Colony-Stimulating Factors (CSFs)

Policy Number: MC/PC 008
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Instructions for Use

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Related Policies

- Oncology Medication Clinical Coverage

Coverage Rationale

<Please refer to Medical Benefit Plan Sponsor for preferred medications. Preferred products may be updated and therefore subject to change>.

This policy refers to the following white blood cell colony stimulating factors (CSFs):

- Long-acting pegfilgrastim agents:
  - Fulphila® (pegfilgrastim-jmdb)
  - Fylnetra® (pegfilgrastim-pbbk)
  - Neulasta® (pegfilgrastim)
  - Nyvepria™ (pegfilgrastim-apgf)
  - Rolvedon™ (eflapegrastim-xnst)
  - Udenyca® (pegfilgrastim-cbqv)
  - Stimufend® (pegfilgrastim-fpgk)
  - Ziextenzo® (pegfilgrastim-bmez)
- Short-acting filgrastim agents:
  - Granix® (tbo-filgrastim)
  - Leukine® (sargramostim)
  - Neupogen® (filgrastim)
  - Nivestym® (filgrastim-aafi)
  - Nypozi™ (filgrastim-txid)
  - Releuko® (filgrastim-ayow)
  - Zarxio® (filgrastim-sndz)

Acute Myeloid Leukemia (AML) Induction or Consolidation Therapy (Le ozi Releuko, or Zarxio)

For initial coverage of Leukine for Acute Myeloid Leukemia (AML) Induction or Consolidation Therapy, the following will be required:

- Diagnosis of acute myeloid leukemia (AML) **and**
- Patient has completed induction or consolidation chemotherapy **and**
- Patient is 55 years of age or older **and**
- Prescribed by or in consultation with a hematologist/oncologist

For initial coverage of Neupogen, Nivestym, Nypozi, Releuko, or Zarxio for Acute Myeloid Leukemia (AML) Induction or Consolidation Therapy, the following will be required:

- Diagnosis of acute myeloid leukemia (AML) **and**
- Patient has completed induction or consolidation chemotherapy **and**
- Prescribed by or in consultation with a hematologist/oncologist

Acute Radiation Syndrome (ARS) (Fulphila (Off-Label), Fylnetra (Off-label), Granix (Off-Label), Leukine, Neulasta/Neulasta Onpro, Neupogen, Nivestym (Off-Label), Nypozi, Nyvepria (Off-Label), Releuko (Off-Label), Stimufend (Off-label), Udenyca/Udenyca Onbody, Zarxio (Off-Label), or Ziextenzo (Off-Label))

For initial coverage of Fulphila (Off-Label), Fylnetra (Off-label), Granix (Off-Label), Leukine, Neulasta/Neulasta Onpro, Neupogen, Nivestym (Off-Label), Nypozi, Nyvepria (Off-Label), Releuko (Off-Label), Stimufend (Off-label), Udenyca**/**Udenyca Onbody, Zarxio (Off-Label), or Ziextenzo (Off-Label) for Acute Radiation Syndrome (ARS), the following will be required:

- Patient was/will be acutely exposed to myelosuppressive doses of radiation **and**
- Prescribed by or in consultation with a hematologist/oncologist

Bone Marrow/Stem Cell Transplant (Leukine, Neupogen, Nivestym, Nypozi, Releuko, or Zarxio)

For initial coverage of Leukine, Neupogen, Nivestym, Nypozi, Releuko, or Zarxio for Bone Marrow/Stem Cell Transplant, the following will be required:

- One of the following:
    - Patient has non-myeloid malignancies undergoing myeloablative chemotherapy followed by autologous or allogeneic bone marrow transplant (BMT) **or**
    - Used for mobilization of hematopoietic progenitor cells into the peripheral blood for collection by leukapheresis **or**
    - Patient has had a peripheral stem cell transplant (PSCT) and has received myeloablative chemotherapy **and**
- Prescribed by or in consultation with a hematologist/oncologist **and**
- Patient is 2 years of age or older (applies to Leukine only)

Febrile Neutropenia Prophylaxis (Fulphila, Fylnetra, Granix, Leukine (Off-Label), Neulasta/Neulasta Onpro, Releuko, Neupogen, Nivestym, Nypozi, Nyvepria, Rolvedon, Stimufend, Udenyca/Udenyca Onbody, Zarxio, or Ziextenzo)

For initial coverage of Fulphila, Fylnetra, Granix, Leukine (Off-Label), Neulasta/Neulasta Onpro, Releuko, Neupogen, Nivestym, Nypozi, Nyvepria, Rolvedon, Stimufend, Udenyca/Udenyca Onbody, Zarxio, or Ziextenzo Febrile Neutropenia Prophylaxis, the following will be required:

- Patient will be receiving prophylaxis for febrile neutropenia (FN) due t
    - Patient is receiving National Cancer Institute's Breast Intergrou apy protocol for primary breast cancer (see Table 1 in Background section) **or**
    - Patient is receiving a dose-dense chemotherapy regimen for which the incidence of FN is unknown **or**
    - One of the following:
        - Patient is receiving chemotherapy regimen(s) associated with greater than 20% incidence of FN (see Table 2 in Background section) **or**
        - Both of the following:
            - Patient is receiving chemotherapy regimen(s) associated with 10-20% incidence of FN (see Table 3 in Background section) **and**
            - Patient has one or more risk factors associated with chemotherapy induced infection, FN, or neutropenia **or**
    - Both of the following:
        - Patient is receiving myelosuppressive anticancer drugs associated with neutropenia (see Table 4 in Background section) **and**
        - Patient has a history of FN or dose-limiting event during a previous course of chemotherapy (secondary prophylaxis) **and**
- Prescribed by or in consultation with a hematologist/oncologist

Note: Some patients may require use of a short-acting GCSF in the presence of scheduled treatment with a long-acting GCSF for prevention of febrile neutropenia in situations where neutropenia is present prior to the next dose of chemotherapy. For this situation, the plan may provide coverage for a long-acting GCSF and a short-acting GCSF.

Treatment of High-Risk Febrile Neutropenia (Off-label) (Fulphila, Fylnetra, Granix, Leukine, Neulasta/Neulasta Onpro, Neupogen, Nivestym, Nypozi, Nyvepria, Releuko, Stimufend, Udenyca/Udenyca Onbody, Zarxio, or Ziextenzo)

For initial coverage of Fulphila, Fylnetra, Granix, Leukine, Neulasta/Neulasta Onpro, Neupogen, Nivestym, Nypozi, Nyvepria, Releuko, Stimufend, Udenyca/Udenyca Onbody, Zarxio, or Ziextenzo for Treatment of High-Risk Febrile Neutropenia (off-label), the following will be required:

- Patient has received or is receiving myelosuppressive anticancer drugs associated with neutropenia (see Table 4 in Background section) **and**
- Diagnosis of febrile neutropenia **and**
- Patient is at high risk for infection-associated complications **and**
- Prescribed by or in consultation with a hematologist/oncologist

Note: Some patients may require use of a short-acting GCSF in the presence of scheduled treatment with a long-acting GCSF for prevention of febrile neutropenia in situations where neutropenia is present prior to the next dose of chemotherapy. For this situation, the plan may provide coverage for a long-acting GCSF and a short-acting GCSF.

