White Blood Cell Colony Stimulating Factors (for Ohio Only)

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Instructions for Use

Table of Contents **Page**

Related Policy

- Oncology Medication Clinical Coverage (for Ohio Only)

Application

This Medical Benefit Drug Policy only applies to the state of Ohio. Any requests for services that are stated as unproven or services for which there is a coverage or quantity limit will be evaluated for medical necessity using Ohio Administrative Code 5160-1-01.

Coverage Rationale

This policy refers to the following white blood cell colony stimulating factors (CSFs) for **non-oncology** conditions:

- Long-acting pegfilgrastim agents:
  - Fulphila® (pegfilgrastim-jmdb)
  - Fylnetra® (pegfilgrastim-pbbk)
  - Neulasta® (pegfilgrastim)
  - Nyvepria™ (pegfilgrastim-apgf)
  - Udenyca® (pegfilgrastim-cbqv)
  - Stimufend® (pegfilgrastim-fpgk)
  - Ziextenzo® (pegfilgrastim-bmez)
- Short-acting filgrastim agents:
  - Granix® (tbo-filgrastim)
  - Neupogen® (filgrastim)
  - Nivestym® (filgrastim-aafi)
  - Releuko® (filgrastim-ayow)
  - Zarxio® (filgrastim-sndz)
- Leukine® (sargramostim)
- Rolvedon™ (eflapegrastim-xnst)
- Any FDA-approved white blood cell colony stimulating factor product not listed here.

For oncology indications, refer to the Medical Benefit Drug Policy titled Oncology Medication Clinical Coverage (for Ohio Only) for updated information based on the National Comprehensive Cancer Network (NCCN) Drugs & Biologics Compendium® (NCCN Compendium®).

Diagnosis-Specific Criteria

For the coverage criteria below, in absence of specified drug products, the term "colony stimulating factors" or "CSFs" will be used in this policy where the coverage criteria apply to all products listed above.

White blood cell colony stimulating factors are proven and medically necessary for the following non-oncology indications.

Treatment of Febrile Neutropenia (FN) (Fulphila®, Fylnetra®, Leukine®, Neulasta®, Neupogen®, Nivestym®, Nyvepria™, Releuko, Rolvedon™, Stimufend®, Udenyca®, Zarxio®, Ziextenzo®) (Off-Label)

Fulphila®, Fylnetra®, Leukine®, Neulasta®, Neupogen®, Nivestym®, Nyvepria™, Releuko®, Rolvedon™, Stimufend®, Udenyca®, Zarxio®, and Ziextenzo® are proven and medically necessary when all of the following criteria are met:[1-3,16,17,40]

- Diagnosis of febrile neutropenia; **and**
- Patient has not received long-acting prophylactic pegfilgrastim in the last 14 days; **and**
- Patient has **one** or more risk factors for an infection-associated complication such as:[16]
  - Sepsis syndrome
  - Age > 65 years
  - Absolute Neutrophil Count (ANC) < 100/mcL
  - Neutropenia expected to be > 10 days in duration
  - Pneumonia
  - Clinically documented infections including invasive fungal infection
  - Hospitalization at the time of fever
  - Prior episode(s) of FN

Severe Chronic Neutropenia (SCN) (Neupogen®, Nivestym®, Releuko®, Zarxio®)

Neupogen®, Nivestym®, Releuko®, and Zarxio® are proven and medically necessary when all of the following criteria are met:[2,16,41]

- Diagnosis of SCN (i.e., congenital, cyclic, and idiopathic neutropenias with chronic ANC ≤ 500 neutrophils/mcL[50]); **and**
- Medication is dosed in accordance with the U.S. Food and Drug Administration (FDA) approved labeling; **and**
- Prescribed by or in consultation with a hematologist or oncologist

Definitions

Adverse Event: An adverse event is any unfavorable symptom, sign, or disease (including an abnormal laboratory finding) temporally associated with the use of a medical treatment or procedure that may or may NOT be considered related to the medical treatment or procedure. The common terminology criteria (CTC) provides descriptive terminology for adverse event reporting. A grading (severity) scale is provided for each adverse event term.[51]

Grades (general definition):

- 0 = No adverse event or within normal limits
- 1 = Mild adverse event
- 2 = Moderate adverse event
- 3 = Severe and undesirable adverse event
- 4 = Life-threatening or disabling adverse event
- 5 = Death related to adverse event

Febrile Neutropenia: Febrile neutropenia is defined as single temperature: ≥ 38.3 °C orally or 38.0 °C for a duration of over 1 hour; and neutropenia: < 500 neutrophils/mcL or < 1,000 neutrophils/mcL and a predicted decline to ≤ 500 neutrophils/mcL over the next 48 hours.[16]

Neutropenia: Neutropenia is defined as an absolute neutrophil count (ANC) of less than 1,500 per microliter (< 1,500 neutrophils/mcL).[50]

Severe Neutropenia: Severe neutropenia is defined as an ANC of less than 500 neutrophils/mcL (< 500 neutrophils/mcL).[50]

Applicable Codes

The following list(s) of procedure and/or diagnosis codes is provided for reference purposes only and may not be all inclusive. Listing of a code in this policy does not imply that the service described by the code is a covered or non-covered health service. Benefit coverage for health services is determined by federal, state, or contractual requirements and applicable laws that may require coverage for a specific service. The inclusion of a code does not imply any right to reimbursement or guarantee claim payment. Other Policies and Guidelines may apply.

HCPCS Code	Description
J1442	Injection, filgrastim, (G-CSF), excludes biosimilars, 1 microgram
J1447	Injection, tbo-filgrastim, 1 microgram
J1449	Injection, eflapegrastim-xnst, 0.1 mg
J2506	Injection, pegfilgrastim, 0.5 mg
J2820	Injection, sargramostim (GM-CSF), 50 mcg
Q5101	Injection, filgrastim-sndz, biosimilar, (Zarxio), 1 microgram
Q5108	Injection, pegfilgrastim-jmdb (Fulphila), biosimilar, 0.5 mg
Q5110	Injection, filgrastim-aafi, biosimilar, (Nivestym), 1 microgram
Q5111	Injection, pegfilgrastim-cbqv (Udenyca), biosimilar, 0.5 mg
Q5120	Injection, pegfilgrastim-bmez (ZIEXTENZO), biosimilar, 0.5 mg
Q5122	Injection, pegfilgrastim-apgf (Nyvepria), biosimilar, 0.5 mg
Q5125	Injection, filgrastim-ayow, biosimilar, (Releuko), 1 mcg
Q5127	Injection, pegfilgrastim-fpgk (stimufend), biosimilar, 0.5 mg
Q5130	Injection, pegfilgrastim-pbbk (fylnetra), biosimilar, 0.5 mg

Background

Neutropenia occurs when an individual has an abnormally low level of neutrophils. Neutrophils are a type of white blood cell important in fighting off infection.[43] Neutropenia and its complications, including febrile neutropenia and infection, remain major toxicities associated with myelosuppressive systemic cancer chemotherapy. In a nationwide prospective cohort study, first-cycle febrile neutropenia occurred in 6% of adults with solid tumors being treated with myelosuppressive chemotherapy. Hematopoietic colony-stimulating factors (CSFs) have been shown to reduce the duration and severity of neutropenia and the risk of febrile neutropenia and enable delivery of more intensive or dose-dense chemotherapy when indicated.[41]

Colony stimulating factors are medications used to stimulate production of infection-fighting white blood cells. There are two main types of colony stimulating factors: granulocyte colony-stimulating factors (G-CSFs) and granulocyte-macrophage colony stimulating factors (GM-CSFs). G-CSFs stimulate the production of neutrophils and include the following FDA approved products: filgrastim (Neupogen®), filgrastim-aafi (Nivestym®), pegfilgrastim (Neulasta®), pegfilgrastim-jmdb (Fulphila®), tbo-filgrastim (Granix®), filgrastim-sndz (Zarxio®), and pegfilgrastim-bmez (Ziextenzo®). GM-CSFs stimulate the production of both neutrophils and macrophages and include the following FDA approved products: sargramostim (Leukine®).

