WHITE BLOOD CELL COLONY STIMULATING FACTORS

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INSTRUCTIONS FOR USE

This Drug Policy provides assistance in interpreting UnitedHealthcare benefit plans. When deciding coverage, the member specific benefit plan document must be referenced. The terms of the member specific benefit plan document [e.g., Certificate of Coverage (COC), Schedule of Benefits (SOB), and/or Summary Plan Description (SPD)] may differ greatly from the standard benefit plan upon which this Drug Policy is based. In the event of a conflict, the member specific benefit plan document supersedes this Drug Policy. All reviewers must first identify member eligibility, any federal or state regulatory requirements, and the member specific benefit plan coverage prior to use of this Drug Policy. Other Policies and Coverage Determination Guidelines may apply. UnitedHealthcare reserves the right, in its sole discretion, to modify its Policies and Guidelines as necessary. This 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 MCG™ Care Guidelines 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.

BENEFIT CONSIDERATIONS

Before using this policy, please check the member specific benefit plan document and any federal or state mandates, if applicable.

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. Benefit coverage for an otherwise unproven service for the treatment of serious rare diseases may occur when certain conditions are met. See the Policy and Procedure addressing the treatment of serious rare diseases.

Essential Health Benefits for Individual and Small Group

For plan years beginning on or after January 1, 2014, the Affordable Care Act of 2010 (ACA) requires fully insured non-grandfathered individual and small group plans (inside and outside of Exchanges) to provide coverage for ten categories of Essential Health Benefits (“EHBs”). Large group plans (both self-funded and fully insured), and small group ASO plans, are not subject to the requirement to offer coverage for EHBs. However, if such plans choose to provide coverage for benefits which are deemed EHBs, the ACA requires all dollar limits on those benefits to be removed on all Grandfathered and Non-Grandfathered plans. The determination of which benefits constitute EHBs is made on a state by state basis. As such, when using this policy, it is important to refer to the member specific benefit plan document to determine benefit coverage.
The policy refers to the following drug products: White Blood Cell Colony Stimulating Factors (CSFs):

- Granix
- Leukine
- Neulasta
- Neupogen
- Zarxio

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.

I. **Bone marrow/stem cell transplant (Leukine, Neupogen, Zarxio)**

Leukine, Neupogen and Zarxio are proven and medically necessary when all of the following criteria are met:

A. **One** of the following:
   1. Patient has non-myeloid malignancies and is undergoing myeloablative chemotherapy followed by autologous or allogeneic bone marrow transplant (BMT); or
   2. Used for mobilization of hematopoietic progenitor cells into the peripheral blood for collection by leukapheresis; or
   3. Patient has had a peripheral stem cell transplant (PSCT) and have received myeloablative chemotherapy; and
B. Medication is dosed in accordance with the United States Food and Drug Administration approved labeling; and
C. Prescribed by or in consultation with a hematologist or oncologist.

II. **Acute myeloid leukemia (AML) induction or consolidation therapy (Leukine, Neupogen, Zarxio)**

Leukine, Neupogen and Zarxio are proven and medically necessary when all of the following criteria are met:

A. Diagnosis of AML; and
B. Patient has completed either induction or consolidation chemotherapy; and
C. Medication is dosed in accordance with the United States Food and Drug Administration approved labeling; and
D. Prescribed by or in consultation with a hematologist or oncologist.

III. **Neutropenia associated with cancer chemotherapy – dose dense chemotherapy (Leukine, Neulasta, Neupogen, Zarxio)**

Leukine, Neulasta, Neupogen and Zarxio are proven and medically necessary when all of the following criteria are met:

A. **One** of the following:
   1. Patient is receiving National Cancer Institute’s Breast Intergroup, INT C9741 dose dense chemotherapy protocol for primary breast cancer; or
   2. Patient is receiving a dose-dense chemotherapy regimen for which the incidence of febrile neutropenia (FN) is unknown; and
B. Medication is dosed in accordance with the United States Food and Drug Administration approved labeling; and
C. Prescribed by or in consultation with a hematologist or oncologist.

IV. **Primary prophylaxis of chemotherapy-induced febrile neutropenia (FN) (Granix, Leukine, Neulasta, Neupogen, Zarxio)**

White blood cell colony stimulating factors are proven and medically necessary when all of the following criteria are met:

A. **One** of the following:
   1. Patient is receiving chemotherapy regimen(s) associated with > 20% incidence of FN; or
   2. Both of the following:
      a. Patient is receiving chemotherapy regimen(s) associated with 10-20% incidence of FN; and
      b. Patient has one or more risk factors associated with chemotherapy-induced infection, FN, or neutropenia (see the list of risk factors in the Clinical Evidence section);
and
B. Medication is dosed in accordance with the United States Food and Drug Administration approved labeling; and
c. Prescribed by or in consultation with a hematologist or oncologist.