Hepatitis-C Treatment Related Neutropenia (Off-Label) (Neupogen, Nivestym, Nypozi, Releuko, Zarxio)

For initial coverage of Neupogen, Nivestym, Nypozi, Releuko, Zarxio for Hepatitis-C Treatment Related Neutropenia (Off-Label), the following will be required:

- One of the following:
    - All of the following:

- Patient is infected with Hepatitis C virus **and**
- Patient is undergoing treatment with Peg-Intron (pegi (peginterferon alfa-2a) **and**
- Patient has neutropenia (absolute neutrophil count [ANC] less than or equal to 500 cells/mm3) after dose reduction of Peg-Intron or Pegasys **or**

  - Both of the following:
    - Patient is experiencing interferon-induced neutropenia (ANC less than or equal to 500 cells/mm3) due to treatment with Peg-Intron (peginterferon alfa-2b) or Pegasys (peginterferon alfa-2a) **and**
    - One of the following:
      - Patient with Human Immunodeficiency Virus (HIV) co-infection **or**
      - Status post liver transplant **or**
      - Patient with established cirrhosis **and**

- Prescribed by or in consultation with one of the following:
  - Hematologist/oncologist
  - Infectious disease specialist
  - Hepatologist
  - Gastroenterologist

Human Immunodeficiency Virus (HIV)-Related Neutropenia (Off-Label) (Leukine, Neupogen, Nivestym, Nypozi, Releuko, or Zarxio)

For initial coverage of Leukine, Neupogen, Nivestym, Nypozi, Releuko, or Zarxio for Human Immunodeficiency Virus (HIV)-Related Neutropenia (Off-Label), the following will be required:

- Patient is infected with HIV virus **and**
- ANC less than or equal to 1,000 (cells/mm3) **and**
- Prescribed by or in consultation with one of the following:
  - Hematologist/oncologist
  - Infectious disease specialist

Severe Chronic Neutropenia (SCN) (Neupogen, Nivestym, Nypozi, Releuko, or Zarxio)

For initial coverage of Neupogen, Nivestym, Nypozi, Releuko, or Zarxio for Severe Chronic Neutropenia (SCN), the following will be required:

- For patients with severe chronic neutropenia (SCN) (i.e., congenital, cyclic, and idiopathic neutropenias with chronic absolute neutrophil count [ANC] less than or equal to 500 cells/mm^3) **and**
- Prescribed by or in consultation with a hematologist/oncologist

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 the member specific benefit plan document 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

HCPCS Code	Description
J1449	Injection, eflapegrastim-xnst, 0.1mg
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), 0.5 mg
Q5130	Injection, pegfilgrastim-pbbk, (Fylnetra), biosimilar, 0.5 mg
Q5148	Injection, filgrastim-txid (Nypozi), biosimilar, 1 microgram

ICD-10 Code	Description
B20	Human immunodeficiency virus [HIV] disease
C00.0-C41.9, C4A.0-C60.9, C62.00-C91.92, C92.30- C96.9	Malignant neoplasms
D46.0-D46.9	Myelodysplastic syndromes
D61.0-D61.9	Aplastic anemia
D70.0-D70.9	Neutropenia
E40-E46	Malnutrition
T36.0-T50.996	Poisoning by, adverse effect of and underdosing of antineoplastic and immunosuppressive drugs, systemic antibiotics, underdosing of other systemic anti-infectives and antiparasitics, hormones and their synthetic substitutes and antagonists, not elsewhere classified, nonopioid analgesics, antipyretics and antirheumatics, narcotics and psychodysleptics (hallucinogens), anesthetics and therapeutic gases, antiepileptic, sedative-hypotonic and antiparkinsonism drugs, primarily affecting the autonomic nervous system, primarily systemic and hematological agents, not elsewhere classified, primarily affecting the cardiovascular system, primarily affecting the gastrointestinal system, primarily acting on smooth and skeletal muscles and the respiratory system, topical agents primarily affecting skin and mucous membrane and by ophthalmological, otorhinorlaryngological and dental drugs and diuretics and other and unspecified drugs, medicaments and biological substances
T66.xxxA-T66.xxxS	Radiation sickness, unspecified
T80.82XA-T80.89XS	Complication of immune effector cellular therapy (CAR-T)
T86.00-T86.02	Unspecified complication of bone marrow transplant, rejection or failure
T86.03	Bone marrow transplant infection
T86.09	Other complications of bone marrow transplant

ICD-10 Code	Description
W88.1XXA-W88.8XXS	Exposure to radioactive isotopes or other ionizing radiatio
Z52.011	Autologous donor, stem cells
Z52.3	Bone marrow donor
Z94.6	Bone transplant status
Z94.81	Bone marrow transplant status [except post allogeneic transplant support in myeloid malignancies]
Z94.84	Stem cells transplant status [except post allogeneic transplant support in myeloid malignancies]

Background

Neutrophils are a key part of the body's defense system against infection. Cytotoxic chemotherapy can cause severe and sometimes prolonged neutropenia, which may lead to fever and/or potentially fatal infection. Although definitions vary, severe neutropenia has been defined as an absolute neutrophil count (ANC) < 500 cells/µL or an ANC that is expected to decrease to this level within 48 hours. Profound neutropenia is defined as an ANC < 100 cells/µL (Larson *2024*).

Colony-stimulating factors (CSFs) are naturally occurring glycoprotein cytokines that regulate the production, differentiation, survival, and activation of hematopoietic cells and are one of the primary groups of immunomodulators (*Page et al 2020*). Granulocyte CSF (G-CSF) and granulocyte-macrophage CSF (GM-CSF) play important roles in this system. Endogenous G-CSF predominantly affects the proliferation, differentiation, and activation of progenitor cells of the neutrophil-granulocyte line. It also enhances certain functions of mature neutrophils, such as phagocytosis, chemotaxis, and antibody-dependent cellular toxicity (*Lexicomp 2025*). Endogenous GM-CSF is predominantly found in T lymphocytes, monocytes-macrophages, fibroblasts, and endothelial cells (*Page et al 2020*). In addition to increasing the production of neutrophils, GM-CSF increases other white blood cells including monocytes, macrophages, and eosinophils in the bone marrow and promotes their function.

Clinical Evidence

To decrease the incidence of infection/febrile neutropenia in patients receiving myelosuppressive chemotherapy:

Two randomized, double-blind, multicenter trials compared sargramostim and filgrastim: The first trial (N = 144) primarily evaluated safety and tolerability. It demonstrated that with the exception of a higher incidence of grade 1 fever (37.1 to 38°C) with sargramostim compared to filgrastim (48% vs 26%, respectively; p = 0.01), there were no statistically significant differences in the incidence or severity of local or systemic adverse events potentially related to CSFs. Although the study was not designed to directly evaluate efficacy, there were also no statistically significant differences between treatment groups in total days of growth factor therapy, days of hospitalization, or days of intravenous (IV) antibiotic therapy. Both agents were well tolerated, and there were no clinically significant differences between treatments (Beveridge et al 1997). Another trial (N = 181) compared filgrastim and sargramostim in patients with chemotherapy-induced neutropenia (ANC ≤ 500 cells/ μ L). Patients were given daily subcutaneous (SC) injections of either agent until ANC levels reached ≥ 1500 cells/ μ L. There was no significant difference among the treatment groups in the mean number of days to reach an ANC of 500 cells/ μ L (3.6 vs 3.3 days, respectively; p = 0.32); however, the mean number of days to reach an ANC of 1000 and 1500 cells/ μ L was significantly shorter in the filgrastim group (4.5 and 4.6 days, respectively) compared to the sargramostim group (5.1 and 5.7 days, respectively; p = 0.009 and p = 0.0001, respectively) (Beveridge et al 1998).

Three randomized, multicenter trials compared filgrastim to pegfilgrastim: A d
filgrastim 5 µg/kg/day to a single dose of pegfilgrastim 100 µg/kg in patients w
demonstrated that in cycle 1, there was no significant difference in the duration of grade 4 neutropenia (the primary endpoint) between the filgrastim group (1.8 days) and the pegfilgrastim group (1.7 days). However, in subsequent cycles, the duration of grade 4 neutropenia was significantly longer in the filgrastim group compared to the pegfilgrastim group (cycle 2, 1.1 vs 0.7 days; p = 0.001; cycle 3, 1.2 vs 0.6 days; p ≤ 0.001; and cycle 4, 1.3 vs 0.9 days; p = 0.019). Febrile neutropenia occurred at least once in 18% of patients in the filgrastim group and 9% in the pegfilgrastim group (p = 0.029). The depth of ANC nadir and the mean time to ANC recovery did not differ significantly between groups (Holmes et al 2002). Another double-blind trial (N = 157) compared the use of filgrastim 5 µg/kg/day to the use of a single dose of pegfilgrastim 6 mg. Results demonstrated no significant differences in the mean duration of grade 4 neutropenia in any of the 4 cycles. Similarly, no significant differences were observed in the incidence of febrile neutropenia or the median time to neutrophil recovery (Green et al 2003). An open-label, crossover, randomized, Phase 3 trial (N = 337) compared the use of a single dose of pegfilgrastim 100 µg/kg to the use of filgrastim 5 µg/kg/day in adults receiving chemotherapy for solid tumors. The study included 2 cycles of chemotherapy, in which patients received either pegfilgrastim followed by filgrastim or filgrastim followed by pegfilgrastim. Results demonstrated no differences in the percentage of patients developing grade 4 neutropenia, grade 3/4 neutropenia, or febrile neutropenia; or in the percentage of patients requiring antibiotics. ANC recovery was slightly faster with pegfilgrastim support compared to filgrastim support (Shi et al 2013).

