



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	Hematopoietic Syndrome of Acute Radiation Syndrome	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 (Increases survival in patients who are acutely exposed to myelosuppressive doses of radiation)	X (Reduce the incidence and duration of neutropenia in symptomatic patients with congenital neutropenia, cyclic neutropenia, or idiopathic neutropenia)
filgrastim-sndz (Zarxio®) ²	Sandoz	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®) ³	Amgen	X	--	--	--	X (Increases survival in patients acutely exposed to myelosuppressive doses of radiation)	--
sargramostim (Leukine®) ⁴	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®) ⁵	Cephalon	X	--	--	--	--	--

OVERVIEW

Myelosuppressive chemotherapy can induce neutropenia (< 500 neutrophils/mcL or < 1,000 neutrophils/mcL and a predicted decline to ≤ 500/mcL over the next 48 hours) and febrile neutropenia (≥ 38.3°C orally or ≥ 38°C over 1 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.⁶ Colony Stimulating Factors are hematopoietic growth factors which have been shown to decrease the likelihood of neutropenic complications resulting from chemotherapy. Filgrastim (Neupogen), filgrastim-sndz (Zarxio), 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) v1.2015 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.⁷ Safety data appear similar between filgrastim (Neupogen) and pegfilgrastim (Neulasta), and the subcutaneous (SC) route is preferred for all 5 agents. To date, there are insufficient head-to-head comparative studies on the clinical benefits of G-CSFs and GM-CSFs. Filgrastim, filgrastim-sndz, and tbo-filgrastim have a category 1 recommendation stating there is high-level evidence from randomized controlled clinical trials and there is uniform NCCN consensus that filgrastim, filgrastim-sndz, and tbo-filgrastim reduce the risk of febrile neutropenia, hospitalization, and intravenous (IV) antibiotics during the course of therapy. Filgrastim, filgrastim-sndz, and tbo-filgrastim can be administered the day after chemotherapy, up to 3 to 4 days after chemotherapy, and through post-nadir recovery. Pegfilgrastim has been designated a category 1 recommendation (for prophylactic use only). Most pegfilgrastim trials administered the medication the day after chemotherapy (category 1); however, administration up to 3 to 4 days after chemotherapy is also reasonable according to the NCCN guidelines. Same-day administration of pegfilgrastim may be considered in certain situations but data are limited to support this. There is evidence to support the use of chemotherapy regimens every 3 weeks with pegfilgrastim (category 1). Efficacy data exist for pegfilgrastim in chemotherapy regimens given every 2 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 a low-level of evidence, and there is consensus that the intervention is appropriate. Sargramostim can be administered the day after chemotherapy, up to 3 to 4 days after chemotherapy, and through post-nadir recovery.

The practice guidelines stratify patients into 3 risk groups based on the chemotherapy regimen and patient-related risk factors: high risk (> 20% risk of developing febrile neutropenia), intermediate risk (10% to 20% risk of developing febrile neutropenia), and low risk (< 10% risk of developing febrile neutropenia).⁸ 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 updated v1.2015 NCCN Myeloid Growth Factors guidelines also address the role of biosimilars.⁹ In general, NCCN recommends filgrastim-sndz in the same instances as filgrastim; however, they do not recommend switching between biosimilars and their corresponding reference products during treatment. The use of filgrastim in mobilization of allogeneic donors (unapproved indication) carries a 2A recommendation, while filgrastim-sndz carries a 2B recommendation.

