UnitedHealthcare Community Plan

UnitedHealthcare® Community Plan
Medical Benefit Drug Policy

WHITE BLOOD CELL COLONY STIMULATING FACTORS

Policy Number: CSLA2020D0061M **Effective Date**: TBD

Instructions for Use

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APPLICATION

This Medical Benefit Drug Policy only applies to the state of Louisiana.

COVERAGE RATIONALE

~~The~~ **This** policy refers to the following ~~drug products:~~white blood cell colony stimulating factors (CSFs):

- **Long-acting pegfilgrastim agents:**
  - Fulphila™ **(pegfilgrastim-jmdb)**
  - Neulasta® **(pegfilgrastim)**
  - Udenyca™ **(pegfilgrastim-cbqv)**
  - **Ziextenzo™ (pegfilgrastim-bmez)**
- **Short-acting filgrastim agents:**
  - Granix® **(tbo-filgrastim)**
  - Neupogen® **(filgrastim)**
  - Nivestym™ **(filgrastim-aafi)**
  - Zarxio® **(filgrastim-sndz)**
- Leukine® **(sargramostim) (see Diagnosis-Specific Criteria)**

Long-Acting Pegfilgrastim Agents (Fulphila, Neulasta, Udenyca, Ziextenzo): Preferred Product
The long-acting preferred product criteria in this section applies to the following states: CA, HI, LA, MD, MI, NE, NJ, NY, OH, PA, RI, TN, VA ~~xxxxxxx~~. For all other states, coverage will be provided contingent on the coverage criteria in the Diagnosis-Specific Criteria section.

Neulasta (pegfilgrastim) is the preferred pegfilgrastim product. Coverage will be provided for Neulasta contingent on the coverage criteria in the Diagnosis-Specific Criteria section.

Coverage for Fulphila, ~~or~~ Udenyca, or Ziextenzo will be provided contingent on the criteria in this section and the coverage criteria in the Diagnosis-Specific Criteria section.

Preferred Product Criteria
Treatment with Fulphila, ~~or~~ Udenyca, 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, resulting in minimal clinical response; and
  - Physician attests that, in their clinical opinion, the clinical response would be expected to be superior with Fulphila, ~~or~~ Udenyca, Ziextenzo, or other pegfilgrastim biosimilar product, than experienced with Neulasta;

  or
- Both of the following:
  - History of intolerance, contraindication, or adverse event to Neulasta; and
  - Physician attests that, in their clinical opinion, the same intolerance, contraindication or adverse event would not be expected to occur with Fulphila, ~~or~~ Udenyca, Ziextenzo, or other pegfilgrastim biosimilar product.

Short-Acting Filgrastim Agents (Granix, Neupogen, Nivestym, & Zarxio): Preferred Product
The short-acting preferred product criteria in this section applies to the following states: CA, HI, LA, MD, MI, NE, NJ, NY, OH, PA, RI, TN, TX, VA. For all other states, coverage will be provided contingent on the coverage criteria in the Diagnosis-Specific Criteria section.

Zarxio is the preferred filgrastim product. Coverage will be provided for Zarxio contingent on the coverage criteria in the Diagnosis-Specific Criteria section.

Coverage for Granix, Neupogen, or Nivestym will be provided contingent on the criteria in this section and the coverage criteria in the Diagnosis-Specific Criteria section.

Preferred Product Criteria
Treatment with Granix, Neupogen or Nivestym, 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, 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, Nivestym, or other filgrastim biosimilar product, than experienced with Zarxio

  or
- Both of the following:
  - History of intolerance, contraindication, or adverse event to Zarxio; and
  - Physician attests that, in their clinical opinion, the same intolerance, contraindication, or adverse event would not be expected to occur with Granix, Neupogen, Nivestym, or other filgrastim biosimilar product

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.

- Bone Marrow/Stem Cell Transplant (Leukine, Neupogen, Nivestym, Zarxio)

  Leukine, Neupogen, Nivestym, and Zarxio are proven and medically necessary when ALL of 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 has received myeloablative chemotherapy;

    and
  - Medication is dosed in accordance with the United States Food and Drug Administration (FDA) approved labeling; **and**

- Prescribed by or in consultation with a hematologist or oncologist.

- Acute Myeloid Leukemia (AML) Induction or Consolidation Therapy (Leukine, Neupogen, Nivestym, Zarxio)

  Leukine, Neupogen, Nivestym, and Zarxio are proven and medically necessary when ALL of the following criteria are met: [2-3,37,40]
  - Diagnosis of AML; **and**
  - Patient has completed either induction or consolidation chemotherapy; **and**
  - Medication is dosed in accordance with the U.S. FDA approved labeling; **and**
  - Prescribed by or in consultation with a hematologist or oncologist.