One randomized, double-blind, multicenter, Phase 3 trial (N = 218) compared filgrastim-sndz to filgrastim in women with breast cancer treated with myelosuppressive chemotherapy (docetaxel, doxorubicin, and cyclophosphamide). Patients received study drug at 5 µg/kg SC daily starting on day 2 of each chemotherapy cycle until the ANC recovered to 10 × 109 cells/L after nadir, or up to 14 days. Patients received 6 cycles of filgrastim-sndz; 6 cycles of filgrastim; alternating cycles (6 total) of each drug starting with filgrastim-sndz; or alternating cycles (6 total) of each drug starting with filgrastim. The primary endpoint, duration of severe neutropenia in the first cycle for the per-protocol set, was 1.17 ± 1.11 days with filgrastim-sndz and 1.20 ± 1.02 days with filgrastim. The mean difference was 0.04 days, demonstrating non-inferiority of filgrastim-sndz. Results were similar with the full-analysis set. Hospitalization due to febrile neutropenia, incidence of infections, depth and time of ANC nadir and time to ANC recovery in cycle 1 and across all cycles were all similar between the biosimilar and reference groups. Alternating between the biosimilar and the reference showed no clinically meaningful differences regarding efficacy and safety. The immunogenic response to filgrastim assessed under the conditions of repeated alternating and nonalternating of products also showed no increased risk of developing anti-drug antibodies, which is consistent with the low immunogenic potential of filgrastim (Blackwell et al 2015).

Two randomized, double-blind, multicenter, Phase 3 trials (PROTECT-1 and PROTECT-2) compared pegfilgrastim-bmez to pegfilgrastim in women with breast cancer treated with myelosuppressive chemotherapy (docetaxel, doxorubicin, and cyclophosphamide). Patients received 6 mg of study drug SC on day 2 of each chemotherapy cycle. Chemotherapy was given for at least 6 cycles. In PROTECT-1, the mean duration of severe neutropenia in the first cycle of chemotherapy was similar between groups (0.75 ± 0.88 days with pegfilgrastim-bmez vs 0.83 ± 0.90 days with pegfilgrastim; difference, 0.07 days). No clinically meaningful differences were observed between the 2 products. Similarly, in PROTECT-2, the mean duration of neutropenia in the first cycle of chemotherapy was 1.36 ± 1.13 days with pegfilgrastim-bmez and 1.19 ± 0.98 days with pegfilgrastim (difference, -0.16 days). No clinically significant differences were seen regarding efficacy and safety (Harbeck et al 2016, Blackwell et al 2016).

A placebo-controlled trial (N = 252) evaluated the use of pegfilgrastim given every 2 weeks in patients with locally advanced or metastatic colorectal adenocarcinoma undergoing treatment with a combination chemotherapy regimen given every 2 weeks. This represents slightly more frequent dosing than most previous studies. Grade 3/4 neutropenia occurred in 43% of the placebo group and 13% of the pegfilgrastim group (p < 0.0001). The incidence of treatment-related adverse effects was higher in the pegfilgrastim group (19%) compared to the placebo group (12%). There were no significant differences between groups in achievement of partial or complete response (Hecht et al 2010).

A randomized, open-label, Phase 3 trial evaluated the use of pegfilgrastim as p chemotherapy (experimental arm) compared to prophylaxis for all 6 cycles of c) in patients receiving chemotherapy for breast cancer. The percentages of patients who developed febrile neutropenia were 36% and 10% in the experimental and standard treatment arms, respectively (odds ratio [OR], 5.5; 95% confidence interval [CI], 2.3 to 12.6). The authors concluded that primary pegfilgrastim prophylaxis should not be limited to the first 2 chemotherapy cycles (Aarts et al 2013).

A randomized, open-label trial (N = 20) compared IV to SC administration of filgrastim in inpatients receiving chemotherapy for acute myelogenous leukemia (AML), acute lymphocytic leukemia (ALL), lymphoma, multiple myeloma, or allogeneic or autologous hematopoietic stem cell transplantation. The primary endpoint, mean time to a stable neutrophil count > 500 cells/µL, was longer with IV administration (7.9 days; 95% CI, 6.6 to 9.1) than with SC administration (5.4 days; 95% CI, 4.6 to 6.2) (p = 0.001). The authors concluded that the SC route should be preferred (Paul et al 2014).

Three randomized, double-blind, placebo-controlled studies evaluated the use of CSFs, either filgrastim or sargramostim, in patients with AML: One study (N = 521) in patients with AML demonstrated that filgrastim reduced the duration of neutropenia (25 vs 20 days; p = 0.0001), duration of fever (8.5 vs 7 days; p = 0.009), and duration of IV antibiotic use (18.5 vs 15 days; p = 0.0001) after induction chemotherapy and led to similar reductions during consolidation chemotherapy. There was no significant difference in placebo-treated and filgrastim-treated patients in complete response rate, disease-free survival, or overall survival. This is important because there are theoretical concerns about the use of myeloid growth factors in AML due to the possibility of stimulating the growth of myeloid leukemia (Heil et al 1997). Another study (N = 388) demonstrated no significant difference between sargramostim and placebo with respect to rates of complete remission or survival. The median duration of neutropenia was significantly shorter in the sargramostim group (15 days) compared to the placebo group (17 days) (p = 0.02) (Stone et al 1995). A study (N = 124) demonstrated a reduced time to neutrophil recovery to ≥ 500 cells/µL in the sargramostim group (13 days) compared to the placebo group (17 days) (p = 0.001). There was also a significantly reduced time to neutrophil recovery to ≥ 1000 cells/µL in the sargramostim group (14 days) compared to the placebo group (21 days) (p = 0.001). There were no differences between groups for treatment-related mortality or toxicities (Rowe et al 1995).

Three randomized, open-label clinical trials compared the use of filgrastim to tbo-filgrastim: The registrational trial for Granix (N = 348) evaluated 3 treatments in patients with high-risk breast cancer: one group received tbo-filgrastim 5 µg/kg/day for 4 cycles, one received filgrastim 5 µg/kg/day for 4 cycles and one received placebo for 1 cycle, followed by tbo-filgrastim 5 µg/kg/day for cycles 2 through 4. Results demonstrated that the mean duration of severe neutropenia was significantly reduced with tbo-filgrastim and with filgrastim compared to placebo (1.1 vs 3.8 days; p < 0.0001). Outcomes, including duration of severe neutropenia, incidence of febrile neutropenia, and time to ANC recovery, were not significantly different between the filgrastim and tbo-filgrastim groups. A trial (N = 92) in patients with non-Hodgkin's lymphoma compared the use of tbo-filgrastim 5 µg/kg/day for 4 cycles to the use of filgrastim 5 µg/kg/day for 1 cycle followed by tbo-filgrastim 5 µg/kg/day for 3 cycles. In cycle 1, the duration of severe neutropenia was 0.5 days in the tbo-filgrastim group and 0.9 days in the filgrastim group (p value not reported). The time to ANC recovery was 6 days in the tbo-filgrastim group and 6.7 days in the filgrastim group (p values not reported). The adverse event profile was similar between the 2 groups (Engert et al 2009). A trial (N = 240) with the same design was performed in patients with lung cancer. In this trial, the duration of severe neutropenia was 0.5 days in the tbo-filgrastim group and 0.3 days in the filgrastim group (p value not reported). The time to ANC recovery was 6.3 days in the tbo-filgrastim group and 4.5 days in the filgrastim group (p values not reported) (Gatzemeier et al 2009).

