Colony Stimulating Factors (CSF) Medical Policy Prior Authorization Program Summary

Precertification/Prior Authorization may be required under certain plans. Please verify each member's benefits.

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.

TARGET AGENTS
Fulphila™ (pegfilgrastim-jmdb)
Granix® (tbo-filgrastim)
Leukine® (sargramostim)
Neulasta® (pegfilgrastim)
Neupogen® (filgrastim)
Nivestym™ (filgrastim-aafi)
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 requested agent is not being given for prophylactic use if the patient is receiving concurrent chemotherapy and radiation
   AND
3. The patient has a diagnosis of ONE of the following:
   a. If Leukine, the patient has a diagnosis of ONE of the following:
      i. The patient has undergone an allogeneic or autologous BMT and has a delayed or failed engraftment
         OR
      ii. Acute myeloid leukemia (AML) receiving induction or consolidation chemotherapy (for reducing the time for neutrophil recovery and duration of fever)
         OR
      iii. Non-myeloid malignancy undergoing myeloablative chemotherapy followed by autologous or allogeneic bone marrow transplantation (BMT)
         OR
      iv. Mobilization of autologous hematopoietic progenitor cells into the peripheral blood for collection by leukapheresis
         OR
      v. The patient has another FDA labeled or guideline supported indication (at highest level of evidence) and prescriber has submitted clinical documentation in support of use

   OR

   b. If Neupogen, Granix, Nivestym, or Zarxio, the patient has a diagnosis of ONE of the following:
      i. Leukemic relapse after allogeneic stem-cell transplantation as an alternative or adjunct to donor leukocyte infusions
         OR
      ii. Patients acutely exposed to myelosuppressive doses of radiation to increase survival
         OR

iii. Acute myeloid leukemia (AML) receiving induction or consolidation chemotherapy (for reducing the time for neutrophil recovery and duration of fever)
OR
iv. Non-myeloid malignancy undergoing myeloablative chemotherapy followed by autologous or allogeneic bone marrow transplantation (BMT)
OR
v. Mobilization of autologous hematopoietic progenitor cells into the peripheral blood for collection by leukapheresis
OR
vi. Myelodysplastic syndrome AND ONE of the following:
    1. ANC ≤500/mm^3 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. The patient currently has adequate iron stores (i.e., ≥20% transferrin saturation or serum ferritin ≥100 ng/ml)

OR
vii. Therapeutic use for febrile neutropenia (FN) AND the following (not approvable for Granix):
    1. The patient has at least one risk factor for infection-related complications or poor clinical outcome (e.g., old age [>65 years], sepsis syndrome, severe [ANC <100 neutrophils/mcL] or anticipated prolonged [>10 days] neutropenia, pneumonia, invasive fungal infections or clinically documented infections, hospitalization, or prior episode of FN)

OR
viii. Severe chronic neutropenia (i.e., congenital neutropenia, cyclic neutropenia, or idiopathic 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
ix. Secondary prophylaxis in patients who had a neutropenic episode or dose-limiting neutropenic event from a prior chemotherapy cycle and ONE of the following:
    1. The patient had prior use of CSFs AND a reduced dose or change in treatment regimen may compromise disease or overall survival or treatment outcomes
    OR
    2. The patient had no prior use of CSFs and the patient meets all primary prophylaxis risk criteria (see primary prophylaxis criteria)

OR
x. Primary prophylaxis for the prevention of febrile neutropenia (FN) in patients receiving a chemotherapy regimen who have an overall risk of >20%
OR
xi. Primary prophylaxis for prevention of FN in patients receiving a chemotherapy regimen who have an overall risk of 10 to 20% AND the following:
    1. The prescriber has assessed the patient risk factors and the patient has one or more risk factors (e.g., prior chemotherapy or radiation therapy, persistent neutropenia, bone marrow involvement by tumor, recent surgery and/or open wounds, liver dysfunction [bilirubin >2.0], renal dysfunction [creatinine clearance <50], age >65 years receiving full chemotherapy dose intensity, poor performance status, HIV infection, etc)

OR

xii. The patient has another FDA labeled or guideline supported (at highest level of evidence) indication