V. Secondary prophylaxis of febrile neutropenia (FN) (Granix, Leukine, Neulasta, Neupogen, Zarxio)

White blood cell colony stimulating factors are proven and medically necessary when all of the following criteria are met: 1-3,16-17,40-41
A. Patient is receiving myelosuppressive anticancer drugs associated with neutropenia (ANC ≤ 500 cells/mm³); and
B. Patient has a history of FN during a previous course of chemotherapy; and
C. Medication is dosed in accordance with the United States Food and Drug Administration approved labeling; and
D. Prescribed by or in consultation with a hematologist or oncologist.

VI. Treatment of Febrile Neutropenia (Leukine, Neulasta, Neupogen, Zarxio) [off-label]

Leukine, Neulasta, Neupogen and Zarxio are proven and medically necessary when all of the following criteria are met: 1-3,16-17,40-41
A. Patient is receiving myelosuppressive anticancer drugs associated with neutropenia (ANC ≤ 500 cells/mm³); and
B. Diagnosis of FN and patient is considered high risk for infection-associated complications; and
C. Medication is dosed in accordance with the United States Food and Drug Administration approved labeling; and
D. Prescribed by or in consultation with a hematologist or oncologist.

VII. Severe Chronic Neutropenia (SCN) (Neupogen, Zarxio)

Neupogen and Zarxio are proven and medically necessary when all of the following criteria are met: 2,16,41
A. Diagnosis of SCN (i.e., congenital, cyclic, and idiopathic neutropenias with chronic ANC ≤ 500 cells/mm³)
B. Medication is dosed in accordance with the United States Food and Drug Administration approved labeling
C. Prescribed by or in consultation with a hematologist or oncologist

VIII. HIV-related neutropenia (Leukine, Neupogen, Zarxio) [off-label]

Leukine, Neupogen and Zarxio are proven and medically necessary when all of the following criteria are met: 2-3,11-15,21,41
A. Diagnosis of HIV infection; and
B. Patient has an ANC ≤ 1,000 (cells/mm³) ; and
C. Medication is dosed in accordance with the United States Food and Drug Administration approved labeling; and
D. Prescribed by or in consultation with a hematologist, oncologist or infectious disease specialist.

IX. Hepatitis-C treatment related neutropenia (Neupogen) [off-label]

Neupogen is proven and medically necessary when all of the following criteria are met: 2,4-10, 22-25
A. One of the following:
   1. All of the following:
      a. Diagnosis of Hepatitis C virus; and
      b. Patient is undergoing treatment with Peg-Intron (peginterferon alfa-2b) or Pegasys (peginterferon alfa-2a); and
      c. Documentation of neutropenia (ANC ≤ 500 cells/mm³) after dose reduction of Peg-Intron or Pegasys;
      or
   2. Both of the following:
      a. Documentation of interferon-induced neutropenia (ANC ≤ 500 cells/mm³) due to treatment with Peg-Intron (peginterferon alfa-2b) or Pegasys (peginterferon alfa-2a); and
      b. One of the following:
         i. Diagnosis of HIV co-infection; or
         ii. Status post liver transplant; or
         iii. Diagnosis of established cirrhosis
         and
B. Medication is dosed in accordance with the United States Food and Drug Administration approved labeling; and
C. Prescribed by or in consultation with a hematologist or oncologist.

U.S. FOOD AND DRUG ADMINISTRATION (FDA)

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; and for patients who have undergone allogeneic or autologous BMT in whom engraftment is delayed or has failed.  

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.

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).

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.

Zarxio (filgrastim-sniz) 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.

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. 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 to increase neutrophil recovery and enable delivery of more intensive or dose-dense chemotherapy when indicated.

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), pegfilgrastim (Neulasta), tbo-filgrastim (Granix) and filgrastim-sniz (Zarxio). GM-CSFs stimulate the production of both neutrophils and macrophages and include the following FDA approved products: sargramostim (Leukine).
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 Coverage Determination Guidelines may apply.

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<thead>
<tr>
<th>HCPCS Code</th>
<th>Description</th>
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<tr>
<td>J1442</td>
<td>Injection, filgrastim, (G-CSF), excludes biosimilars, 1 microgram</td>
</tr>
<tr>
<td>J1447</td>
<td>Injection, tbo-filgrastim, 1 microgram</td>
</tr>
<tr>
<td>J2505</td>
<td>Injection, pegfilgrastim, 6 mg</td>
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<tr>
<td>J2820</td>
<td>Injection, sargramostim (GM-CSF), 50 mcg</td>
</tr>
<tr>
<td>Q5101</td>
<td>Injection, filgrastim, (G-CSF), biosimilar, 1 microgram</td>
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CLINICAL EVIDENCE

Professional Societies

The National Comprehensive Cancer Network (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. Risk factors may include:
- A. Prior chemotherapy or radiation therapy
- B. Persistent neutropenia
- C. Bone marrow involvement by tumor
- D. Recent surgery and/or open wounds
- E. Liver dysfunction (bilirubin>2.0)
- F. Renal dysfunction (creatinine clearance <50)
- G. 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, or tbo-filgrastim 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, 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.” 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
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.”

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

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- **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: strong. Strength of recommendation: moderate.)**

- **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: weak.)**

- **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.)**
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.

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**REFERENCES**