Eflapegrastim-xnst was compared with pegfilgrastim in 2 Phase 3 non-inferiority clinical trials (ADVANCE and RECOVER) (Cobb et al 2020; Schwartzberg et al 2020). Both trials were conducted in patients with early-stage breast cancer undergoing chemotherapy with docetaxel + cyclophosphamide on day 1 of 4 treatment cycles. Eflapegrastim-xnst or pegfilgrastim were administered on day 2 of each cycle. In the open-label ADVANCE trial, patients were randomized to eflapegrastim-xnst 13.2 mg (n = 196) or pegfilgrastim 6 mg (n = 210) (Schwartzberg et al 2020). The duration of severe neutropenia with eflapegrastim-xnst was non-inferior to pegfilgrastim with a mean difference of -0.148 days (p <

0.0001). Other endpoints, such as mean time to ANC recovery, mean depth of neutropenia, incidence of neutropenic complications, and safety were similar between groups. This was also an open-label, randomized trial comparing eflapegrastim-xnst 13.2 mg (n = 118) to pegfilgrastim 6 mg (n = 119) administered 1 day after chemotherapy (Cobb et al 2020). The duration of severe neutropenia with eflapegrastim-xnst was non-inferior to pegfilgrastim with a mean difference of -0.074 days (p < 0.0001). Other endpoints, such as mean time to ANC recovery, mean depth of ANC nadir, incidence of febrile neutropenia, incidence of neutropenic complications, and safety were similar between groups.

A meta-analysis of 20 randomized controlled trials in patients with solid tumors or lymphoma demonstrated reductions in the risk of developing febrile neutropenia in patients treated with filgrastim vs placebo (relative risk [RR], 0.57; 95% CI, 0.48 to 0.69) and patients treated with pegfilgrastim vs placebo (RR, 0.3; 95% CI, 0.14 to 0.65). The incidence of febrile neutropenia was lower for patients treated with pegfilgrastim compared to those treated with filgrastim (RR, 0.66; 95% CI, 0.44 to 0.98) (Cooper et al 2011).

A systematic review evaluated the efficacy and safety of neutropenia prophylaxis with long-acting G-CSFs in cancer patients receiving chemotherapy. A total of 41 trials were included; of these, 33 evaluated pegfilgrastim (5 randomized trials, 11 other clinical trials, and 17 observational studies). Although results were not uniform across all studies, the majority supported the use of pegfilgrastim compared to daily G-CSF, no G-CSF, placebo, or no upfront pegfilgrastim for outcomes including a lower incidence of chemotherapy-induced neutropenia (4 of 7 studies), febrile neutropenia (11 of 14 studies), chemotherapy dose delays and reductions (6 of 8 studies), antibiotic use (6 of 7 studies) and neutropenia-related hospitalizations (9 of 13 studies). The investigators noted a greater degree of reduction in chemotherapy-induced neutropenia incidence with pegfilgrastim vs filgrastim in the observational studies than in the randomized trials and suggested that this could be due to a shorter duration of G-CSF use in practice (5 to 6 days) than in clinical trials (10 to 11 days). The incidence of G-CSF-related adverse events was similar between pegfilgrastim and filgrastim (Pfeil et al 2015).

A meta-analysis of 30 randomized controlled trials evaluated the impact of primary prophylaxis with G-CSF products on febrile neutropenia during myelosuppressive chemotherapy for solid tumors or non-Hodgkin lymphoma. The analysis included filgrastim and pegfilgrastim (as well as 2 products not marketed in the US, lenograstim and lipegfilgrastim). Across all cycles and without adjustment for relative dose intensity, the following results were demonstrated (Wang et al 2015): Using direct comparison, the risk of febrile neutropenia was significantly reduced for pegfilgrastim vs placebo or no G-CSF (OR, 0.24; 95% credible interval [CrI]; 0.13 to 0.43) and for filgrastim vs placebo or no G-CSF (OR, 0.42; 95% CrI, 0.29 to 0.59). Using indirect comparison, the risk of febrile neutropenia was significantly reduced for pegfilgrastim vs placebo or no G-CSF (OR, 0.26; 95% CrI, 0.13 to 0.55) and for filgrastim vs placebo or no G-CSF (OR, 0.38; 95% CrI, 0.16 to 0.93). Using mixed-treatment comparisons, the risk of febrile neutropenia was significantly reduced for pegfilgrastim vs placebo or no G-CSF (OR, 0.25; 95% CrI, 0.17 to 0.40), filgrastim vs placebo or no G-CSF (OR, 0.42; 95% CrI, 0.30 to 0.57), and pegfilgrastim vs filgrastim (OR, 0.61; 95% CrI, 0.40 to 0.98).

A systematic review was conducted to compare the effectiveness of long-acting G-CSF (pegfilgrastim) and the short-acting G-CSFs (filgrastim, lenograstim [not available in the US], and filgrastim biosimilars) to prevent febrile neutropenia and related complications in cancer patients in clinical practice. Data from 18 observational trials were included; 15 trials were retrospective and 3 were prospective (Mitchell et al 2016). Seven trials provided statistical comparisons of the risk of febrile neutropenia; of these, pegfilgrastim was associated with a significantly lower risk of febrile neutropenia compared to short-acting G-CSF in 3 studies, a numerically lower risk in 3 studies, and a numerically higher risk in 1 study. Six studies provided statistical comparisons of the risk of febrile neutropenia-related hospitalization; risk among patients receiving prophylaxis with pegfilgrastim vs short-acting G-CSF was significantly lower in all 6 studies, though some variation was seen in subanalyses. The authors noted that in the pivotal clinical trials that established the comparable efficacy of pegfilgrastim vs filgrastim, 10 to 11 days of filgrastim was needed for ANC recovery. Across the studies included in this review, duration of use of short-acting G-CSFs ranged from 4.5 to 7.5 days per cycle, which may have contributed to the lower effectiveness seen in many studies.

A meta-analysis of 9 randomized controlled trials found no significant differenc[illegible]penia, febrile neutropenia, and grade 4 adverse events between pegylated G-CSF and [illegible]; of chemotherapy-induced neutropenia in patients with breast cancer. Durations of grade ≥ 3 neutropenia, grade 4 neutropenia, and time to ANC recovery also did not differ between the groups. Of note, some of the trials included filgrastim and pegfilgrastim products sourced from other countries and pegfilgrastim biosimilars (eg, tripegfilgrastim, mecapegfilgrastim) that are not available in the US (Li et al 2020).

A meta-analysis of 13 placebo-controlled trials in patients with Hodgkin's disease or non-Hodgkin's lymphoma demonstrated that treatment with CSFs had no significant effect on overall survival (hazard ratio [HR], 0.97; 95% CI, 0.87 to 1.09) or freedom from treatment failure (HR, 1.11; 95% CI, 0.91 to 1.35) compared to patients receiving placebo or no treatment. In addition, there was no difference in quality of life between CSFs and placebo (Bohlius et al 2008).

A meta-analysis of 8 randomized controlled trials in patients with breast cancer undergoing chemotherapy demonstrated a reduction in early mortality in CSF-treated patients (RR, 0.14; 95% CI, 0.02 to 1.29). However, the significance was attributed to a single trial. There was no significant difference in infection-related mortality (Renner et al 2012).

A meta-analysis of 19 randomized trials in patients with AML treated with CSFs demonstrated no difference in all-cause mortality at 30 days, rate of complete remission, episodes of febrile neutropenia, or incidence of bacteremia or invasive fungal infections (Gurion et al 2012).

To accelerate myeloid recovery after autologous or allogeneic hematopoietic stem cell transplant/delayed or failed engraftment after hematopoietic stem cell transplant:

Randomized clinical trials have demonstrated the effectiveness of sargramostim compared to placebo after hematopoietic stem cell transplantation. A double-blind placebo-controlled trial (N = 128) demonstrated the efficacy of sargramostim administered IV for shortening the time to ANC recovery after autologous bone marrow transplant (BMT) in patients with non-Hodgkin's lymphoma, Hodgkin's disease and ALL. The time to ANC recovery was reduced from 26 days in the placebo group to 19 days in the sargramostim group ($p < 0.001$) (Nemunaitis et al 1991). However, an extension study demonstrated no significant differences between the sargramostim group and the placebo group in disease-free survival or overall survival (Rabinowe et al 1993). In a double-blind placebo-controlled trial (N = 109) in patients undergoing allogeneic BMT for hematologic malignancies, the median time to myeloid engraftment (ANC ≥ 500 cells/µL) in patients given sargramostim IV was 13 days, compared to 17 days in the placebo group ($p = 0.0001$) (Nemunaitis et al 1995).

Comparisons between filgrastim and sargramostim after hematopoietic stem cell transplantation are very limited. A small, randomized, open-label trial (N = 47) compared the use of sargramostim 250 μ g/m2/day SC for 14 days to the use of sargramostim 250 μ g/m2/day SC for 7 days followed by filgrastim 5 μ g/kg/day SC for 7 days in patients with graft failure after BMT. There was no significant difference in development of a sustained ANC of ≥ 500 cells/ μ L for 3 consecutive days between the sargramostim alone group (8 days) and the sequential treatment group (6 days) (Weisdorf et al 1995).