OR

c. If Neulasta or Fulphila, the patient has a diagnosis of ONE of the following:
   i. Patients acutely exposed to myelosuppressive doses of radiation to increase survival
   OR
   ii. Secondary prophylaxis in patients who had a neutropenic episode or dose-limiting neutropenic event from a prior chemotherapy cycle AND ONE of the following:
      1. The patient had prior use of CSFs AND a reduced dose or change in treatment regimen may compromise disease or overall survival or treatment outcomes
      OR
      2. The patient had no prior use of CSFs and the patient meets all primary prophylaxis risk criteria (see primary prophylaxis criteria)

   OR
   iii. Primary prophylaxis for the prevention of febrile neutropenia (FN) in patients receiving a chemotherapy regimen who have an overall risk of >20%
   OR
   iv. Primary prophylaxis for prevention of FN in patients receiving a chemotherapy regimen who have an overall risk of 10 to 20% AND BOTH of the following:
      1. The prescriber has assessed the patient risk factors and the patient has one or more risk factors (e.g., prior chemotherapy or radiation therapy, persistent neutropenia, bone marrow involvement by tumor, recent surgery and/or open wounds, liver dysfunction [bilirubin >2.0], renal dysfunction [creatinine clearance <50], age >65 years receiving full chemotherapy dose intensity, poor performance status, HIV infection, etc)
      AND
      2. The patient's chemotherapy is not being administered on a weekly basis

   OR
   v. The patient has another FDA labeled or guideline supported (at highest level of evidence) indication

Length of approval: 6 months

Contraindication(s) Table

Agent(s)	Contraindication(s)
Fulphila (pegfilgrastim-jmbd)	Patients with a history of serious allergic reactions to human granulocyte colony-stimulating factors such as pegfilgrastim or filgrastim products
Granix (tbo-filgrastim)	Patients with a history of serious allergic reactions to filgrastim or pegfilgrastim products
Leukine (sargramostim)	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
Neulasta (pegfilgrastim)	Patients with a history of serious allergic reactions to human granulocyte colony-stimulating factors such as filgrastim or pegfilgrastim
Neupogen (filgrastim)	History of serious allergic reactions to human granulocyte colony-stimulating factors such as filgrastim or pegfilgrastim
Nivestym (filgrastim-aafi)	Patients with a history of serious allergic reactions to human granulocyte colony-stimulating factors

	such as filgrastim products or pegfilgrastim products
Zarxio (filgrastim-sndz)	Patients with a history of serious allergic reactions to human granulocyte colony-stimulating factors such as filgrastim or pegfilgrastim products

Your health plan 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. Your health plan 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, pre-determinations, and pre-procedure review) in your health plan's administration of plan contracts.

Prime Therapeutics LLC is an independent limited liability company providing pharmacy benefit management services.

FDA APPROVED INDICATIONS AND DOSAGE[1-4,13,16]

Agent(s)	Indication(s)	Dosing
Fulphila™ (pegfilgrastim-jmdb)	• Decrease the incidence of infection, as manifested by febrile neutropenia, in patients with non-myeloid malignancies receiving myelosuppressive anti-cancer drugs associated with a clinically significant incidence of febrile neutropenia Limitations of Use: Fulphila is not indicated for the mobilization of peripheral blood progenitor cells for hematopoietic stem cell transplation	• 6 mg subcutaneously once per chemotherapy cycle. Do not administer fulphila between 14 days before and 24 hours after administration of cytotoxic chemotherapy
Granix®^ (tbo-filgrastim)	• 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	• 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.
Leukine® (sargramostim)	• Use following induction chemotherapy in patients with acute myelogenous leukemia (AML): To shorten time to neutrophil recovery and to reduce the incidence of severe and life-threatening infections and infections resulting in death. Efficacy not assessed in patients <55 years of age • Use in Mobilization and Following Transplantation of Autologous Peripheral Blood Progenitor Cells: Mobilization of hematopoietic progenitor cells into peripheral blood (PBPC) for collection by leukapheresis •Use in Myeloid Reconstitution after Autologous Bone Marrow Transplantation: Acceleration of myeloid recovery in patients with non-Hodgkin's lymphoma (NHL), acute	• **AML:** 250 mcg/m^2/day IV starting approximately on day 11 or 4 days after completion of induction chemotherapy if day 10 bone marrow is hypoplastic with <5% blasts. Continue until ANC >1500 cells/mm^3 for 3 consecutive days or max of 42 days. Reduce dose by 50% if ANC > 20,000 cells/mm^3 • **Mobilization:** 250 mcg/m^2/day IV over 24 hours or SC once daily. Continue through period of PBPC collection. Reduce dose by 50% if WBC >50,000 cells/mm^3 • **Post Autologous Transplantation:** 250 mcg/m^2/day IV over 24 hours or SC once daily immediately following infusion of progenitor cells and