- Neutropenia Associated with Cancer Chemotherapy – Dose Dense Chemotherapy (Fulphila, Leukine, Neulasta, Neupogen, Nivestym, Udenyca, Zarxio, **Ziextenzo**)

  Fulphila, Leukine, Neulasta, Neupogen, Nivestym, Udenyca, and Zarxio are proven and medically necessary when ALL of the following criteria are met: [16-19]
  - **One** of the following:
    - Patient is receiving National Cancer Institute's Breast Intergroup, INT C9741 dose dense chemotherapy protocol for primary breast cancer; **or**
    - Patient is receiving a dose-dense chemotherapy regimen for which the incidence of febrile neutropenia (FN) is unknown;

    and
  - Medication is dosed in accordance with the U.S FDA approved labeling; **and**
  - Prescribed by or in consultation with a hematologist or oncologist.

- Primary Prophylaxis of Chemotherapy-Induced Febrile Neutropenia (FN) (Fulphila, Granix, Leukine, Neulasta, Neupogen, Nivestym, Udenyca, Zarxio, **Ziextenzo**)

  White blood cell colony stimulating factors are proven and medically necessary when ALL of the following criteria are met: [16-17]
  - **One** of the following:
    - 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 associated with chemotherapy-induced infection, FN, or neutropenia (see risk factor list);

    and
  - Medication is dosed in accordance with the U.S. FDA approved labeling; **and**
  - Prescribed by or in consultation with a hematologist or oncologist.

- Secondary Prophylaxis of Febrile Neutropenia (FN) (Fulphila, Granix, Leukine, Neulasta, Neupogen, Nivestym, Udenyca, Zarxio, **Ziextenzo**)

  White blood cell colony stimulating factors are proven and medically necessary when ALL of the following criteria are met: [1-3,16-17,39-40]
  - Patient is receiving myelosuppressive anticancer drugs associated with neutropenia (ANC ≤ 500 cells/mm^3); **and**
  - Patient has a history of FN during a previous course of chemotherapy; **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.

- Treatment of Febrile Neutropenia (FN) (Fulphila, Leukine, Neulasta, Neupogen, Nivestym, Udenyca, Zarxio, **Ziextenzo**) [Off-Label]

  Fulphila, Leukine, Neulasta, Neupogen, Nivestym, Udenyca, and Zarxio are proven and medically necessary when ALL of the following criteria are met: [1-3,16-17,40]
  - Patient is receiving myelosuppressive anticancer drugs associated with neutropenia (ANC ≤ 500 cells/mm^3); **and**
  - Diagnosis of FN and patient is considered high risk for infection-associated complications; **and**
  - Medication is dosed in accordance with the U.S. FDA approved labeling; **and**

- Prescribed by or in consultation with a hematologist or oncologist.

- Severe Chronic Neutropenia (SCN) (Neupogen, Nivestym, Zarxio)

  Neupogen, Nivestym, and Zarxio are proven and medically necessary when ALL of the following criteria are met: [2,16,40]
  - Diagnosis of SCN (i.e., congenital, cyclic, and idiopathic neutropenias with chronic ANC ≤ 500 cells/mm^3); **and**
  - Medication is dosed in accordance with the U.S. FDA approved labeling; **and**
  - Prescribed by or in consultation with a hematologist or oncologist.

- HIV-Related Neutropenia (Leukine, Neupogen, Nivestym, Zarxio) [Off-Label]

  Leukine, Neupogen, Nivestym, and Zarxio are proven and medically necessary when ALL of the following criteria are met: [2-3,11-15,21,40]
  - Diagnosis of HIV infection; **and**
  - Patient has an ANC ≤ 1,000 (cells/mm^3); **and**
  - Medication is dosed in accordance with the U.S FDA approved labeling; **and**
  - Prescribed by or in consultation with a hematologist, oncologist or infectious disease specialist.

