired severe aplastic anemia treated with the 4-drug combination of horse antilymphocyte globulin (ALG), CyA, methylprednisolone, and G-CSF.21 A case report of 17 patients with severe aplastic anemia found a good response when G-CSF was added to the immunosuppressive regimen of methylprednisolone, ATG or ALG, and CyA.22 The British Committee for Standards in Haematology guidelines for the diagnosis and management of aplastic anemia note that G-CSF should not be used on their own in newly diagnosed patients to attempt to ‘treat’ the aplastic anemia but may be considered for severe systematic infection not responding to IV antibiotics and antifungal drugs. Discontinue after 1 week if there is no increase in the neutrophil count.23

Crohn’s Disease
A pilot study revealed that patients with moderately to severely active Crohn’s disease treated with sargramostim 4-8 mcg/kg/day saw a decrease in disease symptoms over an eight week period. Of the 15 patients enrolled in this pilot study, eight patients achieved clinical remission.26

HIV Infection
Neutropenia is a common consequence of HIV infection. Direct bone marrow infection or infiltration may occur. Bone marrow stromal cells may also be directly infected with HIV and neoplastic cells such as those of B-cell lymphoma may be present.

**Ganciclovir Induced Neutropenia**

Ganciclovir can cause significant hematological toxicity. Drug-induced neutropenia may occur in 3%-29% of patients; incidence tends to be higher in immunocompromised patients.

**Malignant melanoma**

A phase II trial of sargramostim given as adjuvant treatment to patients with malignant melanoma (stage III or IV) with high risk for recurrence, it was observed that patients receiving sargramostim had better overall survival when compared to historical trials.

**Myelodysplastic syndrome (MDS)**

MDS represent myeloid clonal hemopathies with relatively heterogenous spectrums of presentation. The major clinical problems in these disorders are morbidities caused by patients’ cytopenias and the potential for MDS to evolve into acute myeloid leukemia (AML). NCCN guidelines note that CSF products are not recommended for routine infection prophylaxis, but should be considered for use in recurrent or resistant infections in neutropenic patients. The American Society of Clinical Oncology (ASCO) recommendations for the use of white blood cell growth factors note that CSFs can increase the absolute neutrophil count in neutropenic patients with MDS. However, data supporting the routine use of long-term continuous use of CSFs is lacking. Intermittent administration of CSFs may be considered in a subset of patients with severe neutropenia and recurrent infection.

**Zidovudine Induced Neutropenia**

The major adverse effect of zidovudine is bone marrow toxicity resulting in severe anemia and/or neutropenia. Neutropenia generally occurs after 6-8 weeks with an incidence of 8% in the pediatric population and 21% in neonates.

### Dosing

<table>
<thead>
<tr>
<th>FDA Labeled Indications</th>
<th>Granix⁴ (tbo-filgrastim)</th>
<th>Leukine³ (sargramostim)</th>
<th>Neupogen¹ (filgrastim)</th>
<th>Neulasta² (pegfilgrastim)</th>
<th>Zarxio³¹ (filgrastim-sndz)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reduction in the duration of severe neutropenia in patients with non-myeloid malignancies receiving myelosuppressive anti-cancer drugs associated with a clinically significant incidence of febrile neutropenia</td>
<td>5 mcg/kg/day as SC injection. Give the first dose no earlier than 24 hours following myelosuppressive chemotherapy. Continue dosing until expected neutrophil nadir is passed and count has recovered to normal range.</td>
<td>5 mcg/kg/day by SC injection, short IV infusion, or continuous IV infusion. Adjust dose based on ANC nadir. Use should be discontinued if ANC surpasses 10,000/mm³</td>
<td>5 mcg/kg/day by SC injection, short IV infusion, or continuous IV infusion. Adjust dose based on ANC nadir. Use should be discontinued if ANC surpasses 10,000/mm³</td>
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<td></td>
</tr>
<tr>
<td>Following induction chemotherapy in patients with AML. Efficacy not assessed in patients &lt;55 years</td>
<td>250 mcg/m²/day IV starting approximately on day 11 or 4 days after completion of induction</td>
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of age.