The American Society of Clinical Oncology (ASCO) published an updated set of guidelines in 2015 for the use of white blood cell growth factors. They note their ability to reduce the duration and severity of neutropenia and febrile neutropenia and allow more intensive or dose-dense chemotherapy.¹⁰ The guidelines made no recommendation regarding the equivalency of the 2 colony-stimulating agents, granulocyte CSFs, and granulocyte-macrophage CSFs. Pegfilgrastim, filgrastim, tbo-filgrastim, and filgrastim-sndz can be used for the prevention of treatment-related febrile neutropenia. The choice of agent should be based on the clinical situation, convenience, and cost (Type: evidence-based, benefit outweigh harms; Evidence quality: high; Strength of recommendation: strong). 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% or higher starting with the first cycle and continuing through subsequent cycles of chemotherapy. The decision on whether to use prophylactic CSF should take into consideration concerns such as the optimal chemotherapy regimen, individual patient risk factors, and the intention of treatment, that is, curative, prolongation of life, or symptom control and palliation. Alternative, but equally effective and safe, chemotherapy options not requiring CSFs should be considered (Type: evidence-based, benefit outweigh harms; Evidence quality: high; Strength of recommendation: strong). ASCO recommends secondary prophylaxis with CSF 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.¹¹ In many clinical situations, dose reduction or delay may be a reasonable alternative (Type: evidence-based, benefits outweigh harms; Evidence quality: high; Strengths of recommendation: strong). CSF should not be routinely used for patients with neutropenia who are afebrile (Type: evidence-based, benefits outweigh harms; Evidence quality: high; Strengths of recommendation: strong). 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 (Type: evidence-based, benefits outweigh harms; Evidence quality: high; Strengths of recommendation: strong). High-risk features include expected prolonged (> 10 days) and profound (< 0.1 x 10⁹/L) neutropenia, age > 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 2015 ASCO guidelines, CSFs can be used during or after chemotherapy or with plerixafor to mobilize peripheral-blood progenitor cells (PBPC) depending on the type of cancer and transplantation (Type: evidence-based, benefit outweigh harms; Evidence quality: strong; Strength of recommendation: high). CSF administration should be administered after autologous stem-cell transplantation (Type: evidence-based, benefits outweigh harms; Evidence quality: high; Strength of recommendation: strong) and may be administered after allogenic stem-cell transplantation (Type: evidence-based; Evidence quality: low; Strength of recommendation: weak). They recommend filgrastim-sndz, and future biosimilars may be used for the prevention of neutropenia. ASCO recommends that the choice of agent depends on convenience, cost, and clinical situation. ASCO's dosing and administration recommendations for filgrastim-sndz are identical to those for filgrastim.

In August 2012, the FDA announced the approval of tbo-filgrastim (Granix) based on results of 3 randomized clinical trials.¹² 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 (BLA). Filgrastim-sndz, approved in March 2015, is the first FDA-approved biosimilar product. It was approved through the 351(k) biosimilar pathway. The reference product for filgrastim-sndz is Amgen's filgrastim (Neupogen).¹³ Biosimilars must demonstrate there are no clinically meaningful differences in safety or effectiveness from the reference product; however, small differences in clinically inactive compounds are permissible in biosimilar products. Currently, biosimilars are not considered interchangeable products.

PHARMACOLOGY^{14,15,16,17,18}

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 that 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), filgrastim-sndz (Zarxio), pegfilgrastim (Neulasta), and tbo-filgrastim (Granix) are G-CSFs 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, filgrastim-sndz, and tbo-filgrastim stimulate the growth and development of neutrophils within the bone marrow. Filgrastim and filgrastim-sndz cause 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^{19,20,21,22,23}

Drug	Half-Life Intravenous Administration	Half-Life Subcutaneous Administration
filgrastim (Neupogen)	231 minutes	210 minutes
filgrastim-sndz (Zarxio)	231 minutes	210 minutes
pegfilgrastim (Neulasta)	--	15–80 hours
sargramostim (Leukine)	60 minutes	162 minutes
tbo-filgrastim (Granix)	--	3.2–3.8 hours

CONTRAINDICATIONS/WARNINGS^{24,25,26,27,28}

filgrastim (Neupogen), filgrastim-sndz (Zarxio), pegfilgrastim (Neulasta), and tbo-filgrastim (Granix)

Filgrastim (Neupogen), filgrastim-sndz (Zarxio), and pegfilgrastim (Neulasta) are contraindicated in patients with known hypersensitivity to *E. coli*-derived proteins, filgrastim, filgrastim-sndz, 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, filgrastim-sndz, 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.