Several trials, most open-label, have compared filgrastim to pegfilgrastim after hematopoietic stem cell transplantation. In open-label trials, the 2 treatments have generally led to comparable outcomes for endpoints such as the duration of neutropenia, grade 4 neutropenia, and febrile neutropenia, as well as length of hospital stay (Castagna et al 2010, Cesaro et al 2013, Rifkin et al 2010, Sebban et al 2012). One study demonstrated that the incidence of febrile neutropenia was lower with pegfilgrastim compared to filgrastim (61% vs 100%; $p = 0.003$) (Martino et al 2006). One double-blind trial (N = 78) confirmed the results of the open-label trials, demonstrating that pegfilgrastim and filgrastim led to similar time to neutrophil engraftment (12 days in both groups), time to resolution of severe neutropenia (9 days with pegfilgrastim and 10 days with filgrastim; $p = 0.15$), and median hospital stay (19 days in both groups) (Gerds et al 2010).

A meta-analysis of 7 randomized trials in patients receiving PBSC transplant aft
demonstrated a reduction in the risk of documented infections with the use of G-CSF compared to placebo or no treatment (RR, 0.77; 95% CI, 0.68 to 0.87). However, no significant differences were noted in all-cause mortality, infection-related mortality, or fever (Kim et al 2012).

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

Two randomized, open-label trials have compared regimens of filgrastim and sargramostim for mobilization of hematopoietic stem cells. A multicenter trial (N = 156) included 3 study arms: filgrastim 6 μ g/kg/day SC until PBSC harvests were completed; sargramostim 250 μ g/m2/day SC until PBSC harvests were completed, and sargramostim 250 μ g/m2/day SC for 5 days followed by filgrastim 6 μ g/kg/day SC until PBSC harvests were completed. All patients had first received mobilizing myelosuppressive chemotherapy. Significantly more CD34+ cells were harvested in the filgrastim alone group (7.1 cells/kg/apheresis) and in the sequential dosing group (5.5 cells/kg/apheresis) compared to the sargramostim group (2 cells/kg/apheresis; p = 0.0001 and p = 0.0002, respectively). In addition, ANC recovery was significantly faster in patients who received filgrastim alone compared to sargramostim alone (11 vs 14 days; p = 0.001) and for patients who received sequential dosing of filgrastim and sargramostim compared to sargramostim alone (12 vs 14 days; p = 0.001) (Weaver et al 2000). Another multicenter trial (N = 72) compared the use of filgrastim 250 µg/m2/day SC to sargramostim 250 µg/m2/day SC, each given after myelosuppressive chemotherapy, for 2 cycles. The median number of CD34+ cells collected after the first cycle of priming chemotherapy was similar in both groups (16.4 × 106 cells/kg in the filgrastim group vs 12.8 ×106 cells/kg in the sargramostim group; p = 0.8). In cycle 2, the CD34+ yield was very low in both groups (≤ 0.3 × 106 cells/kg). In addition, time to neutrophil recovery (ANC > 500 cells/µL for 2 days) occurred more quickly in the filgrastim group than the sargramostim group after both cycle 1 and cycle 2. The median time to ANC recovery in cycle 1 was 13 and 16 days in the filgrastim and sargramostim groups, respectively (p < 0.01), and in cycle 2 was 13 and 17 days, respectively (p = 0.03) (Arora et al 2004).

A randomized, double-blind study compared filgrastim 5 µg/kg/day to single doses of pegfilgrastim 6 mg or 12 mg, each after myelosuppressive chemotherapy, in patients with non-Hodgkin's lymphoma. The mean CD34+ cell harvest per leukapheresis was 1.2 × 106 cells/kg (95% CI, 0.7 to 2) in the filgrastim group, 0.8 × 106 cells/kg (95% CI, 0.5 to 1.4) in the pegfilgrastim 6 mg group, and 0.8 × 106 cells/kg (95% CI, 0.5 to 1.6) in the pegfilgrastim 12 mg group. The mean total harvest was 2.2 × 106 cells/kg (95% CI, 1.2 to 4) in the filgrastim group, 1.7 × 106 cells/kg (95% CI, 0.8 to 3.3) in the pegfilgrastim 6 mg group, and 1.4 × 106 cells/kg (95% CI, 0.7 to 2.8) in the pegfilgrastim 12 mg group. The days to ANC recovery to ≥ 500 cells/µL were 11 (95% CI, 10 to 12), 12 (95% CI, 10 to 13), and 11 (95% CI, 10 to 13) in the filgrastim, pegfilgrastim 6 mg, and pegfilgrastim 12 mg groups. Differences were not shown to be statistically significant; however, the study may not have been adequately powered to detect differences (Russell et al 2008).

A meta-analysis of 5 clinical trials comparing the efficacy and safety of pegylated and non-pegylated G-CSF for PBSC mobilization showed no evidence for a difference in the successful mobilization rate between pegfilgrastim 6 mg (early administration) and filgrastim 5 mg/kg/day; the risk ratio was 0.8 (95% CI, 0.67 to 1.11; p = 0.26). Pooling data from the studies showed no difference in the incidence of adverse events between pegylated and non-pegylated G-CSF (RR, 0.86; 95% CI, 0.34 to 2.17; p = 0.75). No difference was found on the quantity of CD34+ cells collected, number of apheresis procedures in successful mobilization, level of peak peripheral blood CD34+ cells achieved, and day of neutrophil and platelet engraftment (Kuan et al 2017).

For chronic administration to reduce incidence and duration of sequelae of neutropenia in symptomatic patients with congenital, cyclic or idiopathic neutropenia

A randomized, multicenter, Phase 3 trial evaluated 2 groups of patients: One group received filgrastim for 5 months, and another group underwent a 4-month observation period followed by treatment with filgrastim for 5 months. Of the 120 treated patients, 108 showed a complete response (median ANC ≥ 1500 cells/µL). Four additional patients showed a partial response (median ANC < 1500 cells/µL but ≥ 500 cells/µL and a minimum of 100% increase of ANC over baseline).

The incidence and duration of infection-related events were significantly decre
treatment ($p \leq 0.05$) (Dale et al 1993).

Biosimilarity Data

The approvals of filgrastim-sndz and filgrastim-ayow were supported by evidence including comparative structural and functional characterization, animal studies, human pharmacokinetics and pharmacodynamics, and clinical immunogenicity data. The filgrastim-sndz molecule has the same amino acid sequence as filgrastim and highly similar higher-order structure; filgrastim-ayow is identical to filgrastim, except for an additional methionine residue as a consequence of production in bacterial culture. Functional properties such as biological activity, receptor binding, physicochemical properties, and product-related substances and impurities are all highly similar between filgrastim-sndz and filgrastim-ayow and the reference product. Filgrastim-sndz was also found to have a similar stability profile to filgrastim (FDA summary review [filgrastim-sndz] 2015; FDA summary review [filgrastim-ayow] 2022).

A Phase 1 trial in 50 healthy volunteers determined that Nivestym is bioequivalent to Neupogen in terms of its pharmacodynamic characteristics (Waller et al 2010).

Two separate open-label, crossover-design pharmacokinetic and pharmacodynamic studies supported the demonstration of biosimilarity between Nivestym and Neupogen in 84 healthy volunteers. Comparative immunogenicity between Nivestym and Neupogen met pre-specified endpoints for non-inferiority (Yao et al 2019).

The pharmacokinetic, pharmacodynamic, and immunogenicity similarity studies comparing pegfilgrastim-cbqv to pegfilgrastim in over 600 healthy subjects led to the approval of pegfilgrastim-cbqv (FDA press release 2018[b]). A multicenter, randomized, 3-sequence crossover study in 122 healthy subjects demonstrated the pharmacokinetic and pharmacodynamic bioequivalence of pegfilgrastim-cbqv to pegfilgrastim along with similar immunogenicity and safety profiles (Finck et al 2020). An additional pooled analysis of 3 randomized studies (1 study assessed immunogenicity similarity and 2 studies evaluated pharmacokinetics and pharmacodynamics bioequivalence) in healthy subjects confirmed the similar immunogenicity of pegfilgrastim-cbqv and pegfilgrastim (Civoli et al 2022).