Clinical Evidence

The National Comprehensive Cancer Network (NCCN) publishes clinical practice guidelines for Oncology (NCCN Guidelines®) specific to myeloid growth factors.[16] The “NCCN Guidelines for Myeloid Growth Factors” are focused on the use of myeloid growth factors (MGFs) in the cancer setting. The guidelines begin with an evaluation of risk for chemotherapy-induced FN prior

to the first cycle of chemotherapy. The risk assessment includes disease type, chemotherapy regimen (high-dose, dose-dense, or standard-dose therapy), patient risk factors, and treatment intent (curative/adjuvant vs. palliative). Based on the chemotherapy regimen and patient-related risk factors, the patient is assigned to either an overall high-risk group (> 20% risk of FN), intermediate-risk group (10%-20% risk), or low-risk group (< 10% risk). Of note, there is currently no consensus nomogram for risk assessment. While the NCCN Panel outlines criteria to aid in the assessment of FN risk, independent clinical judgment should be exercised based on the patient's situation.

The NCCN Panel identifies possible patient risk factors for febrile neutropenia. According to the NCCN panel, risk factors may include:

- Prior chemotherapy or radiation therapy
- Persistent neutropenia
- Bone marrow involvement by tumor
- Recent surgery and/or open wounds
- Liver dysfunction (bilirubin > 2.0)
- Renal dysfunction (creatinine clearance < 50)
- Age > 65 years receiving full chemotherapy dose intensity.

(Back to criteria)

Other recommendations include:

- The NCCN Panel recommends that patients with FN who received prophylactic G-CSF should continue with the same G-CSF.
- For patients who have not received prophylactic MGFs, the NCCN Panel recommends an evaluation for risk factors for infection-related complications or poor clinical outcome.
- The NCCN Panel recommends administration of filgrastim, filgrastim-sndz, tbo-filgrastim, or filgrastim-aafi as a single agent or as part of a chemo-mobilization regimen, starting on the day after completion of chemotherapy.
- The NCCN Panel recommends single-agent filgrastim, filgrastim-sndz, or tbo-filgrastim for allogeneic hematopoietic cell mobilization and for granulocyte transfusion.
- The NCCN Panel recommends consideration of MGFs in the supportive care setting post-autologous hematopoietic cell transplant. Filgrastim, filgrastim-sndz, tbo-filgrastim, filgrastim-aafi, and pegfilgrastim can be considered in the supportive care setting.

Patients with Acute Myeloid Leukemia Receiving Induction or Consolidation Chemotherapy

The safety and efficacy of filgrastim to reduce the time to neutrophil recovery and the duration of fever, following induction or consolidation chemotherapy treatment of patients with acute myeloid leukemia (AML) was established in a randomized, double-blind, placebo-controlled, multi-center trial in patients with newly diagnosed, de novo AML. The initial induction therapy consisted of intravenous daunorubicin days 1, 2, and 3; cytosine arabinoside days 1 to 7; and etoposide days 1 to 5. Patients were randomized to receive subcutaneous filgrastim (n = 259) at a dose of 5 mcg/kg/day or placebo (n = 262) from 24 hours after the last dose of chemotherapy until neutrophil recovery (ANC ≥ 1,000/mm^3 for 3 consecutive days or ≥ 10,000/mm^3 for 1 day) or for a maximum of 35 days. The demographic and disease characteristics were balanced between arms with a median age of 54 (range 16 to 89) years; 54% males; initial white blood cell count (65% < 25,000/mm^3 and 27% > 100,000/mm^3); 29% unfavorable cytogenetics. The main efficacy endpoint was median duration of severe neutropenia defined as neutrophil count < 500/mm^3. Treatment with filgrastim resulted in a clinically and statistically significant reduction in median number of days of severe neutropenia, filgrastim-treated patients 14 days, placebo-treated patients 19 days [p = 0.0001: difference of 5 days (95% CI: -6.0, -4.0)]. There was a reduction in the median duration of intravenous antibiotic use, filgrastim-treated patients: 15 days versus placebo-treated patients: 18.5 days; a reduction in the median duration of hospitalization, filgrastim-treated patients: 20 days versus placebo-treated patients: 25 days. There were no statistically significant differences between the filgrastim and the placebo groups in complete remission rate (69% - filgrastim, 68% - placebo), median time to progression of all randomized patients (165 days - filgrastim, 186 days - placebo), or median overall survival (380 days - filgrastim, 425 days - placebo).

The efficacy of sargramostim in the treatment of AML was evaluated in a multicenter, randomized, double-blind placebo-controlled trial of 99 newly diagnosed adult patients, 55-70 years of age, receiving induction with or without consolidation. A combination of standard doses of daunorubicin (days 1-3) and ara-C (days 1-7) was administered during induction and high dose ara-C was administered days 1-6 as a single course of consolidation, if given. Bone marrow evaluation was performed on day 10 following induction chemotherapy. If hypoplasia with < 5% blasts was not achieved, patients immediately received a

second cycle of induction chemotherapy. If the bone marrow was hypoplastic with < 5% blasts on day 10 or four days following the second cycle of induction chemotherapy, sargramostim (250 mcg/m2/day) or placebo was given intravenously over four hours each day, starting four days after the completion of chemotherapy. Study drug was continued until an ANC ≥ 1,500 cells/mm^3 for three consecutive days was attained or a maximum of 42 days. Sargramostim or placebo was also administered after the single course of consolidation chemotherapy if delivered. Study drug was discontinued immediately if leukemic regrowth occurred.

Sargramostim significantly shortened the median duration of ANC < 500 cells/mm^3 by 4 days and < 1,000 cells/mm^3 by 7 days following induction. Of patients receiving sargramostim, 75% achieved ANC > 500 cells/mm^3 by day 16, compared to day 25 for patients receiving placebo. Sargramostim significantly shortened the median times to neutrophil recovery whether one cycle (12 vs. 15 days) or two cycles (14 vs. 23 days) of induction chemotherapy was administered. Median times to platelet (> 20,000 cells/mm^3) and RBC transfusion independence were not significantly different between treatment groups.