Filgrastim and filgrastim-sndz users have reported allergic-type reactions during initial or subsequent treatments, including anaphylactic reactions. However, a majority of reports of allergic type reactions occurred with initial exposure to pegfilgrastim, filgrastim, and filgrastim-sndz. These have generally been characterized by systemic symptoms involving at least 2 body systems, most often skin (e.g., rash, urticaria, facial edema), cardiovascular (e.g., hypotension, tachycardia), and respiratory (e.g., wheezing, dyspnea). Rapid resolution of symptoms occurred in most cases associated with 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, filgrastim, or filgrastim-sndz, 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, or filgrastim-sndz. Filgrastim, filgrastim-sndz, pegfilgrastim, and tbo-filgrastim should be permanently discontinued in patients with serious allergic reactions.

The on-body injector for pegfilgrastim (Neulasta) delivery kit uses acrylic adhesive; therefore, its use may result in serious reactions in patients who have allergies to acrylic adhesives. Patients should avoid activities such as traveling, driving, or operating heavy machinery 26 to 29 hours following application of the on-body injector for pegfilgrastim. This includes the 45-minute delivery period, plus 1 hour post-delivery. A caregiver should be close by for the first use.

The pegfilgrastim on-body injector is intended to be used in an electromagnetic environment. Do not expose the on-body injector to medical imaging studies (e.g., X-ray scan, MRI, CT scan, ultrasound, oxygen-rich environments, such as hyperbaric chambers), as it may cause injector damage or patient injury. The injector must be at least 4 inches away from electrical equipment, including cell phones, cordless telephones, microwaves, and other common appliances, as these may interfere with operation and can lead to a missed or incomplete dose.

The pegfilgrastim injector should not be used in hot tubs, saunas, and whirlpools. Direct sunlight should be avoided and the injector should be worn under clothing. Patients should not sleep on the injector or apply pressure during wear. Lotions, creams, oils, and cleaning agents can loosen the adhesive and should be avoided near the injector.

Acute respiratory distress syndrome (ARDS) has been reported in patients receiving filgrastim, filgrastim-sndz, 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, filgrastim-sndz, pegfilgrastim, or tbo-filgrastim who develop fever, lung infiltrates, or respiratory distress should be evaluated for the possibility of ARDS. If ARDS occurs, filgrastim, filgrastim-sndz, 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 and filgrastim-sndz. The use of filgrastim or filgrastim-sndz 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, filgrastim-sndz, 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, filgrastim-sndz, pegfilgrastim, or tbo-filgrastim for such patients. Patients experiencing a sickle cell crisis should discontinue tbo-filgrastim therapy.

The G-CSF receptor that filgrastim, filgrastim-sndz, pegfilgrastim, and tbo-filgrastim act upon has been found on tumor cell lines. It is possible that filgrastim, filgrastim-sndz, pegfilgrastim, and tbo-filgrastim act as growth factors for any tumor type; however, more data are needed since the limited data that are available are inconclusive. The safety of filgrastim and filgrastim-sndz in treating chronic myeloid leukemia (CML) and myelodysplasia has not been established.

The safety and efficacy of filgrastim and filgrastim-sndz used concurrently with chemotherapy have not been established. However, due to the sensitivity of rapidly dividing myeloid cells during chemotherapy, the use of filgrastim and filgrastim-sndz 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 and filgrastim-sndz have 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 or filgrastim-sndz since cytogenetic abnormalities and transformation to MDS and AML have been observed in patients treated with filgrastim products 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 or filgrastim-sndz on the development of abnormal cytogenetics and the effect of continued filgrastim or filgrastim-sndz administration in patients with abnormal cytogenetics or MDS are unknown. The risks and benefits of continuing filgrastim or filgrastim-sndz 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 and filgrastim-sndz. These cases most often occurred in patients with SCN receiving long-term filgrastim or filgrastim-sndz therapy. Filgrastim and filgrastim-sndz therapy should be held if cutaneous vasculitis occurs and may be restarted at a reduced dose when symptoms resolve and the ANC has decreased.