The approval of pegfilgrastim-jmdb was based on structural and functional characterization, animal studies, human pharmacokinetic and pharmacodynamics data, clinical immunogenicity data, and other clinical effectiveness and safety data showing that pegfilgrastim-jmdb is biosimilar to Neulasta (FDA press release 2018[a]).

The approval of pegfilgrastim-bmez was based on analytical, preclinical, and clinical research, including data from a pivotal 3-way pharmacokinetic and pharmacodynamic study (Sandoz press release 2019). The study compared pegfilgrastim-bmez to 2 reference pegfilgrastim products (1 sourced from the US and 1 sourced from Europe) and found that the 3 products were similar in terms of pharmacokinetics, pharmacodynamics, safety, immunogenicity, and tolerability (Bellon et al 2020).

The approval of pegfilgrastim-pbbk was based on analytical data demonstrating that it is highly similar to its reference product (Neulasta) and that there are no clinically meaningful differences between these products (FDA multidiscipline review [pegfilgrastim-pbbk] 2022).

An additional Phase 1 trial in 169 healthy subjects found that pegfilgrastim-bmez is similar to reference pegfilgrastim with respect to pharmacokinetics, pharmacodynamics, immunogenicity, safety, and tolerability (Nakov et al 2018).

Pegfilgrastim-fpgk showed similar pharmacokinetic, pharmacodynamic, immunogenicity, safety, and tolerability to reference pegfilgrastim in 292 healthy subjects (Lickliter et al 2020).

A meta-analysis of 3 Phase 1 studies confirmed the pharmacokinetics and pharmacodynamics similarity of pegfilgrastim-bmez vs the reference pegfilgrastim products sourced from the US and Europe (Gattu et al 2021).

The approval of pegfilgrastim-apgf was based on nonclinical and clinical studies which determined that the agent is highly similar to reference pegfilgrastim in safety, purity, and potency (FDA multi-discipline review [pegfilgrasim-apgf] 2020). A Phase 1 trial in 573 healthy subjects found that pegfilgrastim-apgf has similar pharmacokinetics, pharmacodynamics, safety, and immunogenicity compared with reference pegfilgrastim marketed in the US (Moosavi et al 2020).

A meta-analysis of 8 randomized controlled trials (N = 1843) comparing G-CSF reference medicines (5 studies with filgrastim and 3 studies with pegfilgrastim) to biosimilar medicines in patients with breast cancer demonstrated no difference in duration of severe neutropenia between G-CSF reference and biosimilar agents (mean difference of duration, 0.06 days; 95% CI, -0.05 to 0.17). The secondary efficacy endpoint of mean ANC depth between G-CSF reference and biosimilar medicine was 0.06 x 109 cells/L (95% CI, -0.06 to 0.18). The difference in mean time to ANC recovery was -0.06 days (95% CI, -0.13 to 0.12). The number of patients experiencing febrile neutropenia was similar between G-CSF reference and biosimilar groups (RR, 0.96; 95% CI, 0.71 to 1.30). These results demonstrate small but not significant differences between G-CSF reference and biosimilar agents. Safety end points between G-CSF reference and biosimilar groups were similar; this included bone pain (RR, 1.01; 95% CI, -0.76 to 1.34), myalgia events (RR, 0.94; 95% CI, 0.63 to 1.40), and serious adverse events (RR, 0.98; 95% CI, 0.70 to 1.36). This meta-analysis showed no significant differences between G-CSF reference and biosimilar medicine in terms of clinical efficacy and safety in breast cancer patients receiving cytotoxic chemotherapy (Botteri et al 2018).

Filgrastim-txid has demonstrated that it is highly similar to filgrastim, notwithstanding minor differences in clinically inactive components. Furthermore, filgrastim-txid has demonstrated adequate purity and potency requirements (FDA multi-discipline review [filgrasim-txid] 2024).

Clinical Guidelines

- Guidelines generally recommend CSF prophylaxis in patients whose overall risk of febrile neutropenia from myelosuppressive chemotherapy is ≥ 20% (*Klastersky et al 2016, National Comprehensive Cancer Network [NCCN] 2025, Smith et al 2015*).
  - For regimens with a general risk between 10% and 20%, the patient's age and comorbidities should be considered to determine his or her overall risk. Additionally, G-CSF may be considered in patients who have a lowered bone marrow reserve due to extensive radiotherapy or in neutropenic patients with human immunodeficiency virus (HIV) infection (*Klastersky et al 2016, NCCN 2025*).
  - The risk of febrile neutropenia is usually greatest during the first course of therapy, so primary prophylaxis is generally recommended for patients at risk rather than routinely using secondary prophylaxis (using G-CSF in a subsequent treatment course after an episode of febrile neutropenia). However, secondary prophylaxis is indicated if dose reductions or chemotherapy delays are not desirable (such as treatment with a curative intent) and for patients who have had no prior use of G-CSFs (*Klastersky et al 2016, NCCN 2025*). The risks and benefits of G-CSF versus dose reduction or delay during modern chemoradiotherapy are uncertain at this time (NCCN 2025).
  - Patients who present with febrile neutropenia and are receiving or have received prophylactic G-CSFs may continue daily prophylactic filgrastim or tbo-filgrastim, or if long lasting prophylactic pegfilgrastim was received, no additional G-CSFs are warranted. Those who did not receive prophylactic G-CSFs and have risk factors for an infection-associated complication should consider therapy with filgrastim, filgrastim biosimilars, tbo-filgrastim, or sargramostim. Pegfilgrastim, pegfilgrastim biosimilars, and eflapegrastim-xnst are not recommended for therapeutic use in this setting (*NCCN 2025*).
- Consensus guidelines focusing on autologous stem cell mobilization strategies are available from the American Society for Transplantation and Cellular Therapy (ASTCT). These guidelines note that GM-CSF is inferior to G-CSF based on the number of stem cells collected and in post-transplant hematopoietic recovery, transfusions, antibiotic support, febrile episodes, and hospitalizations. The guideline also notes that GM-CSF is most often used in remobilization strategies, alone or in combination with other cytokines or chemotherapy (*Giralt et al 2014*). A second guideline from the ASTCT focusing on both autologous and allogeneic hematopoietic cell transplantation is in agreement that G-CSF is the

standard CSF for mobilization for both types of transplants (*Duong et al 2014*). In autologous hematopoietic cell transplantation from the NCCN recommends the use of filgrastim, a filgrastim biosimilar, sargramostim, pegfilgrastim, or a pegfilgrastim biosimilar for stem cell mobilization in the autologous setting. Filgrastim, filgrastim biosimilars, or tbo-filgrastim are the preferred agents for stem cell mobilization of allogeneic donors (*NCCN 2025*).

- Several guidelines include brief statements on the use of biosimilar CSFs.
  - The NCCN guideline on hematopoietic growth factors, endorses the use of filgrastim (or an FDA-approved biosimilar), tbo-filgrastim, eflapegrastim-xnst, or pegfilgrastim (or an FDA-approved biosimilar) for prophylaxis of febrile neutropenia. Of note, pegfilgrastim should not be used with chemotherapy regimens that are administered weekly. Filgrastim (or an FDA-approved biosimilar), tbo-filgrastim, and sargramostim are recommended for the therapeutic treatment of febrile neutropenia (*NCCN 2025*).
  - The NCCN guideline on hematopoietic cell transplantation comments that an FDA-approved biosimilar is an appropriate substitute for filgrastim and pegfilgrastim (*NCCN 2025*).
  - The American Society of Clinical Oncology (ASCO) guideline notes that 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 (*Smith et al 2015*).
  - A guideline from the European Society for Medical Oncology (ESMO) states that use of biosimilars approved by the FDA or the European Medicines Agency (EMA) can be considered (*Klastersky et al 2016*).
  - A guideline from ASTCT states that approved biosimilar G-CSFs are produced and manufactured by a similar process to the innovator biologic and generally available at lower prices. Data support their role in chemotherapy-induced neutropenia with cost efficiency; however, less data are available regarding their use in peripheral blood progenitor cell (PBPC) mobilization. Thus, larger controlled studies with longer term follow-up are necessary before recommending the use of these agents for mobilization (*Duong et al 2014*).

