



Colony Stimulating Factors

Therapeutic Class Review (TCR)

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FDA-APPROVED INDICATIONS

Drug	Manufacturer	Cancer patients receiving myelosuppressive chemotherapy – to reduce incidence of infection (febrile neutropenia)	Acute Myeloid Leukemia (AML) patients receiving chemotherapy	Bone Marrow Transplant (BMT)	Peripheral Blood Progenitor Cell Collection and Therapy	Severe Chronic Neutropenia
filgrastim (Neupogen®) ¹	Amgen	X	X (Following induction or consolidation chemotherapy – reduces time to neutrophil recovery and the duration of fever in adults)	X (Cancer patients receiving BMT – to reduce duration of neutropenia and febrile neutropenia)	X	X (Reduce the incidence and duration of neutropenia in symptomatic patients with congenital neutropenia, cyclic neutropenia, or idiopathic neutropenia)
pegfilgrastim (Neulasta®) ²	Amgen	X	--	--	--	--
sargramostim (Leukine®) ³	Genzyme	--	X (Following induction for patients 55 years old and older; shorten time to neutrophil recovery, and to reduce incidence of severe and life-threatening infections)	X (For myeloid reconstitution after BMT; Treatment of BMT failure or engraftment delay)	X	--
tbo-filgrastim(Granix™) ⁴	Cephalon	X	--	--	--	--

OVERVIEW

Myelosuppressive chemotherapy can induce neutropenia (less than 500 neutrophils/mcL or less than 1,000 neutrophils/mcL and a predicted decline to less than or equal to 500/mcL over the next 48 hours) and febrile neutropenia (greater than or equal to 38.3°C orally or greater than or equal to 38.0°C over one hour) which is a dose-limiting toxicity of chemotherapy. Febrile neutropenia can cause increased diagnostic and treatment costs, prolonged hospitalizations, and broad-spectrum antibiotic use which may cause chemotherapy dose reductions, treatment delays, and may ultimately compromise treatment outcomes. Prophylactic Colony Stimulating Factor (CSF) use can reduce the severity, risk, and duration of febrile neutropenia.⁵ Colony Stimulating Factors are hematopoietic growth factors which have been shown to decrease the likelihood of neutropenic complications resulting from chemotherapy. Filgrastim (Neupogen), pegfilgrastim (Neulasta), and tbo-filgrastim (Granix) are granulocyte colony-stimulating factors (G-CSF). Sargramostim (Leukine) is a granulocyte-macrophage colony stimulating factor (GM-CSF). These factors affect product and function of myeloid cells, and they accelerate myeloid recovery following bone marrow transplantation and amelioration of chemotherapy-induced neutropenia.

The National Comprehensive Cancer Network (NCCN) v2.2014 practice guidelines for Myeloid Growth Factors base recommendations on evidence derived mainly from G-CSF studies and adult patients with solid tumors and non-myeloid malignancies.⁶ Safety data appears similar between filgrastim (Neupogen) and pegfilgrastim (Neulasta), and the subcutaneous (SC) route is preferred for all four agents. To date, there are insufficient head-to-head comparative studies on the clinical benefits of G-CSFs and GM-CSFs. Filgrastim and tbo-filgrastim have a category one recommendation stating there is high-level evidence from randomized controlled clinical trials and there is uniform NCCN consensus that filgrastim and tbo-filgrastim reduce the risk of febrile neutropenia, hospitalization, and intravenous (IV) antibiotics during the course of therapy. Filgrastim and tbo-filgrastim can be administered the day after chemotherapy, up to three to four days after chemotherapy, and through post-nadir recovery. Pegfilgrastim has been designated a category one recommendation (for prophylactic use only). Most pegfilgrastim trials administered the medication the day after chemotherapy (category one); however, administration up to three to four days after chemotherapy is also reasonable according to the NCCN guidelines. Same day administration of pegfilgrastim may be considered in certain situations but data is limited to support this. There is evidence to support the use of chemotherapy regimens every three weeks with pegfilgrastim (category one). Efficacy data exist for pegfilgrastim in chemotherapy regimens given every two weeks. There are insufficient data to support dose/schedule of weekly chemotherapy regimens; therefore, the use of pegfilgrastim cannot be recommended by the NCCN. Sargramostim (Leukine) has a category 2B recommendation; the recommendation is based on low-level of evidence and there is consensus that the intervention is appropriate. Sargramostim can be administered the day after chemotherapy, up to three to four days after chemotherapy, and through post-nadir recovery.

The practice guidelines stratify patients into three risk groups based on the chemotherapy regimen and patient-related risk factors: high risk (greater than 20 percent risk of developing febrile neutropenia), intermediate risk (ten to 20 percent risk of developing febrile neutropenia), and low risk (less than ten percent risk of developing febrile neutropenia).⁷ It is the recommendation of NCCN that high-risk patients receive prophylactic CSF regardless of the intent of treatment. If the patient falls into the intermediate risk group, NCCN recommends individualized consideration of CSF based on the

likelihood of developing febrile neutropenia, consequences of developing febrile neutropenia, and the implications of interfering with chemotherapy treatments. Lastly, NCCN does not recommend the routine use of CSF in patients with low risk of developing febrile neutropenia due to lack of cost effectiveness and availability of alternative treatments. However, choosing to administer a CSF should be individualized to the patient and clinical implications.