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

Capillary leak syndrome (CLS) can occur in patients using human GCSFs. Symptoms include hypotension, hypoalbuminemia, edema, and hemoconcentration and can be life-threatening, especially if treatment is delayed. Patients who develop symptoms of CLS should be monitored closely and receive symptomatic treatment.

Glomerulonephritis has occurred in patients taking filgrastim products and pegfilgrastim based on findings of azotemia, hematuria, proteinuria, and renal biopsy. Reducing the dose of or discontinuing filgrastim have generally resulted in resolution of glomerulonephritis.

White blood cell counts of $100,000/\text{mm}^3$ or more were observed in approximately 2% of patients taking filgrastim at doses above 5 mcg/kg/day when receiving myelosuppressive chemotherapy and have been reported in patients receiving pegfilgrastim. In order to avoid potential risks of excessive leukocytosis, it is recommended that filgrastim and filgrastim-sndz be stopped if the ANC surpasses $10,000/\text{mm}^3$ after the chemotherapy-induced ANC nadir occurs. Patients using filgrastim and filgrastim-sndz should have their CBCs monitored at least twice weekly during therapy. Monitoring of CBC is also recommended for pegfilgrastim although a monitoring schedule is not specified.

sargramostim (Leukine)

Sargramostim (Leukine) is contraindicated in patients with excessive leukemic myeloid blasts in the bone marrow or peripheral blood ($\geq 10\%$); 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%), edema, capillary leak syndrome (< 1% incidence), and pleural (1%) and/or pericardial effusion (4%) have been reported in patients after sargramostim administration. In patients with pre-existing 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 pre-existing 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 pre-existing 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 pre-existing cardiac disease.

In uncontrolled clinical trials with sargramostim, elevations of serum creatinine or bilirubin and liver enzymes were reported in patients with pre-existing 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 3 to 7 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^{29,30,31,32,33}

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

Drugs that 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^{34,35,36,37,38}

Drug	Bone (Skeletal) Pain	Pyrexia	Skin Rash	Edema
filgrastim (Neupogen) cancer patients receiving chemotherapy	11 (6)	48 (29)	14 (5)	reported
filgrastim-sndz (Zarxio) cancer patients receiving chemotherapy	11 (6)	48 (29)	14 (5)	reported
pegfilgrastim (Neulasta)	31 (26)	nr	reported	nr
sargramostim (Leukine) patients with AML	21 (5)	77–95 (74–96)	44–77 (38–73)	13–34 (11–35)
tbo-filgrastim (Granix)	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.

Lactate dehydrogenase and alkaline phosphatase occurred in 6% of 294 patients receiving filgrastim following chemotherapy treatment. There is a potential for immunogenicity when using therapeutic proteins; however, the incidence of antibody development in patients taking filgrastim or filgrastim-sndz has not been adequately determined. In clinical studies, the incidence of antibodies binding to filgrastim was 3% but no evidence of a neutralizing response was observed. In studies, evidence of binding antibodies was detected (< 1%) with pegfilgrastim use but there was no evidence of neutralizing antibodies. Cytopenias resulting from an antibody response to exogenous growth factor have been reported rarely.