During the consolidation phase of treatment, sargramostim did not shorten the median time to recovery of ANC to 500 cells/mm^3 (13 days) or 1,000 cells/mm^3 (14.5 days) compared to placebo. There were no significant differences in time to platelet and RBC transfusion independence. The incidence of severe infections and deaths associated with infections was significantly reduced in patients who received sargramostim. During induction or consolidation, 27 of 52 patients receiving sargramostim and 35 of 47 patients receiving placebo had at least one grade 3, 4, or 5 infection (p = 0.02). Twenty-five patients receiving sargramostim and 30 patients receiving placebo experienced severe and fatal infections during induction only. There were significantly fewer deaths from infectious causes in the sargramostim arm (3 vs. 11, p = 0.02). The majority of deaths in the placebo group were associated with fungal infections with pneumonia as the primary infection.

Patients with Cancer Undergoing Bone Marrow Transplantation

The safety and efficacy of filgrastim to reduce the duration of neutropenia in patients with nonmyeloid malignancies undergoing myeloablative chemotherapy followed by autologous bone marrow transplantation was evaluated in two randomized controlled trials of patients with lymphoma (Study 1 and Study 2). The safety and efficacy of filgrastim to reduce the duration of neutropenia in patients undergoing myeloablative chemotherapy followed by allogeneic bone marrow transplantation was evaluated in a randomized placebo-controlled trial (Study 3). In Study 1, patients with Hodgkin's disease received a preparative regimen of intravenous cyclophosphamide, etoposide, and BCNU ("CVP"), and patients with non-Hodgkin's lymphoma received intravenous BCNU, etoposide, cytosine arabinoside and melphalan ("BEAM"). There were 54 patients randomized 1:1:1 to control, filgrastim10 mcg/kg/day, and Neupogen® 30 mcg/kg/day as a 24-hour continuous infusion starting 24 hours after bone marrow infusion for a maximum of 28 days. The median age was 33 (range 17 to 57) years; 56% males; 69% Hodgkin's disease and 31% non-Hodgkin's lymphoma. The main efficacy endpoint was duration of severe neutropenia ANC < 500/mm^3. A statistically significant reduction in the median number of days of severe neutropenia (ANC < 500/mm^3) occurred in the filgrastim-treated groups versus the control group [23 days in the control group, 11 days in the 10 mcg/kg/day group, and 14 days in the 30 mcg/kg/day group (11 days in the combined treatment groups, p = 0.004)]. In Study 2, patients with Hodgkin's disease and non-Hodgkin's lymphoma received a preparative regimen of intravenous cyclophosphamide, etoposide, and BCNU ("CVP"). There were 43 evaluable patients randomized to continuous subcutaneous infusion filgrastim 10 mcg/kg/day (n = 19), filgrastim30 mcg/kg/day (n = 10) and no treatment (n = 14) starting the day after marrow infusion for a maximum of 28 days. The median age was 33 (range 17 to 56) years; 67% males; 28% Hodgkin's disease and 72% non-Hodgkin's lymphoma. The main efficacy endpoint was duration of severe neutropenia. There was statistically significant reduction in the median number of days of severe neutropenia (ANC < 500/mm^3) in the filgrastim-treated groups versus the control group (21.5 days in the control group versus 10 days in the filgrastim-treated groups, p < 0.001). The number of days of febrile neutropenia was also reduced significantly in this study (13.5 days in the control group versus 5 days in the filgrastim-treated groups, p < 0.0001). In Study 3, 70 patients scheduled to undergo bone marrow transplantation for multiple underlying conditions using multiple preparative regimens were randomized to receive filgrastim 300 mcg/m^2 /day (n = 33) or placebo (n = 37) days 5 through 28 after marrow infusion. The median age was 18 (range 1 to 45) years, 56% males. The underlying disease was: 67% hematologic malignancy, 24% aplastic anemia, 9% other. A statistically significant reduction in the median number of days of severe neutropenia occurred in the treated group versus the control group (19 days in the control group and 15 days in the treatment group, p < 0.001) and time to recovery of ANC to ≥ 500/mm^3 (21 days in the control group and 16 days in the treatment group, p < 0.001).

The efficacy of sargramostim on time to myeloid reconstitution following autologous BMT was established by three single-center, randomized, placebo-controlled and double-blinded studies (studies 301, 302, and 303) in adult and pediatric patients undergoing autologous BMT for lymphoid malignancies. A total of 128 patients (65 sargramostim, 63 placebo) were enrolled in

these three studies. The median age was 38 years (range 3-62 years), and 12 patients were younger than 18 years of age. The majority of the patients had lymphoid malignancy (87 NHL, 17 all), 23 patients had Hodgkin's lymphoma, and one patient had AML. In 72 patients with NHL or all, the bone marrow harvest was purged with one of several monoclonal antibodies prior to storage. Compared to placebo, administration of sargramostim in two studies (study 301: 44 patients, 23 patients treated with sargramostim, and study 303: 47 patients, 24 treated with sargramostim) significantly improved the following hematologic and clinical endpoints: time to neutrophil recovery, duration of hospitalization and infection experience or antibacterial usage. In the third study (study 302: 37 patients who underwent autologous BMT, 18 treated with sargramostim) there was a positive trend toward earlier myeloid engraftment in favor of sargramostim.

Patients Undergoing Autologous Peripheral Blood Progenitor Cell Collection and Therapy

The safety and efficacy of filgrastim to mobilize autologous peripheral blood progenitor cells for collection by leukapheresis was supported by the experience in uncontrolled trials, and a randomized trial comparing hematopoietic stem cell rescue using filgrastim mobilized autologous peripheral blood progenitor cells to autologous bone marrow. Patients in all these trials underwent a similar mobilization/collection regimen: filgrastim was administered for 6 to 7 days, in most cases the apheresis procedure occurred on days 5, 6, and 7. The dose of filgrastim ranged between 10 to 24 mcg/kg/day and was administered subcutaneously by injection or continuous intravenous infusion.

Engraftment was evaluated in 64 patients who underwent transplantation using filgrastim mobilized autologous hematopoietic progenitor cells in uncontrolled trials. Two of the 64 patients (3%) did not achieve the criteria for engraftment as defined by a platelet count ≥ 20,000/mm^3 by day 28. In clinical trials of filgrastim for the mobilization of hematopoietic progenitor cells, filgrastim was administered to patients at doses between 5 to 24 mcg/kg/day after reinfusion of the collected cells until a sustainable ANC (≥ 500/mm^3) was reached. The rate of engraftment of these cells in the absence of filgrastim post transplantation has not been studied. A randomized, unblinded study of patients with Hodgkin's disease or non-Hodgkin's lymphoma undergoing myeloablative chemotherapy, 27 patients received filgrastim-mobilized autologous hematopoietic progenitor cells and 31 patients received autologous bone marrow. The preparative regimen was intravenous BCNU, etoposide, cytosine arabinoside and melphalan ("BEAM").

Patients received daily filgrastim 24 hours after stem cell infusion at a dose of 5 mcg/kg/day. The median age was 33 (range 1 to 59) years; 64% males; 57% Hodgkin's disease and 43% non-Hodgkin's lymphoma. The main efficacy endpoint was number of days of platelet transfusions. Patients randomized to filgrastim-mobilized autologous peripheral blood progenitor cells compared to autologous bone marrow had significantly fewer days of platelet transfusions (median 6 vs. 10 days).