	lymphoblastic leukemia (ALL), and Hodgkin's disease	continuing until an ANC >1500 cells/mm^3 for 3 consecutive days.
	● Use in Myeloid Reconstitution after Allogeneic Bone Marrow Transplantation: Acceleration of myeloid recovery in patients undergoing allogeneic BMT from HLA-matched related donors	**Post Allogeneic transplantation:** 250 mcg/m^2/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 <500 cells/mm^3, continue until ANC >1500 cells/mm^3 for 3 consecutive days.
	● Use in Bone Marrow Transplantation Failure or Engraftment Delay: Patients who have undergone allogeneic or autologous BMT who have delayed or failed engraftment	**Bone Marrow Transplantation Failure or Engraftment Delay:** 250 mcg/m2/day for 14 days as 2 hour IV infusion. Dose can be repeated after 7 days
**Neulasta® (pegfilgrastim)	● Patients with Cancer Receiving Myelosuppressive Chemotherapy: Decrease the incidence of infection, as manifested by febrile neutropenia, in patients with non-myeloid malignancies receiving myelosuppressive anti-cancer drugs associated with a clinically significant incidence of febrile neutropenia *Neulasta is not indicated for the mobilization of peripheral blood progenitor cells for hematopoietic stem cell transplantation	● **Cancer:** 6 mg SC once per chemotherapy cycle. Do not administer 14 days before and 24 hours after cytotoxic chemotherapy
	● Patients with Hematopoietic Subsyndrome of Acute Radiation Syndrome: Increase survival in patients acutely exposed to myelosuppressive doses of radiation (Hematopoietic Subsyndrome of Acute Radiation Syndrome)	● **Acute Radiation Syndrome:** Two doses, 6 mg each, administered SC one week apart. Administer the first dose as soon as possible after suspected or confirmed exposure of radiation levels >2 gray (Gy). Administer the 2nd dose 1 week after the first dose
*Neupogen® (filgrastim)	● Patients with Cancer receiving Myelosuppressive Chemotherapy: Decrease the incidence of infection, as manifested by febrile neutropenia, in patients with	● **Cancer:** 5 mcg/kg/day by SC injection, short IV infusion, or continuous IV infusion. Adjust dose based on ANC nadir.

	nonmyeloid malignancies receiving myelosuppressive anti-cancer drugs associated with a significant incidence of severe neutropenia with fever	Administer daily for up to 2 weeks or until ANC has reached 10,000/mm^3. Use should be discontinued if ANC surpasses 10,000/mm^3
	• Patients with Acute Myeloid Leukemia (AML) Receiving Induction or Consolidation Chemotherapy: Reduce the time to neutrophil recovery and the duration of fever, following induction or consolidation chemotherapy treatment of patients with acute myeloid leukemia (AML)	• **AML:** 5 mcg/kg/day by SC injection, short IV infusion, or continuous IV infusion. Adjust dose based on ANC nadir. Administer daily for up to 2 weeks or until ANC has reached 10,000/mm^3. Use should be discontinued if ANC surpasses 10,000/mm^3
	• Patients with Cancer Undergoing Bone Marrow Transplantation: 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	• **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
	• Patients Undergoing Autologous Peripheral Blood Progenitor Cell Collection and Therapy: Mobilization of autologous hematopoietic progenitor cells into the peripheral blood for collection by leukapheresis	• **Autologous Peripheral Blood Progenitor Cell Collection:** 10 mcg/kg/day SC injection. Give at least 4 days before first leukapheresis and continue to last. Dose modifications based on WBC and discontinue when WBC is >100,000/mm^3
	• Patients with Severe Chronic Neutropenia: Severe chronic neutropenia 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	• **Chronic Neutropenia:** **Congenital**: 6 mcg/kg SC twice daily SC injection **Idiopathic/Cyclic:** 5 mcg/kg/day SC injection. Dose adjust based on patient clinical course and ANC
	• Patients Acutely Exposed to Myelosuppressive Doses of Radiation (Hematopoietic Syndrome	• **Acute Radiation Syndrome:** 10 mcg/kg SC daily until ANC