The American Society of Clinical Oncology (ASCO) published an updated set of guidelines in 2006 for the use of white blood cell growth factors.⁸ The guidelines made no recommendation regarding the equivalency of the two colony-stimulating agents, sargramostim (Leukine) and filgrastim (Neupogen). The recommendations for the use of CSF for primary prophylaxis include the prevention of febrile neutropenia in patients who are at high risk based on age, medical history, disease characteristics, and myelotoxicity of the chemotherapy regimen. Clinical trial data support the use of CSF when the risk of febrile neutropenia is at least 20 percent or higher. The decision on whether to use prophylactic CSF should take into consideration the optimal chemotherapy regimen, individual patient risk factors, and the intention of treatment, that is, curative, prolongation of life, or symptom control and palliation. Pegfilgrastim (Neulasta) did not have extensive experience at the time of guideline review according to the updating Committee; therefore, comments regarding its use were limited. Additionally, tbo-filgrastim (Granix) was not available at the time of the review.

Secondary prophylaxis with CSF is recommended for patients who experienced a neutropenic complication from a prior cycle of chemotherapy (for which primary prophylaxis was not received), in which a reduced dose may compromise disease-free, overall survival, or treatment outcome.⁹ In many clinical situations, dose reduction or delay may be a reasonable alternative. CSF should not be routinely used for patients with neutropenia who are afebrile. CSF should not be routinely used as adjunctive treatment with antibiotic therapy for patients with fever and neutropenia. However, CSF should be considered in patients with fever and neutropenia who are at high-risk for infection-related complications or who have prognostic factors that are predictive of poor clinical outcomes. High-risk features include expected prolonged (greater than ten days) and profound ($<0.1 \times 10^9/L$) neutropenia, age greater than 65 years, uncontrolled primary disease, pneumonia, hypotension and multiorgan dysfunction (sepsis syndrome), invasive fungal infection, or being hospitalized at the time of the development of fever.

Per the 2006 ASCO guidelines, administration of CSF to mobilize peripheral-blood progenitor cell (PBPC) often in conjunction with chemotherapy and their administration after autologous, but not allogeneic, PBPC transplantation is the current standard of care.

In August 2012, the FDA announced the approval of tbo-filgrastim (Granix) based on results of three randomized clinical trials.¹⁰ In Europe, tbo-filgrastim is available as a biosimilar to filgrastim; however, in the United States (U.S.), tbo-filgrastim (Granix) was approved through an original biologic license application.

PHARMACOLOGY^{11,12,13,14}

Sargramostim (Leukine) is a recombinant human GM-CSF produced by recombinant DNA technology in yeast. GM-CSF is a hematopoietic growth factor which triggers proliferation and differentiation of hematopoietic progenitor cells. GM-CSF is included in a group of growth factors termed CSF which promote survival, clonal expansion, and differentiation of hematopoietic progenitor cells. GM-CSF induces partially committed progenitor cells to divide and differentiate in the granulocyte-macrophage

pathways which include neutrophils, monocytes/macrophages, and myeloid derived dendritic cells. GM-CSF also has the capability of activating mature granulocytes and macrophages. GM-CSF is a multilineage factor and, in addition to dose-dependent effects on the myelomonocytic lineage, can encourage the proliferation of megakaryocytic and erythroid progenitors.

Filgrastim (Neupogen), pegfilgrastim (Neulasta), and tbo-filgrastim (Granix) are G-CSF that are produced by recombinant technology using *Escherichia coli*. G-CSF acts on hematopoietic cells by binding to specific cell surface receptors, thereby stimulating differentiation, commitment, proliferation, and end cell functional activation. Filgrastim and tbo-filgrastim stimulate the growth and development of neutrophils within the bone marrow. Filgrastim causes a shift towards earlier granulocyte progenitor cells (left shift), including the appearance of promyelocytes and myeloblasts, usually during neutrophil recovery following the chemotherapy-induced nadir. Studies on cellular proliferation, receptor binding, and neutrophil function demonstrate that filgrastim and pegfilgrastim have the same mechanism of action. Pegfilgrastim is a conjugate of filgrastim and monomethoxypolyethylene glycol. Pegfilgrastim has reduced renal clearance and prolonged persistence *in vivo* as compared to filgrastim, but dosing adjustments in renal impairment are not necessary.

PHARMACOKINETICS

Drug	Half-Life Intravenous Administration	Half-Life Subcutaneous Administration
filgrastim (Neupogen) ¹⁵	231 minutes	210 minutes
pegfilgrastim (Neulasta) ¹⁶	--	15 - 80 hours
sargramostim (Leukine) ¹⁷	60 minutes	162 minutes
tbo-filgrastim (Granix) ¹⁸	--	3.2 to 3.8 hours

CONTRAINDICATIONS/WARNINGS^{19,20,21,22}

filgrastim (Neupogen) and pegfilgrastim (Neulasta) and tbo-filgrastim (Granix)

Filgrastim (Neupogen) and pegfilgrastim (Neulasta) are contraindicated in patients with known hypersensitivity to *E coli*-derived proteins, filgrastim, pegfilgrastim, or any component of the product. There are no known contraindications for tbo-filgrastim (Granix) but the medication should not be administered to patients with a history of serious allergic reactions to filgrastim or pegfilgrastim.

Splenic rupture, including fatal cases, has been reported following the administration of filgrastim, pegfilgrastim, and tbo-filgrastim. Patients receiving any agent who report left upper abdominal and/or shoulder tip pain should be evaluated for an enlarged spleen or splenic rupture.