A retrospective review was conducted of data from adult patients with cancer undergoing collection of peripheral blood progenitor cells (PBPC) at a single transplant center. Mobilization of PBPC and myeloid reconstitution post-transplant were compared between four groups of patients (n = 196) receiving sargramostim for mobilization and a historical control group who did not receive any mobilization treatment [progenitor cells collected by leukapheresis without mobilization (n = 100)]. Sequential cohorts received sargramostim. Leukaphereses were initiated for all mobilization groups after the WBC reached 10,000 cells/mm^3. Leukaphereses continued until both a minimum number of mononucleated cells (MNC) were collected (6.5 or 8.0 × 10^8/kg body weight) and a minimum number of apheresis (5-8) were performed. Both minimum requirements varied by treatment cohort and planned conditioning regimen. Marked mobilization effects were seen in patients administered the higher dose of sargramostim (250 mcg/m^2) either IV (n = 63) or SC (n = 41). PBPCs from patients treated at the 250 mcg/m^2/day dose had a significantly higher number of granulocyte-macrophage colony-forming units (CFU-GM) than those collected without mobilization. A second retrospective review of data from patients undergoing PBPC at another single transplant center was also conducted. Sargramostim was given SC at 250 mcg/m^2/day once a day (n = 10) or twice a day (n = 21) until completion of apheresis. Apheresis was begun on day 5 of sargramostim administration and continued until the targeted MNC count of 9 × 10^8/kg or CD34 + cell count of 1 × 10^6/kg was reached. There was no difference in CD34 + cell count in patients receiving sargramostim once or twice a day.

Hematopoietic Syndrome of Acute Radiation Syndrome

Efficacy studies of filgrastim, pegfilgrastim, or sargramostim could not be conducted in humans with acute radiation syndrome for ethical and feasibility reasons. Approval of this indication was based on efficacy studies conducted in animals and data supporting filgrastim and pegfilgrastim's effect on severe neutropenia in patients with cancer receiving myelosuppressive chemotherapy.

The efficacy of pegfilgrastim for the acute radiation syndrome setting was studied in a randomized, placebo-controlled non-human primate model of radiation injury. Rhesus macaques were randomized to either a control (n = 23) or treated (n = 23) cohort. On study day 0, animals (n = 6 to 8 per irradiation day) were exposed to total body irradiation (TBI) of 7.50 ±0.15 Gy delivered at 0.8 ±0.03 Gy/min, representing a dose that would be lethal in 50% of animals by 60 days of follow-up (LD50/60). Animals were administered subcutaneous injections of a blinded treatment [control article (5% dextrose in water) or pegfilgrastim (300-319 mcg/kg/day)] on study day 1 and on study day 8. The primary endpoint was survival. Animals received medical management consisting of intravenous fluids, antibiotics, blood transfusions, and other support as required. Pegfilgrastim significantly (at 0.0014 level of significance) increased 60-day survival in irradiated non-human primates: 91% survival (21/23) in the pegfilgrastim group compared to 48% survival (11/23) in the control group.

The efficacy of filgrastim was studied in a randomized, blinded, placebo-controlled study in a non-human primate model of radiation injury. The planned sample size was 62 animals, but the study was stopped at the interim analysis with 46 animals because efficacy was established. Rhesus macaques were randomized to a control (n = 22) or treated (n = 24) group. Animals were exposed to total body irradiation of 7.4 ±0.15 Gy delivered at 0.8 ±0.03 Gy/min, representing a dose that would be lethal in 50% of animals by 60 days of follow-up (LD50/60). Starting on day 1 after irradiation, animals received daily subcutaneous injections of placebo (5% dextrose in water) or filgrastim (10 mcg/kg/day). Blinded treatment was stopped when one of the following criteria was met: ANC ≥ 1,000/mm^3 for 3 consecutive days, or ANC ≥ 10,000/mm^3 for more than 2 consecutive days within study day 1 to 5, or ANC ≥ 10,000/mm^3 any time after study day 5. Animals received medical management consisting of intravenous fluids, antibiotics, blood transfusions, and other support as required. Filgrastim significantly (at 0.023 level of significance) reduced 60-day mortality in the irradiated non-human primates: 21% mortality (5/24) in the filgrastim group compared to 59% mortality (13/22) in the control group.

The efficacy of sargramostim was studied in a randomized, blinded, placebo-controlled study in a nonhuman primate model of radiation injury. Rhesus macaques (50% male) were randomized to a control (n = 36) or treated (n = 36) group. Animals were exposed to total body irradiation at a dose that would be lethal in 50% to 60% of animals (655 cGy) by day 60 post irradiation [lethal dose (LD) 50-60/60]. Starting 48 ±1 hour after irradiation, animals received daily SC injections of placebo (sterile water for injection, USP) or sargramostim (7 mcg/kg/day). Blinded treatment was stopped when one of the following criteria was met: ANC ≥ 1,000 cells/mm^3 for three consecutive days or if the ANC ≥ 10,000 cells/mm^3. Animals received minimal supportive care that included a prophylactic antibiotic, antiemetic, analgesics, and parenteral fluids. No whole blood, blood products or individualized antibiotics were provided. sargramostim significantly (p = 0.0018) increased survival at day 60 in irradiated nonhuman primates: 78% survival (28/36) in the sargramostim group compared to 42% survival (15/36) in the control group. In the same study, an exploratory cohort of 36 rhesus macaques randomized to control (n = 18) or treated (n = 18) was exposed to total body irradiation at a dose that would be lethal in 70-80% of animals (713 cGY) by day 60 post irradiation. Sargramostim increased survival at day 60 in irradiated nonhuman primates: 61% survival (11/18) in the sargramostim group compared to 17% survival (3/18) in the control group.

Professional Societies

American Society of Clinical Oncology (ASCO)

The ASCO published guidelines in 2015 entitled, "Recommendations for the Use of WBC Growth Factors: American Society of Clinical Oncology Clinical Practice Guideline Update."[41] The ASCO guidelines provide direction as to how colony-stimulating factors (CSFs) should be used in people with cancer. Recommendations include:

- Primary prophylaxis with a CSF starting with the first cycle and continuing through subsequent cycles of chemotherapy is recommended in patients who have an approximately 20% or higher risk for febrile neutropenia based on patient-, disease- and treatment-related factors. Primary CSF prophylaxis should also be administered in patients receiving dose dense chemotherapy when considered appropriate. Consideration should be given to alternative, equally effective, and safe chemotherapy regimens not requiring CSF support when available. (Type: evidence based; benefits outweigh harms. Evidence quality: high. Strength of recommendation: strong.)
- Secondary prophylaxis with a 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 or treatment delay may compromise disease-free or overall survival or treatment outcome. In many clinical situations, dose reduction or delay may be a reasonable alternative. (Type: evidence based; benefits outweigh harms. Evidence quality: high. Strength of recommendation: strong.)
- CSFs should not be routinely used for patients with neutropenia who are afebrile. (Type: evidence based; benefits outweigh harms. Evidence quality: high. Strength of recommendation: strong.)