	of Acute Radiation Syndrome): Increase survival in patients acutely exposed to myelosuppressive doses of radiation	remains greater than 1,000/mm^3 for 3 consecutive CBCs or exceeds 10,000/mm^3 after a radiation-induced nadir
Nivestym™ (filgrastim-aafi)	● 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	● **Cancer:** 5 mcg/kg/day by SC injection, short IV infusion, or continuous IV infusion. Adjust dose based on ANC nadir. Administer daily for up to 2 weeks or until ANC has reached 10,000/mm^3. Use should be discontinued if ANC surpasses 10,000/mm^3
	● Reduce the time to neutrophil recovery and the duration of fever, following induction or consolidation chemotherapy treatment of patients with acute myeloid leukemia (AML)	● **AML:** 5 mcg/kg/day by SC injection, short IV infusion, or continuous IV infusion. Adjust dose based on ANC nadir. Administer daily for up to 2 weeks or until ANC has reached 10,000/mm^3. Use should be discontinued if ANC surpasses 10,000/mm^3
	● 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)	● **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
	● Mobilize autologous hematopoietic progenitor cells into the peripheral blood for collection by leukapheresis	● **Autologous Peripheral Blood Progenitor Cell Collection:** 10 mcg/kg/day SC injection. Give at least 4 days before first leukapheresis and continue to last. Dose modifications based on WBC and discontinue when WBC is >100,000/mm^3
	● Reduce the incidence and duration of sequelae of severe neutropenia (e.g., fever, infections, oropharyngeal ulcers) in symptomatic patients with congenital neutropenia, cyclic	● **Chronic Neutropenia:** **Congenital**: 6 mcg/kg SC twice daily SC injection **Idiopathic/Cyclic:** 5 mcg/kg/day SC injection. Dose adjust based on patient

	neutropenia, or idiopathic neutropenia	clinical course and ANC

*Zarxio™ (filgrastim-sndz)	● Patients with Cancer Receiving Myelosuppressive Chemotherapy: 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 ● Patients with Acute Myeloid Leukemia Receiving Induction or Consolidation Chemotherapy: Reduce the time to neutrophil recovery and the duration of fever, following induction or consolidation chemotherapy treatment of patients with acute myeloid leukemia (AML) ● Patients with Cancer Undergoing Bone Marrow Transplantation: 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) ● Patients Undergoing Autologous Peripheral Blood Progenitor Cell Collection and Therapy: Mobilize autologous hematopoietic progenitor cells into the peripheral blood for collection by leukapheresis ● Patients with Severe Chronic Neutropenia: 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	● **Cancer:** 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 ● **AML:** 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 ● **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 ● **Autologous Peripheral Blood Progenitor Cell Collection:** 10 mcg/kg/day SC injection. Give at least 4 days before first leukapheresis and continue to last. Discontinue when WBC >100,000/mm^3 ● **Chronic Neutropenia:** **Congenital**: 6 mcg/kg SC twice daily SC injection **Idiopathic/Cyclic:** 5 mcg/kg/day SC injection. Dose adjust based on patient clinical course and ANC.

SC=subcutaneous; BMT=bone marrow transplant; ANC=absolute neutrophil count; AML; acute myelogenouALL=acute lymphoblastic leukemia; AML=acute myelogenous leukemia; ANC=absolute neutrophil count; BMT=bone marrow transplant; HD=Hodgkin's disease; NHL=non-Hodgkin's lymphoma; SC=subcutaneous; 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.