Adverse reactions with ≥ 2% higher incidence in filgrastim and filgrastim-sndz compared to placebo-treated patients for AML include epistaxis, back pain, extremity pain, erythema, and maculo-papular rash. Adverse reactions with ≥ 5% higher incidence in filgrastim and filgrastim-sndz patients compared to placebo-treated patients for BMT include rash, hypersensitivity, thrombocytopenia, anemia, hypertension, sepsis, bronchitis, and insomnia. Adverse reactions for the treatment of PBPC when using filgrastim or filgrastim-sndz include bone pain (30%), pyrexia (16%), alkaline phosphatase increases (11%), and headache (10%). Adverse reactions with ≥ 5% higher incidence in filgrastim- or filgrastim-sndz-treated patients compared to placebo when treating SCN include arthralgia, bone pain, back pain, muscle spasms, musculoskeletal pain, extremity pain, splenomegaly, anemia, upper

respiratory tract infection, urinary tract infection, epistaxis, chest pain, diarrhea, hypoesthesia, and alopecia.

In phase 3 studies, immunogenicity and safety profiles were similar between tbo-filgrastim and filgrastim.³⁹

Monitoring

With sargramostim, a CBC is recommended twice per week to avoid excessive leukocytosis (white blood cell counts $> 50,000$ cells/mm³; absolute neutrophil count $> 20,000$ cells/mm³). Patients with pre-existing 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, filgrastim-sndz, pegfilgrastim, and tbo-filgrastim therapy. For cancer patients receiving BMT, frequent CBC and platelet counts are recommended during filgrastim and filgrastim-sndz therapy.

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 4 weeks of filgrastim or filgrastim-sndz therapy and during the 2 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 and filgrastim-sndz. Thereafter, quarterly CBC with differential and platelet counts is recommended.

Patients using filgrastim or filgrastim-sndz for PBPC should have their neutrophil counts monitored after 4 days of filgrastim or filgrastim-sndz and therapy should be discontinued if the WBC count increases $> 100,000$ /mm³.

For Hematopoietic Syndrome of Acute Radiation Syndrome, a baseline CBC and serial CBC should be taken approximately every third day until the ANC remains $> 1,000$ /mm³ for 3 consecutive CBCs when using filgrastim. Filgrastim therapy should not be delayed if a CBC is not readily available. Filgrastim therapy should continue until the ANC remains $> 1,000$ /mm³ for 3 consecutive CBCs or exceeds $10,000$ /mm³ after radiation-induced nadir. When using pegfilgrastim, a baseline CBC should be obtained. However, therapy should not be delayed if a CBC is not readily available. The amount of radiation absorbed should be estimated based on information from public authorities, biodosimetry, or clinical findings, such as time to onset of vomiting or lymphocyte depletion kinetics.

SPECIAL POPULATIONS^{40,41,42,43,44}

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 3 study to assess the safety and efficacy of use in the treatment of SCN in 70 patients ages 7 months to 16 years. Long-term follow-up data from the post-marketing surveillance study suggest that height and weight are not adversely affected in patients who received up to 5 years of filgrastim treatment (n=429). After 1.5 years, limited data did not suggest that alterations in sexual maturation or endocrine function occurred. In the cancer setting, 15 (median age 2.6 years) pediatric patients with neuroblastoma have received cyclophosphamide, cisplatin, doxorubicin, and etoposide chemotherapy concurrently with filgrastim for 10 days; filgrastim was well tolerated. No age-related differences in filgrastim pharmacokinetics were observed compared to adults. Pediatric patients receiving chronic filgrastim therapy who have congenital types of neutropenia have developed cytogenetic abnormalities and have undergone MDS and AML transformation. The use of filgrastim to increase survival in pediatric patients acutely exposed to radiation is based on animal studies and clinical data supporting its use in other approved indications.

Pregnancy

All products in this category are Pregnancy Category C.