- CSFs should not be routinely used as adjunctive treatment with antibiotic therapy for patients with fever and neutropenia. However, CSFs should be considered in patients with fever and neutropenia who are at high risk for infection-associated complications or who have prognostic factors predictive of poor clinical outcomes. (Type: evidence based; benefits outweigh harms. Evidence quality: high. Strength of recommendation: strong.)
- Dose-dense regimens with CSF support should only be used if supported by convincing efficacy data or within an appropriately designed clinical trial. Efficacy data support the use of dose-dense chemotherapy in the adjuvant treatment of high-risk breast cancer and the use of high-dose intensity methotrexate, vinblastine, doxorubicin, and cisplatin in urothelial cancer. There are limited and conflicting data on the value of dose-dense regimens with CSF support in non-Hodgkin's lymphoma, and it cannot routinely be recommended at this time. (Type: evidence based; benefits outweigh harms. Evidence quality: high for breast cancer and lymphoma; intermediate for urothelial cancer. Strength of recommendation: strong for breast cancer and lymphoma; moderate for urothelial cancer.)
- CSFs may be used alone, after chemotherapy, or in combination with plerixafor to mobilize peripheral-blood progenitor cells. Choice of mobilization strategy depends in part on type of cancer and type of transplantation. (Type: evidence based; benefits outweigh harms. Evidence quality: strong. Strength of recommendation: high.)
- CSFs should be administered after autologous stem-cell transplantation to reduce the duration of severe neutropenia. (Type: evidence based; benefits outweigh harms. Evidence quality: high. Strength of recommendation: strong.)
- CSFs may be administered after allogeneic stem-cell transplantation to reduce the duration of severe neutropenia. (Type: evidence based. Evidence quality: low. Strength of recommendation: weak).
- Prophylactic CSFs for patients with diffuse aggressive lymphoma age ≥ 65 years treated with curative chemotherapy (cyclophosphamide, doxorubicin, vincristine, prednisone, and rituximab) should be considered, particularly in the presence of comorbidities. (Type: evidence based; benefits outweigh harms. Evidence quality: intermediate. Strength of recommendation: moderate.)
- The use of CSFs in pediatric patients will almost always be guided by clinical protocols. As in adults, the use of CSFs is reasonable as primary prophylaxis for pediatric patients with a high likelihood of febrile neutropenia. Similarly, the use of CSFs for secondary prophylaxis or for therapy should be limited to high-risk patients. (Type: evidence based; benefits outweigh harms. Evidence quality: high. Strength of recommendation: strong.)
- For pediatric indications in which dose-intense chemotherapy is known to have a survival benefit, such as Ewing sarcoma, CSFs should be used to enable the administration of these regimens. (Type: evidence based; benefits outweigh harms. Evidence quality: high. Strength of recommendation: strong.)
- CSFs should not be used in pediatric patients with non-relapsed acute lymphoblastic leukemia or non-relapsed acute myeloid leukemia who do not have an infection. (Type: informal consensus. Evidence quality: intermediate. Strength of recommendation: moderate.)
- Pegfilgrastim, filgrastim, tbo-filgrastim, and filgrastim-sndz (and other biosimilars, as they become available) can be used for the prevention of treatment-related febrile neutropenia. The choice of agent depends on convenience, cost, and clinical situation. There have been no additional data comparing granulocyte CSFs and granulocyte-macrophage CSFs since the 2006 update; therefore, there is no change in the recommendation regarding their therapeutic equivalency. (Type: evidence based; benefits outweigh harms. Evidence quality: high. Strength of recommendation: strong.)
- Current recommendations for the management of patients exposed to lethal doses of total-body radiotherapy, but not doses high enough to lead to certain death resulting from injury to other organs, include the prompt administration of CSFs or pegylated granulocyte CSFs. [Type: formal consensus (by others), benefits outweigh harms. Evidence quality: intermediate. Strength of recommendation: moderate.]

European Organisation for Research and Treatment of Cancer (EORTC)

The EORTC published clinical practice guidelines in 2011 entitled, "2010 update of EORTC guidelines for the use of granulocyte-colony stimulating factor to reduce the incidence of chemotherapy-induced febrile neutropenia in adult patients with lymphoproliferative disorders and solid tumors."[43] The EORTC guidelines provide direction on the use of colony-stimulating factors for prevention of chemotherapy-induced febrile neutropenia (FN) in patients with cancer. Recommendations are graded on a scale of A-D, based on levels of evidence applied by the EORTC Guidelines Working Party. Levels of evidence are as follows: I = evidence obtained from meta-analysis of multiple, well-designed, controlled studies or from high-power randomized, controlled clinical trials; II = Evidence obtained from at least one well-designed experimental study or low-power randomized, controlled clinical trial; III = Evidence obtained from well-designed, quasi-experimental studies such as non-randomized, controlled single-group, pre-post, cohort, time or matched case-control series; IV = studies such as comparative and correlational descriptive and case studies; and V= evidence obtained from case reports and clinical examples. Grading recommendations are as follows: A = evidence of type I or consistent findings from multiple studies of types II, III or IV; B =

evidence of types II, III or IV and findings are generally consistent; C = evidence of types II, III or IV but findings are inconsistent; and D = little or no systematic empirical evidence. Recommendations include:

- Recommendation 1: Patient-related risk factors for increased incidence of FN
  - Patient-related risk factors should be evaluated in the overall assessment of FN risk before administering each cycle of chemotherapy. Particular consideration should be given to the elevated risk of FN for elderly patients (aged 65 and over). Other adverse risk factors that may influence FN risk include: advanced stage of disease; experience of previous episode(s) of FN; lack of G-CSF use and absence of antibiotic prophylaxis. However, please note that the indiscriminate use of antibiotic prophylaxis for patients undergoing treatment for solid tumors or lymphoma is not recommended either by this working party or the EORTC Infectious Disease Group. Recommendation grade: B.
- Recommendation 2: Chemotherapy regimens associated with increased risk of FN
  - Consideration should be given to the elevated risk of FN when using certain chemotherapy regimens. Recommendation grade: A/B (depending on the evidence for each chemotherapy regimen). For the list of identified chemotherapy regimens, reference Table 5. It should be noted that this list is not comprehensive and there may be other drugs or regimens associated with an increased risk of FN.
- Recommendation 3: G-CSF to support chemotherapy
  - In situations where dose-dense or dose-intense chemotherapy strategies have survival benefits, prophylactic G-CSF should be used as a supportive treatment. Recommendation grade: A.
  - If reductions in chemotherapy dose intensity or density are known to be associated with a poor prognosis, primary G-CSF prophylaxis should be used to maintain chemotherapy. Examples of this could be when the patient is receiving adjuvant or potentially curative treatment or when the treatment intent is to prolong survival. Recommendation grade A. Where treatment intent is palliative, use of less myelosuppressive chemotherapy or dose/schedule modification should be considered. Recommendation grade: B.
- Recommendation 4: Impact of the overall FN risk on G-CSF use
  - The risk of complications related to FN should be assessed individually for each patient at the beginning of each cycle. When assessing FN risk, the clinician should take into account patient-related risk factors (recommendation 1), the chemotherapy regimen and associated complications (recommendations 2 and 3) and treatment intent (recommendation 3). Prophylactic G-CSF is recommended when there is a P20% overall risk of FN. When chemotherapy regimens associated with an FN risk of 10–20%, particular attention should be given to the assessment of patient characteristics that may increase the overall risk of FN. Recommendation grade: A.
- Recommendation 5: G-CSF in patients with existing FN
  - Treatment with G-CSF for patients with solid tumors and malignant lymphoma and ongoing FN is indicated only in special situations. These are limited to those patients who are not responding to appropriate antibiotic management and who are developing life-threatening infectious complications (such as severe sepsis or septic shock). Recommendation grade: B.
- Recommendation 6: Choice of formulation
  - Filgrastim, lenograstim and pegfilgrastim have clinical efficacy and we recommend the use of any of these agents, according to current administration guidelines, to prevent FN and FN-related complications, where indicated. Filgrastim biosimilars are now also a treatment option in Europe. Recommendation grade: A.