- Hepatitis-C Treatment Related Neutropenia (Neupogen, Nivestym, Zarxio) [Off-Label]

  Neupogen, Nivestym, and Zarxio are proven and medically necessary when ALL of the following criteria are met: [2,4-10,22-25]
  - **One** of the following:
    - **All** of the following:
      - Diagnosis of Hepatitis C virus; **and**
      - Patient is undergoing treatment with Peg-Intron (peginterferon alfa-2b) or Pegasys (peginterferon alfa-2a); **and**
      - Documentation of neutropenia (ANC ≤ 500 cells/mm^3) after dose reduction of Peg-Intron or Pegasys;

      or
    - **Both** of the following:
      - Documentation of interferon-induced neutropenia (ANC ≤ 500 cells/mm^3) due to treatment with Peg-Intron (peginterferon alfa-2b) or Pegasys (peginterferon alfa-2a); **and**
      - **One** of the following:
        - Diagnosis of HIV co-infection; **or**
        - Status post liver transplant; **or**
        - Diagnosis of established cirrhosis;

    and
  - Medication is dosed in accordance with the U.S. FDA approved labeling; **and**
  - Prescribed by or in consultation with a hematologist, oncologist, infectious disease specialist, hepatologist, or gastroenterologist.

- Hematopoietic Syndrome of Acute Radiation Syndrome (Fulphila, Leukine, Neulasta, Neupogen, Nivestym, Udenyca, Zarxio, **Ziextenzo**) [1-3]

  Fulphila, Leukine, Neulasta, Neupogen, Nivestym, Udenyca, and Zarxio are proven and medically necessary when ALL of the following criteria are met: [1-3]
  - Patient has been acutely exposed to myelosuppressive doses of radiation; **and**
  - Medication is dosed in accordance with the U.S FDA approved labeling; **and**
  - Prescribed by or in consultation with a hematologist or 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 federal, state or contractual requirements and applicable laws that may require coverage for a specific service. The inclusion of a code does not imply any right to reimbursement or guarantee claim payment. Other Policies and Coverage Determination Guidelines may apply.

HCPCS Code	Description
J1442	Injection, filgrastim, (G-CSF), excludes biosimilars, 1 microgram
J1447	Injection, tbo-filgrastim, 1 microgram
J2505	Injection, pegfilgrastim, 6 mg
J2820	Injection, sargramostim (GM-CSF), 50 mcg
Q5101	Injection, filgrastim (G-CSF), biosimilar, (Zarxio), 1 mcg
Q5108	Injection, pegfilgrastim-jmdb, biosimilar, (Fulphila), 0.5 mg
Q5110	Injection, filgrastim-aafi, biosimilar, (Nivestym), 1 microgram
Q5111	Injection, pegfilgrastim-cbqv, biosimilar, (Udenyca), 0.5 mg

BACKGROUND

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

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

CLINICAL EVIDENCE

Professional Societies

The National Comprehensive Cancer Network (NCCN) publishes clinical practice guidelines for Oncology (NCCN Guidelines®) specific to myeloid growth factors. [16] The "NCCN Guidelines for Myeloid Growth Factors" are focused on the use of myeloid growth factors (MGFs) in the cancer setting. The guidelines begin with an evaluation of risk for chemotherapy-induced FN prior to the first cycle of chemotherapy. The risk assessment includes disease type, chemotherapy regimen (high-dose, dose-dense, or standard-dose therapy), patient risk factors, and treatment intent (curative/adjuvant vs. palliative). Based on the chemotherapy regimen and patient-related risk factors, the patient is assigned to either an overall high-risk group (>20% risk of FN), intermediate-risk group (10%-20% risk), or low-risk group (<10% risk). Of note, there is currently no consensus nomogram for risk assessment. While the NCCN Panel outlines criteria to aid in the assessment of FN risk, independent clinical judgment should be exercised based on the patient's situation.

The NCCN Panel identifies possible patient risk factors for febrile neutropenia. Risk factors may include:

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

(Back to criteria)

Other recommendations include:

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

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."[41] The ASCO guidelines provide direction as to how colony-stimulating factors (CSFs) should be used in people with cancer. Recommendations include:

