White Blood Cell Colony Stimulating Factors

Policy Number: 2026D0061AE
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➲ Instructions for Use

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Related Commercial/Individual Exchange Policy
- Oncology Medication Clinical Coverage

Community Plan Policy
- White Blood Cell Colony Stimulating Factors

Related Medicare Advantage Policy
- Medicare Part B Step Therapy Programs

Application

UnitedHealthcare Commercial

This Medical Policy applies to UnitedHealthcare Commercial benefit plans.

UnitedHealthcare Individual Exchange

This Medical Policy applies to Individual Exchange benefit plans.

Coverage Rationale

➲ See Benefit Considerations

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

- Long-acting pegfilgrastim agents:
  - Armlupeg® (pegfilgrastim-unne)
  - 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)
  - Nypozi™ (filgrastim-txid)
  - Releuko® (filgrastim-ayow)
  - Zarxio® (filgrastim-sndz)
- Leukine® (sargramostim) (refer to the Diagnosis-Specific Criteria)
- Rolvedon™ (eflapegrastim-xnst)

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- Ryzneuta® (efbemalenograstim alfa-vuxw)
- Any FDA-approved white blood cell colony stimulating factor product not listed here*

*Any U.S. Food and Drug Administration approved white blood cell colony stimulating factor product not listed by name in this policy will be considered non-preferred until reviewed by UnitedHealthcare.

Medical Necessity Plans

Long-Acting Pegfilgrastim Agents (Armlupeg, Fulphila, Fylnetra, Neulasta, Nyvepria, Rolvedon, Ryzneuta, Stimufend Udenyca, and Ziextenzo): Preferred Product

For Medicare reviews, refer to the CMS section.**
Neulasta and Udenyca are the preferred pegfilgrastim products. Coverage will be provided for Neulasta and Udenyca contingent on the coverage criteria in the Diagnosis-Specific Criteria section.

Coverage for Armlupeg, Fulphila, Fylnetra, Nyvepria, Rolvedon, Ryzneuta, Stimufend, or Ziextenzo will be provided contingent on the criteria in this section and the coverage criteria in the Diagnosis-Specific Criteria section. In order to continue coverage, members already on Armlupeg, Fulphila, Fylnetra, Nyvepria, Rolvedon, Ryzneuta, Stimufend, or Ziextenzo will be required to change therapy to Neulasta or Udenyca unless they meet the criteria in this section.

Preferred Product Criteria (For Medicare reviews, refer to the CMS section.**)

Treatment with Armlupeg, Fulphila, Fylnetra, Nyvepria, Rolvedon, Ryzneuta, Stimufend, Ziextenzo, or other pegfilgrastim biosimilar is medically necessary for the indications specified in the policy when one of the following is met:

- **Both** of the following:
  - History of a trial of adequate dose and duration of Neulasta or Udenyca, resulting in minimal clinical response; **and**
  - Physician attests that, in their clinical opinion, the clinical response would be expected to be superior with Armlupeg, Fulphila, Fylnetra, Nyvepria, Rolvedon, Ryzneuta, Stimufend, Ziextenzo, or other pegfilgrastim biosimilar product, than experienced with Neulasta or Udenyca

  or
- **Both** of the following:
  - History of intolerance, contraindication, or Adverse Event to Neulasta or Udenyca; **and**
  - Physician attests that, in their clinical opinion, the same intolerance, contraindication, or Adverse Event would not be expected to occur with Armlupeg, Fulphila, Fylnetra, Nyvepria, Rolvedon, Ryzneuta, Stimufend, Ziextenzo, or other pegfilgrastim biosimilar product

Short-Acting Filgrastim Agents (Granix, Neupogen, Nivestym, Nypozi, Releuko, and Zarxio): Preferred Product

For Medicare reviews, refer to the CMS section.**

Zarxio and Nivestym are the preferred filgrastim products. Coverage will be provided for Zarxio and Nivestym contingent on the coverage criteria in the Diagnosis-Specific Criteria section.

Coverage for Granix, Neupogen, Nypozi, or Releuko will be provided contingent on the criteria in this section and the coverage criteria in the Diagnosis-Specific Criteria section. In order to continue coverage, members already on Granix, Neupogen, Nypozi, or Releuko will be required to change therapy to Zarxio or Nivestym unless they meet the criteria in this section.