U.S. Food and Drug Administration (FDA)

This section is to be used for informational purposes only. FDA approval alone is not a basis for coverage.

Fulphila® (pegfilgrastim-jmdb) is a leukocyte growth factor indicated to decrease the incidence of infection, as manifested by febrile neutropenia, in patients with nonmyeloid malignancies receiving myelosuppressive anti-cancer drugs associated with a clinically significant incidence of febrile neutropenia.[44]

Fylnetra® (pegfilgrastim-pbbk) is a leukocyte growth factor indicated to decrease the incidence of infection, as manifested by febrile neutropenia, in patients with non-myeloid malignancies receiving myelosuppressive anti-cancer drugs associated with a clinically significant incidence of febrile neutropenia.[52]

Granix® (tbo-filgrastim) is a leukocyte growth factor indicated for reduction in the duration of severe neutropenia in patients with nonmyeloid malignancies receiving myelosuppressive anti-cancer drugs associated with a clinically significant incidence of febrile neutropenia.[39]

Leukine® (sargramostim) is a recombinant human granulocyte-macrophage colony stimulating factor indicated for use following induction chemotherapy in older adult patients with acute myelogenous leukemia (AML) to shorten time to neutrophil recovery and to reduce the incidence of severe and life-threatening infection and infections resulting in death; the mobilization of hematopoietic progenitor cells into peripheral blood for collection by leukapheresis; the acceleration of myeloid recovery in patients with non-Hodgkin's lymphoma (NHL), acute lymphoblastic leukemia (all) and Hodgkin's disease undergoing autologous bone marrow transplantation (BMT); the acceleration of myeloid recovery in patients undergoing allogenic BMT from HLA-matched related donors; for patients who have undergone allogeneic or autologous BMT in whom engraftment is delayed or has failed; and to increase survival in adult and pediatric patients from birth to 17 years of age acutely exposed to myelosuppressive doses of radiation (Hematopoietic Syndrome of Acute Radiation Syndrome).[3]

Neulasta® (pegfilgrastim) is a leukocyte growth factor indicated to decrease the incidence of infection, as manifested by febrile neutropenia, in patients with nonmyeloid malignancies receiving myelosuppressive anti-cancer drugs associated with a clinically significant incidence of febrile neutropenia; and to increase survival in patients acutely exposed to myelosuppressive doses of radiation (Hematopoietic Subsyndrome of Acute Radiation Syndrome). Neulasta® is not indicated for the mobilization of peripheral blood progenitor cells for hematopoietic stem cell transplantation.[1]

Neupogen® (filgrastim) is a leukocyte growth factor indicated to decrease the incidence of infection, as manifested by febrile neutropenia, in patients with nonmyeloid malignancies receiving myelosuppressive anti-cancer drugs associated with a significant incidence of severe neutropenia with fever; reduce the time to neutrophil recovery and the duration of fever, following induction or consolidation chemotherapy treatment of patients with AML; reduce the duration of neutropenia and neutropenia-related clinical sequelae, e.g., febrile neutropenia, in patients with nonmyeloid malignancies undergoing myeloablative chemotherapy followed by BMT; mobilize autologous hematopoietic progenitor cells into the peripheral blood for collection by leukapheresis; reduce the incidence and duration of sequelae of severe neutropenia (e.g., fever, infections, oropharyngeal ulcers) in symptomatic patients with congenital neutropenia, cyclic neutropenia or idiopathic neutropenia; and to increase survival in patients acutely exposed to myelosuppressive doses of radiation (Hematopoietic Syndrome of Acute Radiation Syndrome).[2]

Nivestym® (filgrastim-aafi) is a leukocyte growth factor indicated to decrease the incidence of infection, as manifested by febrile neutropenia, in patients with nonmyeloid malignancies receiving myelosuppressive anti-cancer drugs associated with a significant incidence of severe neutropenia with fever; reduce the time to neutrophil recovery and the duration of fever, following induction or consolidation chemotherapy treatment of patients with AML; reduce the duration of neutropenia and neutropenia-related clinical sequelae, e.g., febrile neutropenia, in patients with nonmyeloid malignancies undergoing myeloablative chemotherapy followed by BMT; mobilize autologous hematopoietic progenitor cells into the peripheral blood for collection by leukapheresis; and to reduce the incidence and duration of sequelae of severe neutropenia (e.g., fever, infections, oropharyngeal ulcers) in symptomatic patients with congenital neutropenia, cyclic neutropenia, or idiopathic neutropenia.[45]

Nyvepria™ (pegfilgrastim-apgf) is a leukocyte growth factor indicated to decrease the incidence of infection, as manifested by febrile neutropenia, in patients with nonmyeloid malignancies receiving myelosuppressive anti-cancer drugs associated with a clinically significant incidence of febrile neutropenia.[52]

Releuko® (filgrastim-ayow) is a leukocyte growth factor indicated to decrease the incidence of infection, as manifested by febrile neutropenia, in patients with nonmyeloid malignancies receiving myelosuppressive anti-cancer drugs associated with a significant incidence of severe neutropenia with fever; reduce the time to neutrophil recovery and the duration of fever, following induction or consolidation chemotherapy treatment of patients with acute myeloid leukemia (AML); reduce the duration of neutropenia and neutropenia-related clinical sequelae, e.g., febrile neutropenia, in patients with nonmyeloid malignancies undergoing myeloablative chemotherapy followed by bone marrow transplantation (BMT); reduce the incidence and duration of sequelae of severe neutropenia, (e.g., fever, infections, oropharyngeal ulcers) in symptomatic patients with congenital neutropenia, cyclic neutropenia, or idiopathic neutropenia.[51]

Rolvedon™ is a leukocyte growth factor indicated to decrease the incidence of infection, as manifested by febrile neutropenia, in adult patients with non-myeloid malignancies receiving myelosuppressive anti-cancer drugs associated with clinically significant incidence of febrile neutropenia.[54]

Stimufend® (pegfilgrastim-fpgk) is a leukocyte growth factor indicated to decrease the incidence of infection, as manifested by febrile neutropenia, in patients with non-myeloid malignancies receiving myelosuppressive anti-cancer drugs associated with a clinically significant incidence of febrile neutropenia.[53]

Udenyca® (pegfilgrastim-cbqv) is a leukocyte growth factor indicated to decrease the incidence of infection, as manifested by febrile neutropenia, in patients with nonmyeloid malignancies receiving myelosuppressive anti-cancer drugs associated with a clinically significant incidence of febrile neutropenia.