Reference Tables

Table 1. Intergroup C9741 Protocol

Regimen	Drugs	G-CSF
Sequential	Doxorubicin q2 weeks x4 cycles, then paclitaxel q2 weeks x4 cycles, then cyclophosphamide q2 weeks x 4cycles	Days 3 to 10 of each cycle
Concurrent	Doxorubicin + cyclophosphamide q2 weeks x4 cycles, then paclitaxel q2 weeks x4 cycles	Days 3 to 10 of each cycle

Table 2. Examples of chemotherapy regimens with a high risk of FN (> 20%)

Cancer	Regimen
Bladder Cancer	• Dose-dense MVAC (methotrexate, vinblastine, doxorubicin, cisplatin)
Bone Cancer	• VAI (vincristine, doxorubicin or dactinomycin, ifosfamide) • VDC-IE (vincristine, doxorubicin or dactinomycin, and cyclophosphamide alternating with ifosfamide and etoposide) • Cisplatin/doxorubicin • VDC (cyclophosphamide, vincristine, doxorubicin or dactinomycin) • VIDE (vincristine, ifosfamide, doxorubicin or dactinomycin, etoposide)
Breast Cancer	• Dose-dense AC followed by dose-dense paclitaxel (doxorubicin, cyclophosphamide, paclitaxel) • TAX (docetaxel, doxorubicin, cyclophosphamide) • TC (docetaxel, cyclophosphamide) • TCH (docetaxel, carboplatin, trastuzumab)

Colorectal Cancer	• FOLFOXIRI (fluorouracil, leucovorin, oxalipl
Head and Neck Squamous Cell Carcinoma	• TPF (docetaxel, cisplatin, 5-fluorouracil)
Hodgkin Lymphoma	• Brentuximab vedotin + AVD (doxorubicin, vinblastine, dacarbazine) • Escalated BEACOPP (bleomycin, etoposide, doxorubivin, cyclophosphamide, vincristine, procarbazine, prednisone)
Kidney Cancer	• Doxorubicin/gemcitabine
Non-Hodgkin's Lymphomas	• Dose-adjusted EPOCH (etoposide, prednisone, vincristine, cyclophosphamide, doxorubicin) • ICE (ifosfamide, carboplatin, etoposide) • Dose-dense CHOP-14 (cyclophosphamide, doxorubicin, vincristine, prednisone) • MINE (mesna, ifosfamide, mitoxantrone, etoposide) • DHAP (dexamethasone, cisplatin, cytarabine) • ESHAP (etoposide, methylprednisolone, cisplatin, cytarabine) • HyperCVAD (cyclophosphamide, vincristine, doxorubicin, dexamethasone)
Melanoma	• Dacarbazine-based combination with IL-2, interferon alfa (dacarbazine, cisplatin, vinblastine, IL-2, interferon alfa)
Multiple Myeloma	• DT-PACE (dexamethasone/thalidomide/cisplatin/doxorubicin/cyclophosphamide/etoposide) +/- bortezomib (VTD-PACE)
Ovarian Cancer	• Topotecan • Docetaxel
Pancreatic Cancer	• FOLFIRINOX (fluorouracil, leucovorin, irinotecan, oxaliplatin)
Soft Tissue Sarcoma	• MAID (mesna, doxorubicin, ifosfamide, dacarbazine) • Doxorubicin • Ifosfamide/doxorubicin
Small Cell Lung Cancer	• Topotecan
Testicular Cancer	• VIP (etoposide, ifosfamide, cisplatin) • VeIP (vinblastine, ifosfamide, cisplatin) • TIP (paclitaxel, ifosfamide, cisplatin)

Table 3. Examples of chemotherapy regimens with an intermediate risk of FN (10-20%)

Cancer	Regimen
Occult Primary-Adenocarcinoma	• Gemcitabine/docetaxel
Breast Cancer	• Docetaxel • AC (doxorubicin, cyclophosphamide) + sequential docetaxel (adjuvant) (taxane portion only) • Paclitaxel every 21 days
Cervical Cancer	• Cisplatin/topotecan • Paclitaxel/cisplatin • Topotecan • Irinotecan
Colorectal Cancer	• FOLFOX (fluorouracil, leucovorin, oxaliplatin)

Non-Hodgkin's Lymphomas (NHL)	• GDP (gemcitabine, dex cisplatin/carboplatin) • CHOP (cyclophosphamide, doxorubicin, vincristine, prednisone) including regimens with pegylated liposomal doxorubicin • CHP (cyclophosphamide, doxorubicin, prednisone) + brentuximab vedotin • Bendamustine
Non-Small Cell Lung Cancer	• Cisplatin/paclitaxel • Cisplatin/vinorelbine • Cisplatin/docetaxel • Cisplatin/etoposide • Carboplatin/paclitaxel • Docetaxel
Ovarian Cancer	• Carboplatin/docetaxel
Prostate Cancer	• Cabazitaxel
Testicular Cancer	• Etoposide/cisplatin • BEP (bleomycin, etoposide, cisplatin)
Esophageal and Gastric Cancer	• Irinotecan/cisplatin • Epirubicin/cisplatin/5-flurouracil • Epirubicin/cisplatin/capecitabine
Small Cell Lung Cancer	• Etoposide/carboplatin
Uterine Cancer	• Docetaxel

Table 4. Examples of FDA-approved chemotherapeutic agents with dose-limiting myelosuppression

Generic Name	Brand Name
Busulfan	Busulfex®, Myleran®
Carboplatin	Paraplatin®
Carmustine (BCNU)	BiCNU®, Gliadel®
Chlorambucil	Leukeran®
Cladribine	Luestatin®
Cyclophosphamide	Cytoxan®
Cytarabine	N/A
Dacarbazine (DTIC)	DTIC-Dome®
Dactinomycin	Actinomycin D®, Cosmegen®
Daunorubicin	Cerubidine®
Daunorubicin Liposomal	DaunoXome®
Doxorubicin	Adriamycin PFS®, Adriamycin RDF®, Adriamycin®
Doxorubicin Liposomal	Doxil®
Etoposide	Etopophos®, Toposar®, VePesid®
Fluorouracil (5-FU)	Adrucil®, Efudex®, Fluoroplex®
Floxuridine	FUDR®
Fludarabine	Fludara®
Hydroxyurea	Droxia®, Hydrea®
Ifosfamide/Mesna	Ifex®, Mesnex®
Lomustine (CCNU)	CeeNU®
Mechlorethamine (Nitrogen Mustard)	Mustargen®

Melphalan	Alkeran®
Mercaptopurine (6-MP)	Purinethol®
Methotrexate	Rheumatrex®, Trexall
Mitomycin	N/A
Mitoxantrone	Novantrone®
Paclitaxel	Onxol™, Taxol®
Procarbazine	Matulane®
Teniposide	Vumon®
Thioguanine (6-TG)	Tabloid®
Thiotepa	Thiotepa®
Vinblastine	N/A
Vincristine	Vincasar® PFS
Vinorelbine	Navelbine®

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 non-myeloid malignancies receiving myelosuppressive anti-cancer drugs associated with a clinically significant incidence of febrile neutropenia.

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.

Granix (tbo-filgrastim) is a leukocyte growth factor indicated in adult and pediatric patients 1 month and older for reduction in the duration of severe neutropenia in patients with non-myeloid malignancies receiving myelosuppressive anti-cancer drugs associated with a clinically significant incidence of febrile neutropenia.

Leukine (sargramostim) is a leukocyte growth factor indicated:

- To shorten time to neutrophil recovery and to reduce the incidence of severe and life-threatening infections and infections resulting in death following induction chemotherapy in adult patients 55 years and older with acute myeloid leukemia (AML).
- For the mobilization of hematopoietic progenitor cells into peripheral blood for collection by leukapheresis and autologous transplantation in adult patients.
- For the acceleration of myeloid reconstitution following autologous bone marrow or peripheral blood progenitor cell transplantation in adult and pediatric patients 2 years of age and older.
- For the acceleration of myeloid reconstitution following allogeneic bone marrow transplantation in adult and pediatric patients 2 years of age and older.
- For treatment of delayed neutrophil recovery or graft failure after autologous or allogeneic bone marrow transplantation in adult and pediatric patients 2 years of age and older.
- 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 [H-ARS])

Neulasta (pegfilgrastim) is a leukocyte growth factor indicated to:

- Decrease the incidence of infection, as manifested by febrile neutrope malignancies receiving myelosuppressive anti-cancer drugs associated febrile neutropenia.
- Increase survival in patients acutely exposed to myelosuppressive doses of radiation (Hematopoietic Subsyndrome of Acute Radiation Syndrome).

of

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 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)
- 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
- Increase survival in patients acutely exposed to myelosuppressive doses of radiation (Hematopoietic Syndrome of Acute Radiation Syndrome)

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 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). 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.