Preferred Product Criteria (For Medicare reviews, refer to the CMS section.**)

Treatment with Granix, Neupogen, Nypozi, Releuko, or other filgrastim biosimilar is medically necessary for the indications specified in the policy when one of the following is met:

- **Both** of the following:
  - History of a trial of adequate dose and duration of Zarxio or Nivestym, resulting in minimal clinical response; **and**
  - Physician attests that, in their clinical opinion, the clinical response would be expected to be superior with Granix, Neupogen, Nypozi, Releuko, or other filgrastim biosimilar product, than experienced with Zarxio or Nivestym

  or
- **Both** of the following:
  - History of intolerance, contraindication, or Adverse Event to Zarxio or Nivestym; **and**

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- Physician attests that, in their clinical opinion, the same intolerance, contraindication, or Adverse Event would not be expected to occur with Granix, Neupogen, Nypozi, Releuko, or other filgrastim biosimilar product

Non-Medical Necessity Plans

Any filgrastim or pegfilgrastim product is to be approved contingent on the coverage criteria in the Diagnosis-Specific Criteria section.

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 for the following indications:

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

Leukine, Neupogen, Nivestym, Nypozi, Releuko, and Zarxio are medically necessary when the following criteria are met:[2-3,40]

- **One** of the following:
  - Patient has non-myeloid malignancies and is 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 have received myeloablative chemotherapy

Acute Myeloid Leukemia (AML) Induction or Consolidation Therapy (Leukine, Neupogen, Nivestym, Nypozi, Releuko, and Zarxio)

Leukine, Neupogen, Nivestym, Nypozi, Releuko, and Zarxio are medically necessary when the following criteria are met:[2-3,37,40]

- **Both** of the following:
  - Diagnosis of AML; **and**
  - **One** of the following:
    - Patient achieved complete remission after induction therapy; **or**
    - Patient is receiving consolidation chemotherapy; **or**
    - Patient is receiving fludarabine, cytarabine with or without idarubicin for relapsed or refractory disease; **or**
    - Patient is receiving cladribine, cytarabine with or without mitoxantrone or idarubicin for relapsed or refractory disease

Primary Prophylaxis of Chemotherapy-Induced Febrile Neutropenia (FN) (Armlupeg, Fulphila, Fylnetra, Granix, Leukine, Neulasta, Neupogen, Nivestym, Nypozi, Nyvepria, Releuko, Rolvedon, Ryzneuta, Stimufend, Udenyca, Zarxio, and Ziextenzo)

White blood cell colony stimulating factors are medically necessary when the following criteria are met:[16-17]

- **One** of the following:
  - Patient is receiving dose dense MVAC (methotrexate, vinblastine, doxorubicin, cisplatin) for bladder cancer; **or**
  - Patient is receiving dose dense AC (doxorubicin, cyclophosphamide) followed by dose-dense paclitaxel for breast cancer; **or**
  - Patient is receiving chemotherapy regimen(s) associated with > 20% incidence of FN

  or
- **Both** of the following:
  - Patient is receiving chemotherapy regimen(s) associated with 10-20% incidence of FN; **and**
  - Patient has one or more risk factors for chemotherapy-induced Febrile Neutropenia such as:
    - Persistent Neutropenia due to prior chemotherapy, radiation therapy or bone marrow involvement by tumor (< 500 neutrophils/mcL or < 1,000 neutrophils/mcL and a predicted decline to ≤ 500 neutrophils/mcL over the next 48 hours)[16]
    - Liver dysfunction (bilirubin > 2.0)
    - Renal dysfunction (creatinine clearance < 50)
    - Age > 65 years receiving full chemotherapy dose intensity

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Secondary Prophylaxis of Febrile Neutropenia (FN) (Armlupeg, Fulphila, Fylnetra, Granix, Leukine, Neulasta, Neupogen, Nivestym, Nypozi, Nyvepria, Releuko, Rolvedon, Ryzneuta, Stimufend, Udenyca, Zarxio, and Ziextenzo)

White blood cell colony stimulating factors are medically necessary when the following criteria are met:[1-3,16-17,39-40]