Less than one in 4,000 patients treated with filgrastim have reported allergic-type reactions during initial or subsequent treatments. A majority of reports of allergic type reactions occurred with initial exposure to pegfilgrastim. These have generally been characterized by systemic symptoms involving at least two body systems, most often skin (e.g., rash, urticaria, facial edema), cardiovascular (e.g., hypotension, tachycardia), and respiratory (e.g., wheezing, dyspnea). Reactions usually occurred within the first 30 minutes after administration and tended to occur more often in patients receiving IV filgrastim. Rapid resolution of symptoms occurred in most cases associated with filgrastim and tbo-filgrastim after the administration of steroids, bronchodilators, antihistamines, and/or epinephrine. If

rechallenged, symptoms recurred in more than half the patients. In rare cases following administration of pegfilgrastim, allergic reactions, including anaphylaxis, recurred within days after initial anti-allergic treatment was discontinued. If a serious allergic reaction occurs, appropriate therapy should be administered, with close patient follow-up over several days. The needle cap for the single-dose prefilled syringe contains latex; therefore, persons with latex allergies should not administer pegfilgrastim. Filgrastim, pegfilgrastim, and tbo-filgrastim should be permanently discontinued in patients with serious allergic reactions.

Acute respiratory distress syndrome (ARDS) has been reported in patients receiving filgrastim, pegfilgrastim, and tbo-filgrastim, and it is suggested to be secondary to an invasion of neutrophils to sites of inflammation in the lungs. Patients receiving filgrastim, pegfilgrastim, or tbo-filgrastim who develop fever, lung infiltrates, or respiratory distress should be evaluated for the possibility of ARDS. If ARDS occurs, filgrastim, pegfilgrastim, and tbo-filgrastim should be discontinued and/or withheld until resolution of ARDS, and patients should receive appropriate medical management for this condition.

Healthy donors undergoing PBPC mobilization have reported alveolar hemorrhage manifesting as pulmonary infiltrates and hemoptysis and have required hospitalization. Hemoptysis resolved with discontinuation of filgrastim. The use of filgrastim for PBPC mobilization in healthy donors is not an approved indication. Pegfilgrastim is not indicated for PBPC mobilization.

Severe sickle cell crises, some cases resulting in death, have been associated with the use of filgrastim, pegfilgrastim, and tbo-filgrastim in patients with sickle cell disorders. After careful consideration of the potential risks and benefits, only physicians qualified by specialized training or experience in the treatment of patients with sickle cell disorders should prescribe filgrastim, pegfilgrastim, or tbo-filgrastim for such patients.

The G-CSF receptor that filgrastim, pegfilgrastim, and tbo-filgrastim act upon has been found on tumor cell lines. It is possible that filgrastim, pegfilgrastim, and tbo-filgrastim act as growth factors for any tumor type; however, more data are needed since the limited data that is available is inconclusive.

The safety and efficacy of filgrastim used concurrently with chemotherapy have not been established. However, due to the sensitivity of rapidly dividing myeloid cells during chemotherapy the use of filgrastim should be avoided for 24 hours before and through 24 hours after chemotherapy. Concurrent therapy with radiation should also be avoided.

The safety and efficacy of filgrastim has not been established in the treatment of neutropenia due to other hematopoietic disorders such as myelodysplastic syndrome (MDS). The diagnosis of Severe Chronic Neutropenia (SCN) should be confirmed prior to initiating therapy with filgrastim since cytogenetic abnormalities and transformation to MDS and AML have been observed in patients treated with filgrastim for SCN. The risk of developing MDS and AML appears to be confined to the subset of patients with congenital neutropenia. Eventual development of myeloid leukemia has been associated with abnormal cytogenetics and MDS. The effect of filgrastim on the development of abnormal cytogenetics and the effect of continued filgrastim administration in patients with abnormal cytogenetics or MDS are unknown. The risks and benefits of continuing filgrastim should be carefully considered if a patient with SCN develops abnormal cytogenetics or myelodysplasia.

Cases of moderate to severe cutaneous vasculitis have been reported in patients taking filgrastim. These cases most often occurred in patients with SCN receiving long term filgrastim therapy and

symptoms generally developed simultaneously with an increase in ANC and subsided when the ANC decreased.

Thrombocytopenia has been reported in patients taking filgrastim; therefore, platelet counts should be monitored.

sargramostim (Leukine)

Sargramostim (Leukine) is contraindicated in patients with excessive leukemic myeloid blasts in the bone marrow or peripheral blood (greater than or equal to ten percent); in patients with known hypersensitivity to GM-CSF, yeast- derived products or any component of the product; and for concomitant use with chemotherapy and radiotherapy.

Serious allergic reactions have occurred with the use of sargramostim including anaphylactic reactions. If any reaction occurs, sargramostim should be stopped and appropriate therapy initiated.

Sargramostim should not be administered simultaneously with cytotoxic chemotherapy or radiotherapy or within 24 hours preceding or following chemotherapy or radiotherapy due to the potential sensitivity of rapidly dividing hematopoietic progenitor cells.

Sargramostim contains benzyl alcohol in the liquid formulations and in the bacteriostatic water for injection diluent. Benzyl alcohol has been reported to be associated with a fatal “Gasping Syndrome” in premature infants. Formulations containing benzyl alcohol should not be administered to neonates.

Reports of fluid retention (11 percent), edema, capillary leak syndrome (less than one percent incidence), and pleural (one percent) and/or pericardial effusion (four percent) have been reported in patients after sargramostim administration. In patients with preexisting pleural and pericardial effusions, the use of sargramostim may worsen fluid retention; however, fluid retention linked with or worsened by sargramostim has been reversible after interruption or dose reduction of sargramostim with or without diuretic therapy. Patients with preexisting fluid retention, pulmonary infiltrates, or congestive heart failure should use sargramostim with caution.