CLINICAL RATIONALE

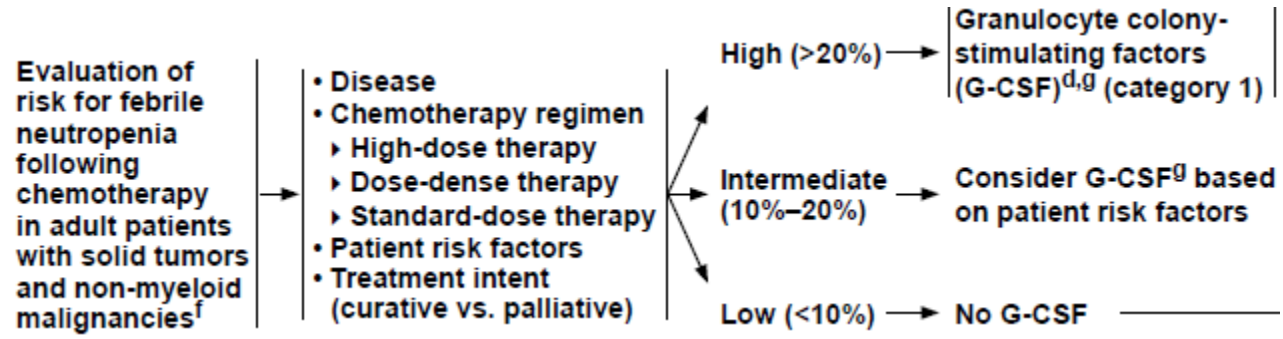
Granulocyte colony-stimulating factor (G-CSF) and granulocyte-macrophage colony-stimulating factor (GM-CSF) are naturally occurring glycoprotein cytokines. Together, G-CSF and GM-CSF exert major control over the reproduction and maturation of committed myeloid-lineage progenitor cells.

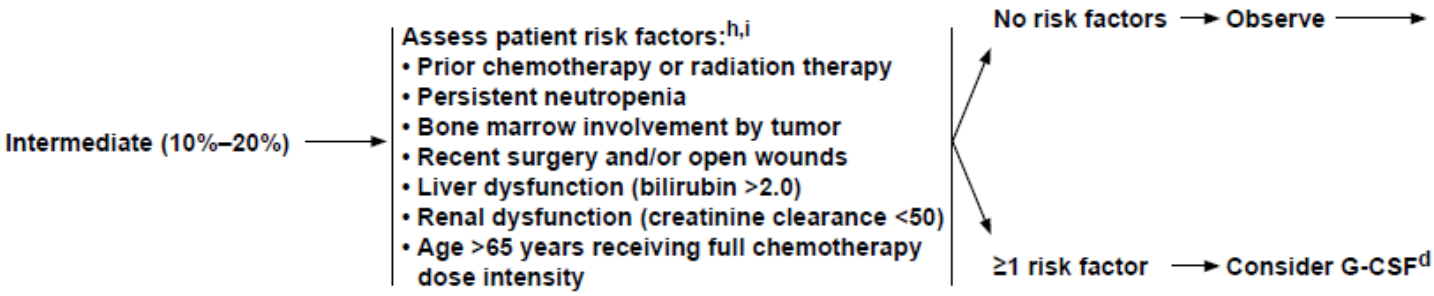
The term myeloid growth factor (MGF) is utilized by the National Comprehensive Cancer Network (NCCN) when data are supported by studies for both G-CSF and GM-CSF. With the advent of recombinant molecular biology techniques, biologically active synthetic copies of MGFs have become available in clinically useful quantities and have been approved by the FDA for clinical use. Recombinant MGFs 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. MGFs incorporated into cancer regimens improve patient care in prophylactic/therapeutic treatment of febrile neutropenia (FN), hematopoietic cell transplant for mobilization/supportive care, and severe chronic neutropenia. Prophylactic use of MGFs improve delivery of full dose chemotherapy on schedule, reducing chemotherapy related neutropenia in small cell lung cancer, breast cancer, sarcoma, solid tumors, non-small cell lung cancer, and non-Hodgkin's lymphoma. In node positive breast cancer and aggressive lymphoma, MGFs improve disease free and overall survival vs conventional chemotherapy.[6]