Zarxio® (filgrastim-sndz) is a leukocyte growth factor indicated to decrease the incidence of infection, as manifested by febrile neutropenia, in patients with nonmyeloid malignancies receiving myelosuppressive anti-cancer drugs associated with a significant incidence of severe neutropenia with fever; reduce the time to neutrophil recovery and the duration of fever, following induction or consolidation chemotherapy treatment of patients with AML; reduce the duration of neutropenia and neutropenia-related clinical sequelae, e.g., febrile neutropenia, in patients with nonmyeloid malignancies undergoing myeloablative chemotherapy followed by BMT; mobilize autologous hematopoietic progenitor cells into the peripheral blood for collection by leukapheresis; and to reduce the incidence and duration of sequelae of severe neutropenia (e.g., fever, infections, oropharyngeal ulcers) in symptomatic patients with congenital neutropenia, cyclic neutropenia, or idiopathic neutropenia.[40]

Ziextenzo® (pegfilgrastim-bmez) is a leukocyte growth factor indicated to decrease the incidence of infection, as manifested by febrile neutropenia, in patients with nonmyeloid malignancies receiving myelosuppressive anti-cancer drugs associated with a clinically significant incidence of febrile neutropenia.[47]

A biosimilar product is a biologic product that is approved based on demonstrating that it is highly similar to an FDA-approved biologic product, known as a reference product, and has no clinically meaningful differences in terms of safety and effectiveness from the reference product. Only minor differences in clinically inactive components are allowable in biosimilar products. The chart below highlights the white blood cell colony stimulating factor reference products and respective biosimilar product.

Reference Product	Biosimilar Product
Neulasta®	Fulphila®, Fylnetra®, Nyvepria™, Stimufend®, Udenyca®, Ziextenzo®
Neupogen®	Nivestym®, Releuko®, Zarxio®

References

1. Neulasta® [package insert]. Thousand Oaks, CA: Amgen; February 2021.
2. Neupogen® [package insert]. Thousand Oaks, CA: Amgen; February 2021.
3. Leukine® [package insert]. Bridgewater, NJ: Sanofi-Aventis; May 2018.
4. Sulkowski M. Managing the hematologic complications of interferon/ribavirin. Clinical Care Options for Hepatitis Annual Update. Milford, MA: IMedoptions, 2003:101-102.
5. Soza A, Everhart JE, Gharny MG, et al. Neutropenia during combination therapy of interferon alfa and ribavirin for chronic hepatitis C. Hepatol. 2002; 36:1273-1279.
6. Van Thiel DH, Faruki H. Combination treatment of advanced HCV associated liver disease with interferon and G-CSF. Hepatogastroenterol.1995;42:907-912.
7. Carreno V, Parra A, Navas S, Quiroga J. Granulocyte macrophage colony stimulating factors as adjuvant therapy for interferon alpha treatment of chronic hepatitis C. Cytokine. 1996; 8:318-322.
8. Shiffman M, Hofmann, Luketic VA, Sanyal AJ. Use of granulocyte macrophage colony stimulating factor alone or in combination with interferon-alpha-2b for treatment of chronic hepatitis C. J Hepatol.1998;28:382-389.
9. Farmer D, Collantes R, Makay S, et al. Filgrastim for the neutropenia associated with combination therapy in chronic hepatitis C. Gastroenterol. 2005; 128(4, Suppl2): a-725.

10. Stein DF, McKenzie SD. Peg-interferon alfa-2b and ribavirin in treatment naïve African American patients infected with HCV genotype 1. Hepatol.2003;38(4):642A.
11. Micromedex® Solutions [Internet database]. Ann Arbor, MI: Truven Health Analytics. Accessed March 8, 2018.
12. Hermans P, Rozenbaum W, Jou A, et al. Filgrastim to treat neutropenia and support myelosuppressive medication dosing in HIV infections. G-CSF 92105 Study Group. AIDS 1996; 10:1627-33.
13. Kuritzkes, DR, Parenti D, Ward DJ, et al. Filgrastim prevents severe neutropenia and reduces infective morbidity in patients with advanced HIV infection; results of a randomized, multicenter, controlled trial. AIDS 1998; 12:65-74.
14. Levine AM, Karim R, Mack W, et al. Neutropenia in human immunodeficiency virus infection: data from the women's interagency HIV study. Arch Intern Med. 2006; 166:405-410.
15. Centers for Disease Control and Prevention. Guidelines for Preventing Opportunistic Infections Among HIV-Infected Persons – 2002 Recommendations of the U.S. Public Health Service and the Infectious Disease Society of America. MMWR 2002;51(No. RR-8):1-52.
16. National Comprehensive Cancer Network (NCCN) Clinical Practice Guidelines in Oncology. Hematopoietic Growth Factors. v.1.2021. Accessed March 30, 2022.
17. Smith TJ, Bohlke K, Lyman GH, et al. Recommendations for the Use of WBC Growth Factors: American Society of Clinical Oncology Clinical Practice Guideline Update. J Clin Oncol. 2015; 33:3199-3212.
18. National Comprehensive Cancer Network (NCCN) Clinical Practice Guidelines in Oncology. Breast Cancer. v.5.2020. Accessed March 30, 2022.
19. Citron ML, Berry DA, Cirrincione C, et al. Randomized trial of dose-dense versus conventionally scheduled and sequential versus concurrent combination chemotherapy as postoperative adjuvant treatment of node-positive primary breast cancer: first report of Intergroup Trial C9741/Cancer and Leukemia Group B trial. J Clin Oncol. 2003;21(8):1431-9.
20. National Comprehensive Cancer Network (NCCN) Clinical Practice Guidelines in Oncology. Prevention and Treatment of Cancer-Related Infections. v.1.2021. Accessed March 30, 2022.
21. Benson CA, Kaplan JE, Masur H, Pau A, Holmes KK. Treating opportunistic infections among HIV-exposed and infected adults and adolescents: recommendations from CDC, the National Institutes of Health, and the Infectious Disease Society of America. MMWR Recomm Rep 2004;53(RR-15):1-118.
22. American Gastroenterological Association. Medical Position Statement on the Management of Hepatitis C. Gastroenterol 2006; 130:225-30.
23. AASLD/IDSA HCV Guidance Panel. Hepatitis C guidance: AASLD-IDSA recommendations for testing, managing, and treating adults infected with hepatitis C virus. Hepatology. 2015;62(3):932-54.
24. Hudis CA, Schmitz. Dose-dense chemotherapy in breast cancer and lymphoma. Seminar in Oncol. 2004;31(Suppl 8):19-23.
25. Nemunaitis J, Rosenfeld CS, Ash R, et al. Phase III Randomized, double-blind placebo-controlled trial of rhGM-CSF following allogenic bone marrow transplantation. Bone Marrow Transplant. 1995; 72:949-54.
26. Nemunaitis J, Buckner CD, Appelbaum FR et al. Phase I/II trial of recombinant human granulocyte-macrophage colony-stimulating factor following allogeneic bone marrow transplantation. Blood. 1991; 77:2065-71.
27. Nemunaitis J, Rabinowe SN, Singer JW et al. Recombinant granulocyte-macrophage colony-stimulating factor after autologous bone marrow transplantation for lymphoid cancer. N Engl J Med. 1991; 324:1773-8.
28. Rabinowe SN, Neuberg D, Bierman PJ et al. Long-term follow-up of a phase III study of recombinant human granulocyte-macrophage colony-stimulating factor after autologous bone marrow transplantation for lymphoid malignancies. Blood. 1993; 81:1903-8.
29. Grant SM, Heel RC. Recombinant granulocyte-macrophage colony-stimulating factor (rGM-CSF): a review of its pharmacological properties and prospective role in the management of myelosuppression. Drugs 1992; 43:516-60.
30. McEvoy GK, ed. AHFS Drug Information 2006. Bethesda, MD: American Society of Health-System Pharmacists; 2006.
31. Nemunaitis J, Singer JW, Buckner CD et al. Use of recombinant human granulocyte-macrophage colony-stimulating factor in graft failure after bone marrow transplantation. Blood. 1990; 76:245-53.