Respiratory symptoms and dyspnea have been reported following sargramostim administration. Sequestration of granulocytes in the pulmonary circulation has been documented. Monitor for respiratory symptoms during or immediately following sargramostim infusion, especially in patients with preexisting lung diseases. If a patient experiences dyspnea during sargramostim infusion, reduce the infusion rate by one-half. If respiratory symptoms worsen despite infusion rate reduction, discontinue the infusion. Subsequent IV infusions may be provided following the standard dose schedule with careful monitoring. Administer sargramostim with caution in patients with hypoxia.

Transient supraventricular arrhythmia has been reported in uncontrolled studies during sargramostim administration especially in patients with a history of cardiac arrhythmia. These arrhythmias have been reversible after discontinuation of sargramostim. Use sargramostim with caution in patients with preexisting cardiac disease.

In uncontrolled clinical trials with sargramostim, elevations of serum creatinine or bilirubin and liver enzymes were reported in patients with preexisting renal or liver dysfunction. Dose reduction or interruption of therapy with sargramostim resulted in a decrease to pretreatment levels. In controlled clinical trials, the incidences of renal and hepatic dysfunction were comparable between sargramostim and placebo-treated patients. Monitoring of renal and hepatic function in patients displaying renal or

hepatic dysfunction prior to the initiation of treatment is recommended at least every other week during sargramostim therapy.

Respiratory distress, hypoxia, flushing, hypotension, syncope, and/or tachycardia have been reported following the first administration of sargramostim in a particular treatment cycle. These signs have resolved with symptomatic treatment and usually do not reappear with successive doses in the same cycle of treatment.

Stimulation of marrow precursors may cause an increase in white blood cell count. If the absolute neutrophil count (ANC) exceeds 20,000 cells/mm³ or platelet count exceeds 500,000/mm³, sargramostim therapy should be stopped or the dose reduced in half. Within three to seven days following therapy termination, excessive blood counts should return to normal or baseline levels. Twice weekly CBC with differential levels should be performed thereafter.

Sargramostim primarily stimulates normal myeloid precursors but may act as a growth factor for any tumor type including myeloid malignancies; therefore, caution should be used when using sargramostim in any malignancy with myeloid characteristics. If disease progression occurs during sargramostim therapy the medication should be discontinued.

DRUG INTERACTIONS^{23,24,25,26}

Interactions between agents in this class and other drugs have not been fully evaluated.

Drugs which may potentiate the myeloproliferative effects of these agents, such as lithium and corticosteroids, should be used with caution. Patients receiving lithium and these agents should have more frequent monitoring of neutrophil counts.

When interpreting bone-imaging results, it should be noted that increased hematopoietic activity of bone marrow in response to growth factor has been associated with transient positive bone-imaging changes.

ADVERSE EFFECTS

Drug	Bone (Skeletal) Pain	Pyrexia	Skin Rash	Edema
filgrastim (Neupogen) ²⁷ cancer patients receiving chemotherapy	22 (11)	12 (11)	6 (9)	reported
pegfilgrastim (Neulasta) ²⁸	31 (26)	nr	reported	nr
sargramostim (Leukine) ²⁹ patients with AML	21 (5)	77-95 (74-96)	44-77(38-73)	13-34 (11-35)
tbo-filgrastim (Granix™) ³⁰	3.4 (1.4)	nr	nr	nr

Adverse effects are reported as a percentage. Adverse effects data are obtained from package inserts and are not meant to be comparative or all inclusive. nr = not reported.

Uric acid, lactate dehydrogenase, and alkaline phosphatase occurred in 27 to 58 percent of 98 patients receiving filgrastim following chemotherapy treatment but were spontaneously reversible. There has

been no evidence of decreased response or development of antibodies in patients receiving filgrastim daily for almost two years.

Adverse reactions for the treatment of AML when using filgrastim include petechiae (17 percent), transfusion reactions (ten percent), and epistaxis (nine percent). Adverse reactions for the treatment of BMT when using filgrastim include rash (12 percent), nausea (ten percent), vomiting (seven percent), hypertension (four percent), and peritonitis (two percent). However, none of these events could be directly linked to filgrastim therapy alone. Adverse reactions for the treatment of PBPC when using filgrastim include **medullary bone pain (33 percent)**, transient alkaline phosphatase increases (21 percent), and headache (seven percent). Adverse reactions for the treatment of SCN when using filgrastim include bone pain (33 percent), palpable splenomegaly (30 percent), epistaxis (15 percent), thrombocytopenia in patients with palpable spleens (12 percent), anemia (ten percent), thrombocytopenia (six percent), injection site reactions, rash, hepatomegaly, arthralgia, osteoporosis, cutaneous vasculitis, hematuria/proteinuria, alopecia, and exacerbation of pre-existing skin disorders.

In phase III studies, immunogenicity and safety profiles were similar between tbo-filgrastim and filgrastim.³¹

Monitoring

With sargramostim, a CBC is recommended twice per week to avoid excessive leukocytosis (white blood cell counts greater than 50,000 cells/mm³; absolute neutrophil count greater than 20,000 cells/mm³). Patients with preexisting renal or hepatic dysfunction should have their renal and hepatic function monitored at least biweekly during sargramostim therapy. Patient hydration and body weight should be monitored carefully during therapy.