For patients with neutropenia, the risk of serious infection increases as the absolute neutrophil count (ANC) falls to the severely neutropenic range (<500/µL). 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 ≥101°F (≥38.3°C) orally or ≥100.4°F (≥38.0°C) over 1 hour) is a major dose limiting toxicity of chemotherapy which can result in hospital stays, chemotherapy dose reductions, and/or treatment delays for subsequent cycles. Reducing chemotherapy doses or delaying subsequent chemotherapy cycles can affect patient outcomes.[6] The use of prophylactic MGFs has been shown to decrease the risk of neutropenia as well as rates of infection.[6] MGFs 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 MGFs has reduced the incidence, length, and severity of chemotherapy-related neutropenia in several different cancers.[6]

The 2017 National Comprehensive Cancer Network (NCCN) Supportive Care: Myeloid Growth Factors guidelines are based on the risk of febrile neutropenia associated with chemotherapy. When considering prophylactic use of MGFs, patients should be placed into one of the following three risk categories based on disease type, chemotherapy regimen (high-dose, dose-dense, or standard-dose therapy), patient risk factors, and treatment intent (curative vs palliative): overall high-risk group (>20% risk of FN), intermediate-risk group (10-20% risk), or low-risk group (<10% risk).[6]





[d]- G-CSF refers to the following approved agents: filgrastim, filgrastim-sndz, tbo-filgrastim, and pegfilgrastim.

[f]- For use of growth factors in myelodysplastic syndromes (MDS), see the NCCN guidelines for MDS, and in acute myeloid leukemia (AML), see the NCCN Guidelines for Acute Myeloid Leukemia.

[g]- There is category 1 evidence for G-CSF for a reduction of: risk of febrile neutropenia, hospitalization, and intravenous antibiotics during the course of therapy. There is category 2A evidence for G-CSF for a reduction in infection-related mortality during the course of treatment.

[h]-Other possible patient risk factors for FN may include poor performance status or HIV infection (in particular, patients with low CD4 counts). The listed patient risk factors are based on a multivariable risk model using a prospective cohort study of several thousand ambulatory cancer patients receiving chemotherapy. This cohort did not include patients with HIV, acute leukemia, or hematopoetic cell transplant.

[i]-Other factors may warrant the use of G-CSF (e.g., chronic immunosuppression in the post-transplant setting, including organ transplant)

Risk for developing FN should be assessed prior to the first chemotherapy cycle and before each subsequent cycle. If a patient had FN or a dose-limiting neutropenic event (a nadir or a day-of-treatment count impacting the planned dose of chemotherapy) in a previous treatment cycle, with the same dose and schedule planned for the current cycle, this patient is now in the high-risk group. If the patient experiences such an episode despite receiving MGF, the recommendation is a dose reduction or change in treatment regimen unless there is an impact on patient survival. When choosing among MGFs for prophylactic treatment of FN, filgrastim, filgrastim-sndz, tbo-filgrastim, and pegfilgrastim are considered NCCN Category 1 recommendations; sargramostim is no longer recommended in this setting.[6] According to NCCN, the use of peg-filgrastim after chemotherapy given every 3 weeks is a category 1 recommendation and category 2A when chemotherapy is administered every 14 days. There are insufficient data to support the dose and schedule for weekly regimens; therefore, use of peg-filgrastim in patients receiving weekly chemotherapy cannot be recommended.[6] The prophylactic use of MGF in patients given concurrent chemotherapy and radiation has not been evaluated and is therefore not recommended. [6]

American Society of Clinical Oncologist (ASCO) 2015 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 no other equally effective and safe regimen that does not require CSFs is available. Similar to NCCN guidelines, high risk determination is based on several factors including age, medical history, disease characteristics, and myelotoxicity of the chemotherapy regimen. ASCO also recommends immediate administration of CSFs when there are lethal doses of total-body radiotherapy given (with the exception of doses high enough to lead to certain death as a result of organ injury). Use for secondary prophylaxis is

recommended when a patient had a neutropenic complication from a prior cycle of chemotherapy and a reduced dose and/or treatment delay will compromise disease-free/overall survival or treatment outcome. CSFs are also supported for use after chemotherapy to mobilize peripheral-blood progenitor cells after autologous or allogeneic stem-cell transplantation to reduce the duration of severe neutropenia, and can be considered in diffuse aggressive lymphoma in those age ≥65 years who are treated with curative chemotherapy especially when the patient has comorbidities.[7]