DOSAGES^{45,46,47,48,49}

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	Hematopoietic Syndrome of Acute Radiation Syndrome	Severe Chronic Neutropenia	Availability
filgrastim (Neupogen)	5 mcg/kg/day, administered as a single daily injection by SC bolus, by short IV infusion (15 to 30 minutes), 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 no longer than 24 hours; 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; give for at least 4 days before the first leukapheresis procedure and continued until the last leukapheresis	10 mcg/kg as single daily SC injection; administer as soon as possible after suspected/confirmed exposure to radiation doses greater than 2 gray (Gy)	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 single-use syringes (SingleJect®): 300 mcg/0.5 mL, 480 mcg/0.8 mL
filgrastim-sndz (Zarxio)	5 mcg/kg/day as single daily injection by SC injection, short IV infusion (15 to 30 minutes), 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 IV infusion no longer than 24 hours; during periods of neutrophil recovery, the daily dose should be titrated against the neutrophil response dosing schedule	10 mcg/kg/day by SC injection; give for at least 4 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	Prefilled single-use syringe: 300 mcg/0.5 mL 480 mcg/0.8 mL

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	Hematopoietic Syndrome of Acute Radiation Syndrome	Severe Chronic Neutropenia	Availability
pegfilgrastim (Neulasta)	6 mg SC once per chemotherapy cycle; pediatric (weight < 45 kg) dosing is weight based per dosing schedule in drug PI	--	--	--	Two doses, 6 mg each, given SC 1 week apart; pediatric (weight < 45 kg) dosing is weight based per dosing schedule in drug PI; first dose given as soon as possible after suspected / confirmed radiation exposure of > 2 gray; second dose given 1 week after	--	6 mg/0.6 mL Neulasta: single use prefilled syringe for manual use Neulasta Onpro™ Delivery Kit: single use delivery kit: 1 prefilled syringe copackaged with 1 on-body injector for healthcare professional administration

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	Hematopoietic Syndrome of Acute Radiation Syndrome	Severe Chronic Neutropenia	Availability
sargramostim (Leukine)	--	250 mcg/m ² /day given IV over 4 hours starting approximately day 11 or 4 days following completion of induction chemotherapy, if the day 10 bone marrow is hypoplastic with less than 5% blasts	250mcg/m ² /day given IV over 2 hours beginning 2 to 4 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 3 consecutive days; treatment of BMT failure or engraftment delay: 250 mcg/m ² /day given IV over 2 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 3 consecutive days	--	--	250 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	Hematopoietic Syndrome of Acute Radiation Syndrome	Severe Chronic Neutropenia	Availability
tbo-filgrastim (Granix™)	5 mcg/kg/day as a SC injection until expected neutrophil nadir is passed and neutrophil count is in normal range	--	--	--	--	--	300 mcg/0.5 mL, 480 mcg/0.8 mL single use, preservative-free prefilled syringe with needle guard (healthcare professional administered); without needle guard (self- or HCP-administered)

PI=Prescribing Information

Due to the potential sensitivity of rapidly dividing myeloid cells to chemotherapy, filgrastim, filgrastim-sndz, and tbo-filgrastim should not be administered within 24 hours before administration of chemotherapy. Filgrastim, filgrastim-sndz, and tbo-filgrastim should be administered no earlier than 24 hours after the administration of cytotoxic chemotherapy. Administer filgrastim or filgrastim-sndz daily for up to 2 weeks or until the ANC has reached $10,000/\text{mm}^3$ following the expected chemotherapy-induced neutrophil nadir. The duration of filgrastim or filgrastim-sndz therapy needed to attenuate chemotherapy-induced neutropenia may be dependent on the myelosuppressive capabilities of the chemotherapy regimen being used. Discontinue filgrastim or filgrastim-sndz if the ANC exceeds $10,000/\text{mm}^3$ after the expected chemotherapy-induced neutrophil nadir.

The first dose of filgrastim or filgrastim-sndz 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.

The filgrastim-sndz prefilled syringe is not designed to allow for direct administration of doses $< 0.3 \text{ mL}$. The spring-mechanism interferes with the visibility of the graduation markings for doses $< 0.3 \text{ mL}$. As a result, patient administration of doses $< 0.3 \text{ mL}$ is not recommended.