For cancer patients receiving myelosuppressive chemotherapy, obtain CBC and platelet count prior to chemotherapy and at regular intervals (twice weekly) during filgrastim, pegfilgrastim, and tbo-filgrastim therapy. For cancer patients receiving BMT, CBC and platelet counts are recommended at least three times weekly following marrow transplantation and filgrastim administration. Neutrophil nadir occurred earlier during cycles and duration of severe neutropenia was reduced when filgrastim was administered. An accelerated recovery in neutrophil counts was also observed.

For patients with severe chronic neutropenia, serial CBC with differential, platelet counts, and an evaluation of bone marrow morphology and karyotype should be performed prior to starting therapy. Twice weekly CBC with differential and platelet counts should be obtained during the initial four weeks of filgrastim therapy and during the two weeks following any dose adjustment. Once a patient is clinically stable, a monthly CBC with differential and platelet count should be performed during the first year of therapy with filgrastim. Thereafter, quarterly CBC with differential and platelet counts is recommended. For patients with congenital neutropenia, annual bone marrow and cytogenetic evaluations should be performed during filgrastim treatment.

SPECIAL POPULATIONS^{32,33,34,35}

Pediatrics

Safety and effectiveness have not been established in pediatric patients for all products in this category.

In a study of 124 pediatric patients, sargramostim (Leukine) did not exhibit greater toxicity in pediatric patients compared to adults. Reconstituted sargramostim using bacteriostatic water for injection should not be administered to neonates.

Safety and pharmacokinetics of pegfilgrastim have been evaluated in 37 pediatric patients with sarcoma.

Filgrastim has been studied in a phase three study to assess the safety and efficacy of use in the treatment of SCN in 120 patients' ages one month to 16 years. Long-term follow-up data from the postmarketing surveillance study suggest that height and weight are not adversely affected in patients who received up to five years of filgrastim treatment. After one and a half years, limited data did not suggest that alterations in sexual maturation or endocrine function occurred. In the cancer setting, 12 pediatric patients with neuroblastoma have received up to six cycles of cyclophosphamide, cisplatin, doxorubicin, and etoposide chemotherapy concurrently with filgrastim; filgrastim was well tolerated. Pediatric patients receiving chronic filgrastim therapy who have congenital types of neutropenia have developed cytogenetic abnormalities and have undergone MDS and AML transformation. The safety and efficacy of filgrastim in neonates and patients with autoimmune neutropenia of infancy has not been established.

Pregnancy

All products in this category are Pregnancy Category C.

DOSAGES

Drug	Cancer patients receiving myelosuppressive chemotherapy – to reduce incidence of infection (febrile neutropenia)	Acute Myeloid Leukemia (AML) patients receiving chemotherapy	Bone Marrow Transplant (BMT)	Peripheral Blood Progenitor Cell Collection and Therapy	Severe Chronic Neutropenia	Availability
filgrastim (Neupogen) ³⁶	5 mcg/kg/day, administered as a single daily injection by SC bolus, by short IV infusion (15 to 30 minutes), or by continuous SC or continuous IV infusion; doses may be increased by increments of 5 mcg/kg for each chemotherapy cycle according to the duration and severity of the ANC nadir		10 mcg/kg/day given as an IV infusion of four or 24 hours, or as a continuous 24hour SC infusion; during periods of neutrophil recovery, the daily dose should be titrated against the neutrophil response dosing schedule	10 mcg/kg/day SC as a bolus or a continuous infusion; give for at least four days before the first leukapheresis procedure and continued until the last leukapheresis	Starting Dose: Congenital Neutropenia: 6 mcg/kg SC twice daily Idiopathic or Cyclic Neutropenia: 5 mcg/kg SC daily	SDV: 300 mcg/1 mL, 480 mcg/1.6 mL prefilled syringes (SingleJect®): 300 mcg/0.5 mL, 480 mcg/0.8 mL
pegfilgrastim (Neulasta) ³⁷	6 mg SC once per chemotherapy cycle	--	--	--	--	6 mg/0.6 mL prefilled syringe
sargramostim (Leukine) ³⁸	--	250 mcg/m ² /day given IV over four hours starting approximately day 11 or four days following completion of induction chemotherapy, if the day ten bone marrow is hypoplastic with less than five percent blasts	250mcg/m ² /day given IV over two hours beginning two to four hours after bone marrow infusion, and not less than 24 hours after the last dose of chemotherapy or radiotherapy; therapy should begin when post marrow infusion ANC is less than 500 cells/mm ³ and continued until ANC is greater than 1,500 cells/mm ³ for three consecutive days; treatment of BMT failure or engraftment delay: 250 mcg/m ² /day given IV over two hours for 14 days	250 mcg/m ² /day administered IV over 24 hours or SC once daily; Continue until ANC is greater than 1,500 cells/mm ³ for three consecutive days	--	250 and 500 mcg vial

Dosages (continued)

Drug	Cancer patients receiving myelosuppressive chemotherapy – to reduce incidence of infection (febrile neutropenia)	Acute Myeloid Leukemia (AML) patients receiving chemotherapy	Bone Marrow Transplant (BMT)	Peripheral Blood Progenitor Cell Collection and Therapy	Severe Chronic Neutropenia	Availability
tbo-filgrastim (Granix™) ³⁹	5 mcg/kg/day as a SC injection until expected neutrophil nadir is passed and neutrophil count is in normal range	--	--	--	--	single use, preservative-free prefilled syringe 300 mcg/0.5 mL, 480 mcg/0.8 mL