COMPENDIA SUPPORTED INDICATIONS

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).[11] 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. NCCN compendia supports filgrastim, filgrastim-sndz, and tbo-filgrastim in MDS (2a level of recommendation) [11] 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.[12]

Therapeutic Use of CSFs in Neutropenia

Compared to prophylactic use, there is less evidence supporting the therapeutic use of MGFs for febrile neutropenia as an adjunct to antibiotics. It has been found that there is no difference in mortality outcomes; however, there is evidence to support shorter hospitalization stays, faster neutrophil recovery, shorter duration of grade 4 neutropenia, and antibiotic therapy with treatment. The National Comprehensive Cancer Network (NCCN) 2017 guidelines recommend patients who have FN and who are already receiving prophylactic G-CSFs (filgrastim, filgrastim-sndz, or tbo-filgrastim) continue with the same CSF. Those who received prophylactic pegfilgrastim should not be treated with additional MGF. NCCN recommends those who have FN and are not on prophylactic CSF that an evaluation for risk factors for infection-related complications or poor clinical outcome be done. NCCN lists the following as factors for consideration: old age (>65 years), sepsis syndrome, severe (ANC <100 neutrophils/mcL) or anticipated prolonged (>10 days) neutropenia, pneumonia, invasive fungal infections or other clinically documented infections, hospitalization, and a prior episode of FN. If risk factors are present, then MSFs should be considered. Filgrastim, filgrastim-sndz, or sargramostim (2b) may be administered in the therapeutic setting. Tbo-filgrastim and pegfilgrastim have only been studied for prophylactic use.[6] ASCO 2015 guidelines suggest CSFs be considered in patients with fever and neutropenia who are at high risk for infection-associated complication or who have prognostic factors predictive of poor clinical outcomes.[7]

Leukemia

NCCN Chronic Myeloid Leukemia guidelines state that growth factors can be used in combination with Tyrosine kinase inhibitor (TKI) therapy (e.g., imatinib, nilotinib, ponatinib, bosutinib, dasatinib) for management of resistant neutropenia.[14] Micromedex also indicates that filgrastim and filgrastim-sndz can be utilized in this setting (2a level recommendation).[9]

References

1. Neupogen prescribing information. Amgen Inc. June 2016.
2. Neulasta prescribing information. Amgen Inc. December 2017.
3. Leukine prescribing information. Sanofi-Aventis. February 2017.
4. Granix (tbo-filgrastim) prescribing information. Teva Pharmaceuticals. June 2017.
5. Godwin JE. Neutropenia. Medscape. Available at: http://emedicine.medscape.com/article/204821-overview. Accessed 1/05/2018.
6. NCCN Guidelines: Myeloid Growth Factors. Version 2.2017.

7. American Society of Clinical Oncologists. Recommendations for the Use of WBC Growth Factors: American Society of Clinical Oncology Clinical Practice Guideline Update. July 2015. Available at: http://www.instituteforquality.org/asco-2006-update-recommendations-use-white-blood-cell-growth-factors-evidence-based-clinical. Assessed 1/05/2018.
8. Deleted.
9. Micromedex monographs: Neupogen, Neulasta, Leukine, Granix, Zarxio. Accessed 1/08/2018.
10. AHFS 2013 monographs on filgrastim, sargramostim, and pegfilgrastim. Accessed 2/8/13.
11. NCCN clinical practice guidelines in oncology. Myelodysplastic syndromes. Version 2.2017.
12. Smith TJ, Khatcheressian J, Lyman GH, et al. 2006 update of recommendations for the use of white blood cell growth factors: an evidence-based clinical practice guidelines. J Clin Oncol 2006; 24 (19): 3187-3205.
13. Zarxio prescribing information. Sandoz Inc. February 2017.
14. NCCN Guidelines: Chronic Myeloid Leukemia. Version 2.2017.
15. Fulphila prescribing information. Mylan. June 2018.
16. Nivestym prescribing information. Pfizer Labs. July 2018.

Your health plan 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. Your health plan 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, pre-determinations, and pre-procedure review) in your health plan's administration of plan contracts.

Prime Therapeutics LLC is an independent limited liability company providing pharmacy benefit management services.