- Primary prophylaxis with a CSF starting with the first cycle and continuing through subsequent cycles of chemotherapy is recommended in patients who have an approximately 20% or higher risk for febrile neutropenia based on patient-, disease- and treatment-related factors. Primary CSF prophylaxis should also be administered in patients receiving dose dense chemotherapy when considered appropriate. Consideration should be given to alternative, equally effective, and safe chemotherapy regimens not requiring CSF support when available. (Type: evidence based, benefits outweigh harms. Evidence quality: high. Strength of recommendation: strong.)
- Secondary prophylaxis with a CSF is recommended for patients who experienced a neutropenic complication from a prior cycle of chemotherapy (for which primary prophylaxis was not received), in which a reduced dose or treatment delay may compromise disease-free or overall survival or treatment outcome. In many clinical situations, dose reduction or delay may be a reasonable alternative. (Type: evidence based, benefits outweigh harms. Evidence quality: high. Strength of recommendation: strong.)
- CSFs should not be routinely used for patients with neutropenia who are afebrile. (Type: evidence based, benefits outweigh harms. Evidence quality: high. Strength of recommendation: strong.)
- CSFs should not be routinely used as adjunctive treatment with antibiotic therapy for patients with fever and neutropenia. However, CSFs should be considered in patients with fever and neutropenia who are at high risk for infection-associated complications or who have prognostic factors predictive of poor clinical outcomes. (Type: evidence based, benefits outweigh harms. Evidence quality: high. Strength of recommendation: strong.)
- Dose-dense regimens with CSF support should only be used if supported by convincing efficacy data or within an appropriately designed clinical trial. Efficacy data support the use of dose-dense chemotherapy in the adjuvant treatment of high-risk breast cancer and the use of high-dose intensity methotrexate, vinblastine, doxorubicin, and cisplatin in urothelial cancer. There are limited and conflicting data on the value of dose-dense regimens with CSF support in non-Hodgkin lymphoma, and it cannot routinely be recommended at this time. (Type: evidence based, benefits outweigh harms. Evidence quality: high for breast cancer and lymphoma; intermediate for urothelial cancer. Strength of recommendation: strong for breast cancer and lymphoma; moderate for urothelial cancer.)
- CSFs may be used alone, after chemotherapy, or in combination with plerixafor to mobilize peripheral-blood progenitor cells. Choice of mobilization strategy depends in part on type of cancer and type of transplantation. (Type: evidence based, benefits outweigh harms. Evidence quality: strong. Strength of recommendation: high.)
- CSFs should be administered after autologous stem-cell transplantation to reduce the duration of severe neutropenia. (Type: evidence based, benefits outweigh harms. Evidence quality: high. Strength of recommendation: strong.)
- CSFs may be administered after allogeneic stem-cell transplantation to reduce the duration of severe neutropenia. (Type: evidence based. Evidence quality: low. Strength of recommendation: weak).
- Prophylactic CSFs for patients with diffuse aggressive lymphoma age ≥ 65 years treated with curative chemotherapy (cyclophosphamide, doxorubicin, vincristine, prednisone, and rituximab) should be considered, particularly in the presence of comorbidities. (Type: evidence based, benefits outweigh harms. Evidence quality: intermediate. Strength of recommendation: moderate.)

- The use of CSFs in pediatric patients will almost always be guided by clinical protocols. As in adults, the use of CSFs is reasonable as primary prophylaxis for pediatric patients with a high likelihood of febrile neutropenia. Similarly, the use of CSFs for secondary prophylaxis or for therapy should be limited to high-risk patients. (Type: evidence based, benefits outweigh harms. Evidence quality: high. Strength of recommendation: strong.)
- For pediatric indications in which dose-intense chemotherapy is known to have a survival benefit, such as Ewing sarcoma, CSFs should be used to enable the administration of these regimens. (Type: evidence based, benefits outweigh harms. Evidence quality: high. Strength of recommendation: strong.)
- CSFs should not be used in pediatric patients with nonrelapsed acute lymphoblastic leukemia or nonrelapsed 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.)

The European Organisation 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."[43] The EORTC guidelines provide direction on the use of colony-stimulating factors for prevention of chemotherapy-induced febrile neutropenia (FN) in patients with cancer. Recommendations are graded on a scale of A-D, based on levels of evidence applied by the EORTC Guidelines Working Party. Levels of evidence are as follows: I= evidence obtained from meta-analysis of multiple, well-designed, controlled studies or from high-power randomized, controlled clinical trials; II= Evidence obtained from at least one well-designed experimental study or low-power randomized, controlled clinical trial; III= Evidence obtained from well-designed, quasi-experimental studies such as non-randomised, controlled single-group, pre-post, cohort, time or matched case-control series; IV= studies such as comparative and correlational descriptive and case studies; and V= evidence obtained from case reports and clinical examples. Grading recommendations are as follows: A= evidence of type I or consistent findings from multiple studies of types II, III or IV; B= evidence of types II, III or IV and findings are generally consistent; C= evidence of types II, III or IV but findings are inconsistent; and D= little or no systematic empirical evidence. Recommendations include:

- Recommendation 1: Patient-related risk factors for increased incidence of FN
  - Patient-related risk factors should be evaluated in the overall assessment of FN risk before administering each cycle of chemotherapy. Particular consideration should be given to the elevated risk of FN for elderly patients (aged 65 and over). Other adverse risk factors that may influence FN risk include: advanced stage of disease; experience of previous episode(s) of FN; lack of G-CSF use and absence of antibiotic prophylaxis. However, please note that the indiscriminate use of antibiotic prophylaxis for patients undergoing treatment for solid tumours or lymphoma is not recommended either by this working party or the EORTC Infectious Disease Group. Recommendation grade: B.
- Recommendation 2: Chemotherapy regimens associated with increased risk of FN
  - Consideration should be given to the elevated risk of FN when using certain chemotherapy regimens. Recommendation grade: A/B (depending on the evidence for each chemotherapy regimen). For the list of identified chemotherapy regimens, reference Table 5. It should be noted that this list is not comprehensive and there may be other drugs or regimens associated with an increased risk of FN.
- Recommendation 3: G-CSF to support chemotherapy
  - In situations where dose-dense or dose-intense chemotherapy strategies have survival benefits, prophylactic G-CSF should be used as a supportive treatment. Recommendation grade: A.
  - If reductions in chemotherapy dose intensity or density are known to be associated with a poor prognosis, primary G-CSF prophylaxis should be used to maintain chemotherapy. Examples of this could be when the patient is receiving adjuvant or potentially curative treatment or when the treatment intent is to prolong survival. Recommendation grade A. Where treatment intent is palliative, use of less myelosuppressive chemotherapy or dose/schedule modification should be considered. Recommendation grade: B.

- Recommendation 4: Impact of the overall FN risk on G-CSF use
  - The risk of complications related to FN should be assessed individually for each patient at the beginning of each cycle. When assessing FN risk, the clinician should take into account patient-related risk factors (recommendation 1), the chemotherapy regimen and associated complications (recommendations 2 and 3) and treatment intent (recommendation 3). Prophylactic G-CSF is recommended when there is a P20% overall risk of FN. When chemotherapy regimens associated with an FN risk of 10–20%, particular attention should be given to the assessment of patient characteristics that may increase the overall risk of FN. Recommendation grade: A.
- Recommendation 5: G-CSF in patients with existing FN
  - Treatment with G-CSF for patients with solid tumours 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)

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. [44]

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. [39]

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

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

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

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.

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

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

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

Reference Product	Biosimilar Product
Neulasta	Fulphila, Udenyca**, Ziextenzo**
Neupogen	Nivestym, Zarxio

CENTERS FOR MEDICARE AND MEDICAID SERVICES (CMS)

Medicare does not have a National Coverage Determination (NCD) for Colony Stimulating Factor (CSF) therapy. Local Coverage Determinations (LCDs) exist; see the LCDs for White Cell Colony Stimulating Factors , G-CSF (Neupogen®, Granix, Zarxio™, Nivestym™) and Pegfilgrastim (Neulasta®)

In general, Medicare covers outpatient (Part B) drugs that are furnished "incident to" a physician's service provided 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. (Accessed March 28, 2019)
~~Medicare does not have a National Coverage Determination (NCD) for colony stimulating factor therapy. However, Local Coverage Determinations (LCDs) exist; see the LCDs for Human Granulocyte/Macrophage Colony Stimulating Factors, G-CSF (Neupogen®, Granix™, Zarxio™) and Pegfilgrastim (Neulasta®). (Accessed March 14, 2018)~~

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POLICY HISTORY/REVISION INFORMATION

Date	Action/Description
TBD	**Coverage Rationale** • **Added Ziextenzo to the coverage rationale. Updated background, FDA, CMS and references.** • **Revised coverage criteria for *Short-Acting Filgrastim Agents (Granix, Neupogen, Nivestym, & Zarxio)* to indicate:** o **The short-acting preferred product criteria applies to the following states: CA, HI, LA, MD, MI, NE, NJ, NY, OH, PA, RI, TN, TX, VA; for all other states, coverage will be provided contingent on the criteria outlined in the *Diagnosis-Specific Criteria* section of the policy** o **Zarxio is the preferred filgrastim product; coverage will be provided for Zarxio contingent on the coverage criteria in the *Diagnosis-Specific Criteria* section of the policy** o **Coverage for Granix, Neupogen, or Nivestym will be provided contingent on the criteria in the *Preferred Product Criteria* and *Diagnosis-Specific Criteria* sections of the policy** • **Added *Preferred Product Criteria* for short-acting filgrastim agents to indicate:** o **Treatment with Granix, Neupogen, or Nivestym, 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, 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, Nivestym, or other filgrastim biosimilar product, than experienced with Zarxio** **or** ▪ **Both of the following:** - **History of intolerance, contraindication, or adverse event to Zarxio; and** - **Physician attests that, in their clinical opinion, the same intolerance, contraindication, or adverse event would not be expected to occur with Granix, Neupogen, Nivestym, or other filgrastim biosimilar product**

INSTRUCTIONS FOR USE

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

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