Due to the potential sensitivity of rapidly dividing myeloid cells to chemotherapy, filgrastim and tbo-filgrastim should not be administered within 24 hours before administration of chemotherapy. Filgrastim and tbo-filgrastim should be administered no earlier than 24 hours after the administration of cytotoxic chemotherapy. Administer filgrastim daily for up to two weeks, until the ANC has reached $10,000/\text{mm}^3$ following the expected chemotherapy-induced neutrophil nadir. The duration of filgrastim therapy needed to attenuate chemotherapy-induced neutropenia may be dependent on the myelosuppressive capabilities of the chemotherapy regimen being used. Discontinue filgrastim if the ANC exceeds $10,000/\text{mm}^3$ after the expected chemotherapy-induced neutrophil nadir. The single use, prefilled tbo-filgrastim syringe should be administered by a healthcare professional.

The first dose of filgrastim for patients receiving BMT should be administered at least 24 hours after chemotherapy treatment and at least 24 hours after bone marrow infusion. Pegfilgrastim should not be administered in the period between 14 days before and 24 hours after administration of cytotoxic chemotherapy.

For sargramostim, treatment should be interrupted or the dose reduced by half if the ANC exceeds $20,000 \text{ cells}/\text{mm}^3$.

CLINICAL TRIALS

Search Strategy

Articles were identified through searches performed on PubMed and review of information sent by manufacturers. Search strategy included the use of all drugs in this class for FDA-approved indications. Randomized, controlled, double-blind, comparative trials are considered the most relevant in this category. Studies included for analysis in the review were published in English, performed with human participants and randomly allocated participants to comparison groups. In addition, studies must contain clearly stated, predetermined outcome measure(s) of known or probable clinical importance, use data analysis techniques consistent with the study question and include follow-up (endpoint assessment) of at least 80 percent of participants entering the investigation. Despite some inherent bias found in all studies, including those sponsored and/or funded by pharmaceutical manufacturers, the studies in this therapeutic class review were determined to have results or conclusions that do not suggest systematic error in their experimental study design. While the potential influence of manufacturer sponsorship/funding must be considered, the studies in this review have also been evaluated for validity and importance.

filgrastim (Neupogen) and pegfilgrastim (Neulasta)

Pegfilgrastim 6 mg SC once per chemotherapy cycle (every 21 days) and filgrastim 5 mcg/kg SC daily were compared in 157 patients with breast cancer (stage II – IV).⁴⁰ The placebo and filgrastim injections were given daily until the absolute neutrophil count was greater than $10 \times 10^9/\text{L}$ or a total of 14 days. This randomized, double-blind, multicenter study evaluated patients for duration of grade four neutropenia, depth of neutrophil nadir, incidence of febrile neutropenia, time to neutrophil recovery, and safety data. Patients received doxorubicin $60 \text{ mg}/\text{m}^2$ and docetaxel $75 \text{ mg}/\text{m}^2$ chemotherapy. A total of 152 patients were evaluated for efficacy. Pegfilgrastim and filgrastim had similar efficacy for all efficacy measures for all cycles. The incidence of severe neutropenia was 83 percent with filgrastim therapy and 84 percent with pegfilgrastim during cycle one. The duration of severe neutropenia during cycle one was 1.6 days with filgrastim and 1.8 days with pegfilgrastim. The

incidence of febrile neutropenia was 20 percent with filgrastim and 13 percent with pegfilgrastim. Nine days was the median time of recovery to an ANC of $>2 \times 10^9 \text{ mm}^3$ in all cycles for both treatment groups. The most frequently reported adverse effect was bone pain (37 percent pegfilgrastim; 42 percent filgrastim).

A randomized, double-blind, non-inferiority study compared the safety and efficacy of filgrastim and pegfilgrastim in 310 patients with advanced breast cancer (stage II-IV) receiving chemotherapy.⁴¹ Patients were randomized to filgrastim 5 mcg/kg body weight once daily or pegfilgrastim 100 mcg/kg body weight once every 21-day chemotherapy cycle plus placebo injection once daily. G-CSF therapy began 24 hours post-chemotherapy. Patients received doxorubicin 60 mg/m^2 and docetaxel 75 mg/m^2 for up to four cycles. Daily injections of filgrastim or placebo were given until the ANC was $10 \times 10^9/\text{L}$ or a total of 14 days. The primary outcome was duration of grade four neutropenia (ANC < 500 in cycle one); the percentage of patients experiencing grade four neutropenia in cycle one was 79 percent and 77 percent for filgrastim and pegfilgrastim, respectively ($p>0.5$). The mean duration of grade four neutropenia for cycle one was 1.8 and 1.7 days for filgrastim and pegfilgrastim, respectively ($p>0.5$). For subsequent cycles (two through four), the mean duration of severe neutropenia for cycles two, three, and four were 0.7, 0.6, and 0.9 days for pegfilgrastim and 1.1, 1.2, and 1.3 days for filgrastim ($p\leq 0.001$ cycles two and three, $p=0.019$ cycle four). The incidence of febrile neutropenia (defined as fever $>38.2^\circ \text{ C}$ with ANC $< 0.5 \times 10^9/\text{L}$) was 12 percent with filgrastim and seven percent with pegfilgrastim during the first cycle. Incidence of febrile neutropenia over the entire study period was 18 percent with filgrastim and nine percent with pegfilgrastim ($p=0.029$). Time to ANC recovery was 9.7 days with filgrastim and 9.3 days with pegfilgrastim [95% Confidence Interval (CI), -0.88 to 0.08]. Adverse event profiles were similar in both groups. The pegfilgrastim dose is different than the current FDA-approved labeling dose of 6 mg as a single dose.