32. Rowe JN, Andersen JW, Mazza JJ et al. A randomized placebo-controlled phase III study of granulocyte-macrophage colony-stimulating factor in adult patients (> 55 to 70 years of age) with acute myelogenous leukemia: a study of the Eastern Cooperative Oncology Group (E1490). Blood. 1995; 86:457-62.
33. Vogel CL, Wojtukiewicz MZ, Carroll RR, et al. First and subsequent cycle use of pegfilgrastim prevents febrile neutropenia in patients with breast cancer: a multicenter, double-blind, placebo-controlled phase III study. J Clin Oncol. 2005;23(6):1178-84.
34. Kuderer NM, Dale DC, Crawford J, Lyman GH. Impact of primary prophylaxis with granulocyte colony-stimulating factor on febrile neutropenia and mortality in adult cancer patients receiving chemotherapy: a systematic review. J Clin Oncol. 2007;25(21):3158-67.
35. National Comprehensive Cancer Network (NCCN) Clinical Practice Guidelines in Oncology. Acute Myeloid Leukemia. v.2.2019. Accessed March 8, 2019.
36. Centers for Disease Control and Prevention. Guidelines for Prevention and Treatment of Opportunistic Infections in HIV-Infected Adults and Adolescents: recommendations from CDC, the National Institutes of Health, and the Infectious Diseases Society of America. MMWR 2009;58(No. RR-4):1-216.
37. Granix® [package insert]. North Wales, PA: Teva Pharmaceutical Industries Ltd.; March 2019.
38. Zarxio® [package insert]. Princeton, NJ: Sandoz Inc.; August 2019.
39. Smith TJ, et al. Recommendations for the Use of WBC Growth Factors: American Society of Clinical Oncology Clinical Practice Guideline Update. Journal of Clin Oncol. 2015;33(28):3199-3212.
40. Neutropenia (low neutrophil count). Mayo Clinic. Available at: http://www.mayoclinic.org/symptoms/neutropenia/basics/definition/sym-20050854. Accessed March 8, 2019.
41. Aapro MS, Bohlius J, Cameron DA, et al. 2010 update of EORTC guidelines for the use of granulocyte-colony stimulating factor to reduce the incidence of chemotherapy-induced febrile neutropenia in adult patients with lymphoproliferative disorders and solid tumors. Eur Journal of Cancer. 2011; 47:8-32.
42. Fulphila® [package insert]. Zurich, Switzerland: Mylan GmbH; March 2021.
43. Nivestym® [package insert]. Lake Forest, IL; Hospira, Inc.; July 2018.
44. Udenyca® [package insert]. Redwood City, CA; Coherus BioSciences, Inc.; September 2019.
45. Ziextenzo® [package insert]. Princeton, NJ; Sandoz, Inc.; March 2021.
46. Taplitz RA, Kennedy EB, Bow EJ, et al. Outpatient Management of Fever and Neutropenia in Adults Treated for Malignancy: American Society of Clinical Oncology and Infectious Diseases Society of America Clinical Practice Guideline Update. J Clin Oncol. 2018;36(14):1443–1453. doi:10.1200/JCO.2017.77.6211.
47. Freifeld AG, Bow EJ, Sepkowitz KA, et al. Clinical practice guideline for the use of antimicrobial agents in neutropenic patients with cancer: 2010 Update by the Infectious Diseases Society of America. Clin Infect Dis. 2011;52(4):427–431. doi:10.1093/cid/ciq147.
48. American Academy of Allergy, Asthma, and Immunology. Neutropenia Definition. Accessed March 3, 2020.
49. National Cancer Institute. Cancer Therapy Evaluation Program: Common Toxicity Criteria Manual (Version 2.0). Accessed March 3, 2020.
50. Nyvepria™ [package inset]. New York, NY: Pfizer Inc.; April 2021.
51. Releuko® [package insert]. Piscataway, NJ: Kashiv BioSciences LLC.; February 2022.
52. Fylnetra® [package insert]. Piscataway, NJ: Kashiv BioSciences LLC.; May 2022.
53. Stimufend® [package insert]. Lake Zurich, IL: Fresenius Kabi USA LLC; September 2022.
54. Rolvedon™ [package insert]. Irvine, CA: Spectrum Pharmaceuticals, Inc.; September 2022.

Policy History/Revision Information

Date	Summary of Changes

01/01/2024	**Template Update**
	• Created state-specific policy version
	Application
	• Modified language to indicate this Medical Benefit Drug Policy only applies to the state of Ohio; any requests for services that are stated as unproven or services for which there is a coverage or quantity limit will be evaluated for medical necessity using *Ohio Administrative Code 5160-1-01*
	Coverage Rationale
	• Replaced language indicating:
	  ○ "This policy refers to the [listed] white blood cell colony stimulating factors (CSFs)" with "this policy refers to the [listed] white blood cell colony stimulating factors (CSFs) *for non-oncology conditions*"
	  ○ "White blood cell colony stimulating factors are proven for the [listed] indications" with "white blood cell colony stimulating factors are proven *and medically necessary* for the [listed] *non-oncology* indications"
	• Added instruction to refer to the Medical Benefit Drug Policy titled *Oncology Medication Clinical Coverage (for Ohio Only)* for updated information based on the National Comprehensive Cancer Network (NCCN) Drugs & Biologics Compendium® (NCCN Compendium®) for oncology indications
	• Removed language indicating any U.S. Food and Drug Administration (FDA) approved white blood cell colony stimulating factor product not listed by name in this policy will be considered non-preferred until reviewed by UnitedHealthcare
	• Removed language pertaining to:
	  ○ Preferred products
	  ○ Oncology indications
	Applicable Codes
	• Added HCPCS codes J1449, Q5127, and Q5130
	• Removed HCPCS code C9399
	• Revised description for HCPCS codes Q5108, Q5110, Q5111, Q5120, and Q5122
	Supporting Information
	• Archived previous policy version CS2022D0061AA

Instructions for Use

This Medical Benefit Drug Policy provides assistance in interpreting UnitedHealthcare standard benefit plans. When deciding coverage, the federal, state (Ohio Administrative Code [OAC]), or contractual requirements for benefit plan coverage must be referenced as the terms of the federal, state (OAC), or contractual requirements for benefit plan coverage may differ from the standard benefit plan. In the event of a conflict, the federal, state (OAC), or contractual requirements for benefit plan coverage govern. Before using this policy, please check the federal, state (OAC), or contractual requirements for benefit plan coverage. UnitedHealthcare reserves the right to modify its Policies and Guidelines as necessary. This Medical Benefit Drug Policy is provided for informational purposes. It does not constitute medical advice.

UnitedHealthcare may also use tools developed by third parties, such as the InterQual® criteria, to assist us in administering health benefits. The UnitedHealthcare Medical Benefit Drug Policies are intended to be used in connection with the independent professional medical judgment of a qualified health care provider and do not constitute the practice of medicine or medical advice.