<table>
<thead>
<tr>
<th>Mobilization of hematopoietic progenitor cells into peripheral blood (PBPC) for collection by leukapheresis</th>
<th>250 mcg/m²/day IV over 24 hours or SC once daily. Continue through period of PBPC collection. Reduce dose by 50% if WBC &gt; 50,000 cells/mm³.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acceleration of myeloid recovery in patients with NHL, ALL and HD undergoing autologous BMT</td>
<td>250 mcg/m²/day IV over 24 hours or SC once daily immediately following infusion of PBPC continuing until an ANC &gt; 1500 cells/mm³ for 3 consecutive days.</td>
</tr>
<tr>
<td>Acceleration of myeloid recovery in patients undergoing allogeneic BMT from HLA-matched related donors</td>
<td>250 mcg/m²/day IV over 2 hours beginning 2-4 hours BMT and not less than 24 hours after last dose of chemotherapy or radiation. Do not administer until post marrow infusion ANC is &lt; 500 cells/mm³, continue until ANC &gt; 1500 cells/mm³ for 3 consecutive days. Reduce dose if ANC &gt; 20,000 cells/mm³.</td>
</tr>
<tr>
<td>Patients who have undergone allogeneic or autologous BMT who have delayed or failed engraftment.</td>
<td>250 mcg/m²/day for 14 days as 2 hour IV infusion. Dose can be repeated after 7 days off therapy if engraftment has not occurred. If still not occurred, a third course of 500 mcg/m²/day for 14 days may be tried after another 7 days off therapy.</td>
</tr>
<tr>
<td>Reduce the time to neutrophil recovery and the duration of fever, following</td>
<td>5 mcg/kg/day by SC injection, short IV infusion, or continuous IV.</td>
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<tr>
<td></td>
<td>5 mcg/kg/day by SC injection, short IV infusion, or continuous IV.</td>
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<tr>
<td><strong>OFF Label Indications</strong></td>
<td><strong>Granix (tbo-filgrastim)</strong></td>
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<tr>
<td><strong>Aplastic Anemia</strong></td>
<td>* 250-500 mcg/day or 5 mcg/kg/day SC for 14-90 days.(^{26})</td>
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**Induction or consolidation chemotherapy in adults with acute myeloid leukemia (AML)**

infusion. Adjust dose based on ANC nadir. Use should be discontinued if ANC surpasses 10,000/mm\(^3\)

Reduce the duration of neutropenia and related clinical sequelae in patients with nonmyeloid malignancies undergoing myeloablative chemotherapy followed by bone marrow transplantation

10 mcg/kg/day after BMT as IV infusion for no longer than 24 hours. First dose should be given at least 24 hours after cytotoxic chemotherapy and marrow infusion. Dose titration recommended based on labeling

Mobilization of hematopoietic progenitor cells into peripheral blood for collection by leukapheresis

10 mcg/kg/day SC injection. Give at least 4 days before first leukapheresis and continue to last. Dose modifications based on WBC >100,000/mm\(^3\)

Severe chronic neutropenia to reduce the incidence and duration of sequelae in patients with congenital, cyclic, or idiopathic neutropenia

**Congenital**: 6 mcg/kg SC injection twice daily

**Idiopathic/Cyclic**: 5 mcg/kg/day SC injection. Dose adjust based on patient clinical course and ANC.

Decrease the incidence of infection in patients with nonmyeloid malignancies receiving myelosuppressive chemotherapy associated with a significant incidence of severe neutropenia

5 mcg/kg/day by SC injection, short IV infusion, or continuous IV infusion. Adjust dose based on ANC nadir. Use should be discontinued if ANC surpasses 10,000/mm\(^3\)

6 mg SC once per chemotherapy cycle. Do not administered 14 days before and 24 hours after cytotoxic chemotherapy

5 mcg/kg/day by SC injection, short IV infusion, or continuous IV infusion. Adjust dose based on ANC nadir. Use should be discontinued if ANC surpasses 10,000/mm\(^3\)
<table>
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<tr>
<th>Condition</th>
<th>Initial Dose Range</th>
<th>Duration/Method</th>
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</table>
| Crohn’s Disease                                       | 4-8 mcg/kg/day SC  | 250 mcg/day<sup>22</sup>  
300-480 mcg/day SC for 14-90 days<sup>26</sup> |
| HIV Infection                                         | 250 mcg/day 3 times weekly for up to 20 months<sup>27</sup> | 5-10 mcg/kg/day (300-600 mcg/day) 1-3 times weekly<sup>26</sup> |
| Ganciclovir induced neutropenia                       | 150-250 mcg/m²/day SC or IV once daily or 2-3 times weekly<sup>26</sup> | 5-10 mcg/kg/day (300-600 mcg/day) 1-3 times weekly<sup>26</sup> |
| Malignant melanoma (adjuvant)                         | 125 mcg/m²/day for 14 days alternating with 14 days off therapy for one year or until disease progression<sup>26, 30</sup> | 5 mcg/kg/day IV/SC roundest to the nearest vial size<sup>26</sup>  
1-2 mcg/kg 1-3 times/week SC<sup>28</sup> |
| Myelodysplastic syndrome                              | 150-500 mcg/m² SC or IV over 1-12 hours<sup>26</sup> | 5 mcg/kg/day IV/SC roundest to the nearest vial size<sup>26</sup>  
1-2 mcg/kg 1-3 times/week SC<sup>28</sup> |
| Zidovudine induced neutropenia                        | 150-250 mcg/m²/day SC or IV once daily or 2-3 times weekly<sup>26</sup> | 5-10 mcg/kg/day (300-600 mcg/day) 1-3 times weekly<sup>26</sup> |

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