Nypozi (filgrastim-txid) 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)
- 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
- Increase survival in patients acutely exposed to myelosuppressive doses of radiation (Hematopoietic Syndrome of Acute Radiation Syndrome)

Nyvepria (pegfilgrastim-apgf) is a leukocyte growth factor indicated to decreas ested by febrile neutropenia, in patients with non-myeloid malignancies receiving m associated with a clinically significant incidence of febrile neutropenia.

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

Rolvedon (eflapegrastim-xnst) 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.

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.
- Increase survival in patients acutely exposed to myelosuppressive doses of radiation (Hematopoietic Subsyndrome of Acute Radiation Syndrome).

Udenyca (pegfilgrastim-cbqv) 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.
- Increase survival in patients acutely exposed to myelosuppressive doses of radiation (Hematopoietic Subsyndrome of Acute Radiation Syndrome).

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 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)
- 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.

Ziextenzo (pegfilgrastim-bmez) 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

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Policy History/Revision Information

Date	Summary of Changes
11/16/2023	Approved by OptumRx P&T Committee
04/17/2024	Annual Review. Addition of Udenyca Onbody. Updated references.
04/16/2025	Annual Review. Updated references.
08/21/2025	Addition of Nypozi to policy. Updated references.

Instructions for Use

This Medical Benefit Drug Policy provides assistance in interpreting standard benefit plans. When deciding coverage, the member specific benefit plan document must be referenced as the terms of the member specific benefit plan may differ from the standard plan. In the event of a conflict, the member specific benefit plan document governs. Before using this policy, please check the member specific benefit plan document and any applicable federal or state mandates. The insurance 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.

OptumRx may also use tools developed by third parties to assist us in administering health benefits. OptumRx 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.

Archived Policy Versions (Internal Only)

Effective Date	Policy Number	Policy Title
mm/dd/yyyy – mm/dd/yyyy	######	Title of Policy Hyperlinked to KL or Other Internal Location

Nondiscrimination & Language Access Policy

Discrimination is Against the Law. Aspirus Health Plan, Inc. complies with applicable Federal civil rights laws and does not discriminate on the basis of race, color, national origin, age, disability, or sex, (including sex characteristics, including intersex traits; pregnancy or related conditions; sexual orientation, gender identity and sex stereotypes), consistent with the scope of sex discrimination described at 45 CFR § 92.101(a)(2). Aspirus Health Plan, Inc. does not exclude people or treat them less favorably because of race, color, national origin, age, disability, or sex.

Aspirus Health Plan, Inc.:
Provides people with disabilities reasonable modifications and free appropriate auxiliary aids and services to communicate effectively with us, such as:

- Qualified sign language interpreters.
- Written information in other formats (large print, audio, accessible electronic formats, other formats).

Provides free language assistance services to people whose primary language is not English, which may include:

- Qualified interpreters.
- Information written in other languages.

If *you* need reasonable modifications, appropriate auxiliary aids and services, or language assistance services, contact the Nondiscrimination Grievance Coordinator at the address, phone number, fax number, or email address below.

If *you* believe that Aspirus Health Plan, Inc. has failed to provide these services or discriminated in another way on the basis of race, color, national origin, age, disability, or sex, *you* can file a *grievance* with:

Nondiscrimination Grievance Coordinator
Aspirus Health Plan, Inc.
PO Box 1890
Southampton, PA 18966-9998
Phone: 1-866-631-5404 (TTY: 711)
Fax: 763-847-4010
Email: customerservice@aspirushealthplan.com

You can file a *grievance* in person or by mail, fax, or email. If *you* need help filing a *grievance*, the Nondiscrimination Grievance Coordinator is available to help *you*.

You can also file a civil rights complaint with the U.S. Department of Health and Human Services, Office for Civil Rights, electronically through the Office for Civil Rights Complaint Portal, available at https://ocrportal.hhs.gov/ocr/portal/lobby.jsf, or by mail or phone at:

U.S. Department of Health and Human Services
200 Independence Avenue, SW
Room 509F, HHH Building
Washington, D.C. 20201
1.800.368.1019, 800.537.7697 (TDD)

Complaint forms are available at http://www.hhs.gov/ocr/office/file/index.html. This notice is available at Aspirus Health Plan, Inc.'s website: https://aspirushealthplan.com/webdocs/70021-AHP-NonDiscrim_Lang-Assist-Notice.pdf.

Language Assistance Services

Albanian: KUJDES: Nëse flitni shqip, për ju ka në dispozicion shërbime të asistencës gjuhësore, pa pagesë.Telefononi në 1-800-332-6501 (TTY: 711).

Arabic تنبيه: إذا كنت تتحدث اللغة العربية، فإن خدمات المساعدة اللغوية متاحة لك مجاناً. اتصل بن اعلى رقم الهاتف1-800-332-6501(رقم هاتف الصم والبك : 711)

French: ATTENTION: Si vous parlez français, des services d'aide linguistique vous sont proposés gratuitement. Appelez le 1-800-332-6501 (ATS: 711).

German: ACHTUNG: Wenn Sie Deutsch sprechen, stehen Ihnen kostenlos sprachliche Hilfsdienstleistungen zurVerfügung. Rufnummer: 1-800-332-6501 (TTY: 711).

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Nondiscrimination & Language Access Policy

Discrimination is Against the Law. Aspirus Health Plan, Inc. complies with applicable Federal civil rights laws and does not discriminate on the basis of race, color, national origin, age, disability, or sex, (including sex characteristics, including intersex traits; pregnancy or related conditions; sexual orientation, gender identity and sex stereotypes), consistent with the scope of sex discrimination described at 45 CFR § 92.101(a)(2). Aspirus Health Plan, Inc. does not exclude people or treat them less favorably because of race, color, national origin, age, disability, or sex.

Aspirus Health Plan, Inc.:
Provides people with disabilities reasonable modifications and free appropriate auxiliary aids and services to communicate effectively with us, such as:

- Qualified sign language interpreters.
- Written information in other formats (large print, audio, accessible electronic formats, other formats).

Provides free language assistance services to people whose primary language is not English, which may include:

- Qualified interpreters.
- Information written in other languages.

If *you* need reasonable modifications, appropriate auxiliary aids and services, or language assistance services, contact the Nondiscrimination Grievance Coordinator at the address, phone number, fax number, or email address below.

If *you* believe that Aspirus Health Plan, Inc. has failed to provide these services or discriminated in another way on the basis of race, color, national origin, age, disability, or sex, *you* can file a *grievance* with:

Nondiscrimination Grievance Coordinator
Aspirus Health Plan, Inc.
PO Box 1890
Southampton, PA 18966-9998
Phone: 1-866-631-5404 (TTY: 711)
Fax: 763-847-4010
Email: customerservice@aspirushealthplan.com

You can file a *grievance* in person or by mail, fax, or email. If *you* need help filing a *grievance*, the Nondiscrimination Grievance Coordinator is available to help *you*.

You can also file a civil rights complaint with the U.S. Department of Health and Human Services, Office for Civil Rights, electronically through the Office for Civil Rights Complaint Portal, available at https://ocrportal.hhs.gov/ocr/portal/lobby.jsf, or by mail or phone at:

U.S. Department of Health and Human Services
200 Independence Avenue, SW
Room 509F, HHH Building
Washington, D.C. 20201
1.800.368.1019, 800.537.7697 (TDD)

Complaint forms are available at http://www.hhs.gov/ocr/office/file/index.html. This notice is available at Aspirus Health Plan, Inc.'s website: https://aspirushealthplan.com/webdocs/70021-AHP-NonDiscrim_Lang-Assist-Notice.pdf.

Language Assistance Services

Albanian: KUJDES: Nëse flitni shqip, për ju ka në dispozicion shërbime të asistencës gjuhësore, pa pagesë.Telefononi në 1-800-332-6501 (TTY: 711).

Arabic تنبيه: إذا كنت تتحدث اللغة العربية، فإن خدمات المساعدة اللغوية متاحة لك مجاناً. اتصل بن اعلى رقم الهاتف1-800-332-6501(رقم هاتف الصم والبك : 711)

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