filgrastim (Neupogen) and sargramostim (Leukine)

A randomized, double-blind, multicenter study compared sargramostim and filgrastim in the treatment of chemotherapy-induced myelosuppression in 181 afebrile cancer patients with ANC levels less than 500/microL.⁴² Patients received daily SC injections of either agent until ANC levels reached at least 1,500/microL. There was no statistical difference between treatment groups in the mean number of days to reach an ANC of 500/microL, but the mean number of days to reach ANC levels of 1,000/microL and 1,500/microL was approximately one day less in patients receiving filgrastim. Fewer patients in the sargramostim arm were hospitalized, and they had a shorter mean length of hospitalization, mean duration of fever, and mean duration of intravenous antibiotic therapy compared with patients who received filgrastim. Both growth factors were well tolerated. Sargramostim and filgrastim have comparable efficacy and tolerability in the treatment of standard-dose chemotherapy-induced myelosuppression in community practice.

A randomized, double-blind, multicenter study in 137 cancer patients receiving myelosuppressive chemotherapy compared the tolerability of sargramostim and filgrastim in the prevention or treatment of chemotherapy-induced neutropenia.⁴³ Patients received sargramostim SC 300 mcg daily or filgrastim SC 480 mcg daily starting one to two days after completion of chemotherapy. The drugs were given prophylactically to 82 percent of patients within 48 hours; the other patients (18 percent) received the drugs when the ANC decreased to less than 500/mL. No statistically significant differences in the incidence or severity of adverse events were detected with the exception of a slightly higher incidence of grade one fever (< 38.1 degrees C) with sargramostim. The study was not designed to evaluate

efficacy, but it was noted that there were no statistically significant differences between treatment groups in total days of growth factor therapy, days of hospitalization, or days of intravenous antibiotics during the treatment period.

META-ANALYSIS

A meta-analysis evaluated a total of five head-to-head studies comparing pegfilgrastim and filgrastim for reducing chemotherapy-induced neutropenia among a total of 617 patients with solid tumors and malignant lymphomas.⁴⁴ Studies included used the approved doses as indicated in the package insert. Although only one study had a statistically significant difference in febrile neutropenia reductions favoring pegfilgrastim over filgrastim (relative risk reduction of 50 percent; $p=0.027$), the pooled relative risk showed a statistically significant favorable result for pegfilgrastim (RR=0.64; 95% CI, 0.43-0.97). Grade IV neutropenia rates (for cycle one: RR=0.99; 95% CI, 0.91-1.08; cycle two: RR=0.88; 95% CI, 0.7-1.11; cycle three: RR=0.80; 95% CI, 0.47-1.36; cycle four: RR=0.9; 95% CI, 0.71-1.13), time to ANC (95% CI, -0.34-0.56), and incidence of bone pain (RR=0.95; 95% CI, 0.76-1.19) were similar between the two G-CSFs. A single dose of pegfilgrastim performed better than a median of ten to 14 days of filgrastim in reducing febrile neutropenia rates for patients undergoing myelosuppressive chemotherapy.

SUMMARY

Myelosuppressive chemotherapy can induce neutropenia and febrile neutropenia which can lead to increased healthcare costs and poor patient health outcomes. Clinical trials have shown that Colony Stimulating Factors promote the recovery of neutrophils following myelosuppressive chemotherapy and decrease the likelihood of neutropenic complications. Limited comparative data suggest that filgrastim (Neupogen) and pegfilgrastim (Neulasta) have similar efficacy, tolerability, and adverse drug reaction profiles. However, though data is limited, pegfilgrastim may have a slightly higher rate of reducing febrile neutropenia compared to filgrastim. In comparison to other products, pegfilgrastim administration frequency may be viewed as more favorable since it only requires a single subcutaneous injection per chemotherapy cycle whereas filgrastim, tbo-filgrastim, and sargramostim administration is a daily subcutaneous injection. Further clinical trials comparing clinical activity, toxicity, and cost-effectiveness of these products are warranted since head-to-head trials are extremely limited.

The [v2.2014](#) NCCN practice guidelines for the Myeloid Growth Factors indicate there is higher level evidence supporting the use of filgrastim [and tbo-filgrastim](#) (prophylaxis and treatment – category one) and pegfilgrastim (prophylaxis – category one) than for sargramostim (category 2B) for the management of febrile neutropenia. However, the guidelines also acknowledge that there are [insufficient head-to-head comparative studies on the clinical benefits of G-CSFs and GM-CSFs. To conclude, the NCCN guidelines recommend clinicians assess the patient and treatment-related risk factors for the development of neutropenic complications and clinicians should use independent judgment when considering appropriate therapy.](#)