- **One** of the following:
  - Patient is receiving myelosuppressive anticancer drug(s) given with a curative intent (curative chemotherapy, chemotherapy in curative adjuvant/neoadjuvant setting); **or**
  - Patient is receiving myelosuppressive anticancer drug(s) for definitive therapy (bridge to stem cell transplant, organ transplant, definitive surgery for oligometastatic disease)

  and
- **One** of the following:
  - Patient has a documented history of a neutropenic event (Febrile Neutropenia or low neutrophil count leading to delay of subsequent cycle) during a previous cycle of the same chemotherapy regimen at full dose for which primary prophylaxis was not received; **or**
  - Patient has a documented history of neutropenic event from a previous course of chemotherapy

  or
- **Both** of the following:
  - Patient is receiving myelosuppressive anticancer drug(s) given with non-curative intent; **and**
  - **One** of the following:
    - Patient has documented history of Febrile Neutropenia; **or**
    - Patient has had a trial of dose reduction, followed by a dose-limiting neutropenic event (nadir count or day of treatment count that could otherwise impact planned dose of chemotherapy) that results in delay in therapy; **or**
    - Patient is receiving myelosuppressive anticancer drug(s) and use of secondary prophylaxis is in accordance with the United States Food and Drug Administration approved label

  or
- Patient is receiving myelosuppressive anticancer drug(s) where primary prophylaxis is indicated

Treatment of Febrile Neutropenia (Armlupeg, Fulphila, Fylnetra, Leukine, Neulasta, Neupogen, Nivestym, Nypozi, Nyvepria, Releuko, Rolvedon, Ryzneuta, Stimufend, Udenyca, Zarxio, and Ziextenzo) (Off-Label)

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

- **All** of the following:
  - 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, Nypozi, Releuko, and Zarxio)

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

- **All** of the following:
  - 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 United States Food and Drug Administration approved labeling; **and**
  - Prescribed by or in consultation with a hematologist or oncologist

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Hematopoietic Syndrome of Acute Radiation Syndrome (Armlupeg, Fulphila, Fylnetra, Leukine, Neulasta, Neupogen, Nivestym, Nypozi, Nyvepria, Releuko, Rolvedon, Ryzneuta, Stimufend, Udenyca, Zarxio, and Ziextenzo)[1-3]

Fulphila, Fylnetra, Leukine, Neulasta, Neupogen, Nivestym, Nypozi, Nyvepria, Releuko, Rolvedon, Ryzneuta, Stimufend, Udenyca, Zarxio, and Ziextenzo are medically necessary when all of the following criteria are met:[1-3]

- **All** of the following:
  - Patient has been acutely exposed to myelosuppressive doses of radiation; **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: 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.]

Febrile Neutropenia: Febrile Neutropenia is defined as single temperature: ≥ 38.3 °C orally or 38.0 °C 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.]

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

Neutropenia: Neutropenia is defined as an absolute neutrophil count (ANC) of less than 1500 per microliter (< 1500 neutrophils/mcL).[50.]

Severe Neutropenia: Severe Neutropenia is defined as an ANC of less than 500 neutrophils/mcL (< 500 neutropils/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 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
J1449	Injection, eflapegrastim-xnst, 0.1 mg
J2506	Injection, pegfilgrastim, 0.5 mg
J2820	Injection, sargramostim (GM-CSF), 50 mcg
J3490	Unclassified drugs
J3590	Unclassified biologics
J9361	Injection, efbemalenograstim alfa-vuxw, 0.5 mg
J9999	Not otherwise classified, antineoplastic drug
Q5101	Injection, filgrastim-sndz, biosimilar, (Zarxio), 1 microgram
Q5108	Injection, pegfilgrastim-jmdb (Fulphila), biosimilar, 0.5 mg

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HCPCS Code	Description
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 mcg
Q5169	Injection, pegfilgrastim-unne (Armlupeg), 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), filgrastim-txid (Nypozi), pegfilgrastim-jmdb (Fulphila), pegfilgrastim-unne (Armlupeg),tbo-filgrastim (Granix), filgrastim-sndz (Zarxio), and pegfilgrastim-bmez (Ziextenzo), eflapegrastim-xnst (Rolvedon), and efbemalenograstim alfa-vuxw (Ryzneuta). GM-CSFs stimulate the production of both neutrophils and macrophages and include the following FDA-approved products: sargramostim (Leukine).

Benefit Considerations

Some Certificates of Coverage allow for coverage of experimental/investigational/unproven treatments for life-threatening illnesses when certain conditions are met. The member specific benefit plan document must be consulted to make coverage decisions for this service. Some states mandate benefit coverage for off-label use of medications for some diagnoses or under some circumstances when certain conditions are met. Where such mandates apply, they supersede language in the benefit document or in the medical or drug policy.

Clinical Evidence

National Comprehensive Cancer Network (NCCN)[4]

The NCCN publishes clinical practice guidelines for Oncology (NCCN Guidelines®) specific to myeloid growth factors. 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

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- Recent surgery and/or open wounds
- Liver dysfunction (bilirubin > 2.0)
- Renal dysfunction (creatinine clearance < 50)
- Age > 65 years receiving full chemotherapy dose intensity

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 pegfilgrastimcan be considered in the supportive care setting.