The prefilled syringe co-packaged with pegfilgrastim (Neulasta Onpro) kit should only be used with the on-body injector as it contains additional solution to compensate for liquid loss during delivery through the on-body injector. If the prefilled syringe co-packaged in the Neulasta Onpro kit is used for manual subcutaneous injection, overdose will occur. Likewise, if the manual single-use prefilled syringe is used with the on-body injector, the patient will be underdosed. The on-body injector should not be used with any other drugs. The on-body injector has not been studied in pediatrics.

Single-use pegfilgrastim (Neulasta) delivery kits should be refrigerated until ready for use. Because the on-body injector for pegfilgrastim is at room temperature during use, the kit should not be held at room temperature longer than 12 hours prior to use. The injector should be kept dry for the last 3 hours prior to the beginning of dose delivery in order to identify potential leaks. It is waterproof for up to 8 feet for 1 hour. Do not reapply if the on-body injector falls off.

A healthcare professional must fill the on-body injector with pegfilgrastim using the prefilled syringe and apply the injector to the patient's intact, non-irritated skin (abdomen or back of arm). The back of the arm may only be used if there is a caregiver available to monitor the status of the on-body injector. A healthcare professional may initiate administration with the on-body injector on the same day as the administration of chemotherapy, as long as the injector delivers pegfilgrastim no less than 24 hours after administration of chemotherapy. Approximately 27 hours after the on-body injector is applied to the patient's skin, pegfilgrastim will be delivered over approximately 45 minutes.

Pegfilgrastim prefilled syringes are not designed to allow for direct administration of doses $< 0.6 \text{ mL}$ as it does not bear the necessary graduation marks. Direct administration to patients needing doses $< 0.6 \text{ mL}$ is not recommended due to potential dosing errors.

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% 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 and/or 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).⁵⁰ The placebo and filgrastim injections were given daily until the absolute neutrophil count was greater than $10 \times 10^9/L$ or a total of 14 days. This randomized, double-blind, multicenter study evaluated patients for duration of grade 4 neutropenia, depth of neutrophil nadir, incidence of febrile neutropenia, time to neutrophil recovery, and safety data. Patients received doxorubicin 60 mg/m^2 and docetaxel 75 mg/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% with filgrastim therapy and 84% with pegfilgrastim during cycle 1. The duration of severe neutropenia during cycle 1 was 1.6 days with filgrastim and 1.8 days with pegfilgrastim. The incidence of febrile neutropenia was 20% with filgrastim and 13% 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% pegfilgrastim; 42% 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.⁵¹ 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 4 cycles. Daily injections of filgrastim or placebo were given until the ANC was $10 \times 10^9/L$ or a total of 14 days. The primary outcome was duration of grade 4 neutropenia (ANC < 500 in cycle 1); the percentage of patients experiencing grade 4 neutropenia in cycle 1 was 79% and 77% for filgrastim and pegfilgrastim, respectively ($p>0.5$). The mean duration of grade 4 neutropenia for cycle 1 was 1.8 and 1.7 days for filgrastim and pegfilgrastim, respectively ($p>0.5$). For subsequent cycles (2 through 4), the mean duration of severe neutropenia for cycles 2, 3, and 4 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 2 and 3, $p=0.019$ cycle 4). The incidence of febrile neutropenia (defined as fever $> 38.2^\circ \text{ C}$ with ANC $< 0.5 \times 10^9/L$) was 12% with filgrastim and 7%

with pegfilgrastim during the first cycle. Incidence of febrile neutropenia over the entire study period was 18% with filgrastim and 9% 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 < 500/microL.⁵² 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 1 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.⁵³ Patients received sargramostim SC 300 mcg daily or filgrastim SC 480 mcg daily starting 1 to 2 days after completion of chemotherapy. The drugs were given prophylactically to 82% of patients within 48 hours; the other patients (18%) received the drugs when the ANC decreased to < 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 1 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.

filgrastim-sndz (Zarxio) and filgrastim (Neupogen)