REFERENCES

1 Neupogen [package insert]. Thousand Oaks, CA; Amgen; February 2014.

2 Neulasta [package insert]. Thousand Oaks, CA; Amgen; February 2014.

3 Leukine [package insert]. Bridgewater, NJ; Genzyme; April 2013.

- 4 Granix [package insert]. North Wales, PA; Cephalon; July 2013.
- 5 The National Comprehensive Cancer Network practice guidelines for Myeloid Growth Factors v2.2014. Available at: http://www.nccn.org/professionals/physician_gls/f_guidelines.asp. Accessed November 6, 2014.
- 6 The National Comprehensive Cancer Network practice guidelines for Myeloid Growth Factors v2.2014. Available at: http://www.nccn.org/professionals/physician_gls/f_guidelines.asp. Accessed November 6, 2014.
- 7 The National Comprehensive Cancer Network practice guidelines for Myeloid Growth Factors v2.2014. Available at: http://www.nccn.org/professionals/physician_gls/f_guidelines.asp. Accessed November 6, 2014.
- 8 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 Guideline. *J Clin Oncol.* 2006; 24:3187-3205. Available at: <http://jco.ascopubs.org/content/24/19/3187.full>. Accessed November 6, 2014.
- 9 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 Guideline. *J Clin Oncol.* 2006; 24:3187-3205. Available at: <http://jco.ascopubs.org/content/24/19/3187.full>. Accessed November 6, 2014.
- 10 The National Comprehensive Cancer Network practice guidelines for Myeloid Growth Factors v2.2014. Available at: http://www.nccn.org/professionals/physician_gls/f_guidelines.asp. Accessed November 6, 2014.
- 11 Neupogen [package insert]. Thousand Oaks, CA; Amgen; February 2014.
- 12 Neulasta [package insert]. Thousand Oaks, CA; Amgen; February 2014.
- 13 Leukine [package insert]. Bridgewater, NJ; Genzyme; April 2013.
- 14 Granix [package insert]. North Wales, PA; Cephalon; July 2013.
- 15 Neupogen [package insert]. Thousand Oaks, CA; Amgen; February 2014.
- 16 Neulasta [package insert]. Thousand Oaks, CA; Amgen; February 2014.
- 17 Leukine [package insert]. Bridgewater, NJ; Genzyme; April 2013.
- 18 Granix [package insert]. North Wales, PA; Cephalon; July 2013.
- 19 Neupogen [package insert]. Thousand Oaks, CA; Amgen; February 2014.
- 20 Neulasta [package insert]. Thousand Oaks, CA; Amgen; February 2014.
- 21 Leukine [package insert]. Bridgewater, NJ; Genzyme; April 2013.
- 22 Granix [package insert]. North Wales, PA; Cephalon; July 2013.
- 23 Neupogen [package insert]. Thousand Oaks, CA; Amgen; February 2014.
- 24 Neulasta [package insert]. Thousand Oaks, CA; Amgen; February 2014.
- 25 Leukine [package insert]. Bridgewater, NJ; Genzyme; April 2013.
- 26 Granix [package insert]. North Wales, PA; Cephalon; July 2013.
- 27 Neupogen [package insert]. Thousand Oaks, CA; Amgen; February 2014.
- 28 Neulasta [package insert]. Thousand Oaks, CA; Amgen; February 2014.
- 29 Leukine [package insert]. Bridgewater, NJ; Genzyme; April 2013.
- 30 Granix [package insert]. North Wales, PA; Cephalon; July 2013.
- 31 Abraham I, Tharmarajah, MacDonald K. Clinical safety of biosimilar recombinant human granulocyte colony-stimulating factors. *Exper Opin. Drug Saf.* 2013; 12(2):235-246.
- 32 Neupogen [package insert]. Thousand Oaks, CA; Amgen; February 2014.
- 33 Neulasta [package insert]. Thousand Oaks, CA; Amgen; February 2014.
- 34 Leukine [package insert]. Bridgewater, NJ; Genzyme; April 2013.
- 35 Granix [package insert]. North Wales, PA; Cephalon; July 2013.
- 36 Neupogen [package insert]. Thousand Oaks, CA; Amgen; February 2014.
- 37 Neulasta [package insert]. Thousand Oaks, CA; Amgen; February 2014.
- 38 Leukine [package insert]. Bridgewater, NJ; Genzyme; April 2013.
- 39 Granix [package insert]. North Wales, PA; Cephalon; July 2013.
- 40 Green MD, Koelbl H, Baselga J, et al for the International Pegfilgrastim 749 Study Group. A randomized double-blind multicenter phase III study of fixed-dose single-administration pegfilgrastim versus daily filgrastim in patients receiving myelosuppressive chemotherapy. *Ann Oncol.* 2003; 14(1):29-35.
- 41 Holmes FA, O'Shaughnessy JA, Vukelia S, et al. Blinded, randomized, multicenter study to evaluate single administration pegfilgrastim once per cycle versus daily filgrastim as an adjunct to chemotherapy in patients with high-risk stage II or stage III/IV breast cancer. *J Clin Oncol.* 2002; 20(3):727-731.
- 42 Beveridge RA, Miller JA, Kales AN, et al. A comparison of efficacy of sargramostim (yeast-derived RhuGM-CSF) and filgrastim (bacteria-derived RhuG-CSF) in the therapeutic setting of chemotherapy-induced myelosuppression. *Cancer Invest.* 1998; 16(6):366-373.
- 43 Beveridge RA, Miller JA, Kales AN, et al. Randomized trial comparing the tolerability of sargramostim (yeast-derived RhuGM-CSF) and filgrastim (bacteria-derived RhuG-CSF) in cancer patients receiving myelosuppressive chemotherapy. *Support Care Cancer.* 1997; 5(4):289-298.
- 44 Pinto L, Liu Z, Doan Q, et al. Comparison of pegfilgrastim with filgrastim on febrile neutropenia, grade IV neutropenia and bone pain: a meta-analysis of randomized controlled trials. *Curr Med Res Opin.* 2007; 23(9):2283-2295.