American Society of Clinical Oncology (ASCO)[5,8,14]

American Society of Clinical Oncology (ASCO) published guidelines in 2015 entitled, “Recommendations for the Use of WBC Growth Factors: American Society of Clinical Oncology Clinical Practice Guideline Update.” 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 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.)

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- 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 Organization for Research and Treatment of Cancer (EORTC)[9]

The European Organization for Research and Treatment of Cancer (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." 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, 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.

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- 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.

Armlupeg (pegfilgrastim-unne) 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 and increase survival in patients acutely exposed to myelosuppressive doses of radiation (Hematopoietic Subsyndrome of Acute Radiation Syndrome).[23]

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.[10]

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.[18]

Granix (tbo-filgrastim) is a leukocyte growth factor indicated 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.[6]

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 non-myeloid 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 non-myeloid 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 non-myeloid malignancies

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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 non-myeloid 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 non-myeloid 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.[11]

Nypozi (filgrastim-txid) 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 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 non-myeloid 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; increase survival in patients acutely exposed to myelosuppressive doses of radiation (Hematopoietic Syndrome of Acute Radiation Syndrome).[21]

Nyvepria (pegfilgrastim-apgf) 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.[16]

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.[17]

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.[20]

Ryzneuta 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 a clinically significant incidence of febrile neutropenia.[22]

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.[19]

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.[12]

Zarxio (filgrastim-sndz) 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 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

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neutropenia and neutropenia-related clinical sequelae, e.g., febrile neutropenia, in patients with non-myeloid 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.[7]

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.[13]

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	Armlupeg, Fulphila, Fylnetra, Nyvepria, Stimufend, Udenyca, Ziextenzo
Neupogen	Nivestym, Nypozi, Releuko, Zarxio

Centers for Medicare and Medicaid Services (CMS)

Coverage guidelines for certain Part B drugs may be found in the Medicare Advantage Medical Policy titled Medications/Drugs (Outpatient/Part B). National Coverage Determinations (NCDs), Local Coverage Determinations (LCDs), and Local Coverage Articles (LCAs) may exist and compliance with these policies is required where applicable. These NCDs/LCDs/LCAs are available at https://www.cms.gov/medicare-coverage-database/new-search/search.aspx.

In general, Medicare covers outpatient (Part B) drugs that are furnished "incident to" a physician's service provided that certain criteria are met, including that the drugs are not usually self-administered by the patients who take them. Refer to the Medicare Benefit Policy Manual, Chapter 15, §50 - Drugs and Biologicals.

**Preferred therapy criteria for Medicare Advantage members, refer to Medicare Part B Step Therapy Programs.

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Policy History/Revision Information

Date	Summary of Changes

09/01/2026	**Template Update**
	• Transferred content to shared policy template that applies to both UnitedHealthcare Commercial and Individual Exchange benefit plans
	• Added *Application* section to indicate this policy applies to:
	  ○ UnitedHealthcare Commercial benefit plans
	  ○ Individual Exchange benefit plans
	Coverage Rationale
	• Revised list of applicable white blood cell colony stimulating factors (CSFs); added Armlupeg® (pegfilgrastim-unne)
	• Added language to indicate coverage for Armlupeg will be provided contingent on the criteria in the *Preferred Product Criteria* and *Diagnosis-Specific Criteria* sections [of the policy]
	Applicable Codes
	• Added HCPCS code Q5169
	Supporting Information
	• Updated *Background*, *Clinical Evidence*, *FDA*, *CMS*, and *References* sections to reflect the most current information
	• Archived previous policy versions 2025D0061AD and IEXD0061.16

Instructions for Use

This Medical Benefit Drug Policy provides assistance in interpreting UnitedHealthcare 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, check the member specific benefit plan document and any applicable federal or state mandates. 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.

This Medical Benefit Drug Policy may also be applied to Medicare Advantage plans in certain instances. In the absence of a Medicare National Coverage Determination (NCD), Local Coverage Determination (LCD), or other Medicare coverage guidance, CMS allows a Medicare Advantage Organization (MAO) to create its own coverage determinations, using objective evidence-based rationale relying on authoritative evidence (Medicare IOM Pub. No. 100-16, Ch. 4, §90.5).

UnitedHealthcare may also use tools developed by third parties, such as the InterQual® criteria, to assist us in administering health benefits. 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.

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