The efficacy and safety of filgrastim-sndz were evaluated in a multicenter, phase 3, randomized, double-blind, active-control, noninferiority study in 218 adult, female breast cancer patients receiving adjuvant myelosuppressive chemotherapy (TAC: docetaxel, doxorubicin, cyclophosphamide).⁵⁴ A notable inclusion criterion was adequate bone marrow function, while exclusion criteria included: history of myelogenous leukemia, myelodysplastic syndrome, or concomitant sickle cell disease; concurrent or prior radiotherapy within 4 weeks of randomization; and use of prophylactic antibiotics, prior chemotherapy, or anticancer treatment of breast cancer, or previous G-CSF therapy. Patients were randomized 1:1:1:1 to 4 treatment arms prior to 6 cycles of chemotherapy: (1) filgrastim-sndz, (2) reference filgrastim, (3) alternating filgrastim-sndz and reference filgrastim each cycle, or (4) alternating reference filgrastim and filgrastim-sndz each cycle. Chemotherapy was administered on day 1 of each cycle and given every 3 weeks for 6 cycles. The assigned filgrastim agent (5 mcg/kg/day) was administered daily as a SC injection beginning on day 2 of each cycle until the ANC recovered to 10,000/mm³ following the nadir or for a maximum of 14 days. The primary endpoint was duration of severe neutropenia, defined as a difference in mean DSN (number of consecutive days from ANC < 500/mm³ to \geq 500/mm³) between the 2 filgrastim agents during cycle 1. Filgrastim-sndz was defined

as noninferior if the lower 97.5% CI for the DSN mean difference in the per-protocol population was larger than -1 day. The mean DSN for the per-protocol population in cycle 1 was 1.17 days (95% CI, 0.95 to 1.39) in the biosimilar group (n=101) and 1.2 days (95% CI, 1 to 1.4) in the reference arm (n=103). The DSN mean difference was 0.04 days, and the lower 97.5% CI was -0.26 days. Thus, filgrastim-sndz met the noninferiority requirement. Results in the full analysis set for cycle 1 were similar to the per-protocol analysis. The authors found no clinically meaningful differences between the 2 agents across all cycles in secondary efficacy measures, including incidence of febrile neutropenia (FN), hospitalization secondary to FN, infection incidence, and extent and timing of nadir.

META-ANALYSIS

A meta-analysis evaluated a total of 5 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.⁵⁵ Studies included used the approved doses as indicated in the package insert. Although only 1 study had a statistically significant difference in febrile neutropenia reductions favoring pegfilgrastim over filgrastim (relative risk [RR] reduction of 50%; p=0.027), the pooled RR showed a statistically significant favorable result for pegfilgrastim (RR, 0.64; 95% CI, 0.43 to 0.97). Grade 4 neutropenia rates (for cycle 1: RR, 0.99; 95% CI, 0.91 to 1.08; cycle 2: RR, 0.88; 95% CI, 0.7 to 1.11; cycle 3: RR, 0.80; 95% CI, 0.47 to 1.36; cycle 4: RR, 0.9; 95% CI, 0.71 to 1.13), time to ANC (95% CI, -0.34 to 0.56), and incidence of bone pain (RR, 0.95; 95% CI, 0.76 to 1.19) were similar between the 2 G-CSFs. A single dose of pegfilgrastim performed better than a median of 10 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 are 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, filgrastim-sndz (Zarxio), tbo-filgrastim (Granix), and sargramostim (Leukine) administration is a daily subcutaneous injection. The pegfilgrastim delivery kit offers an alternative delivery option with the on-body injector. Filgrastim-sndz is the first FDA-approved biosimilar; the reference product for filgrastim-sndz is filgrastim (Neupogen). Further clinical trials comparing clinical activity, toxicity, and cost-effectiveness of these products are warranted since head-to-head trials are extremely limited.

The v1.2015 NCCN practice guidelines for myeloid growth factors indicate there is higher level evidence supporting the use of filgrastim, filgrastim-sndz, and tbo-filgrastim (prophylaxis and treatment – category 1) and pegfilgrastim (prophylaxis – category 1) 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.

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