UnitedHealthcare Community Plan

Clinical Pharmacy Program Guidelines for Colony Stimulating Factors

Program	Prior Authorization
Medication	Neulasta (pegfilgrastim, G-CSF), Neulasta Onpro (pegfilgrastim G-CSF), Leukine (sargramostim, GM-CSF), Zarxio (filgrastim, G-CSF), Neupogen (filgrastim, G-CSF), Granix (tbo-filgrastim, G-CSF), Fulphila (pegfilgrastim-jmdb), Nivestym (filgrastim-aafi), Udenyca (pegfilgrastim-cbqv), Ziextenzo (pegfilgrastim-bmez), Nyvepria (pegfilgrastim-apgf)
Markets in Scope	California, Colorado, Hawaii, Maryland, Nevada, New Jersey, New York, New York EPP, Pennsylvania-CHIP, Rhode Island, South Carolina
Issue Date	12/2009
Pharmacy and Therapeutics Approval Date	1/2021
Effective Date	3/2021

1. Background:

Fulphila (pegfilgrastim-jmdb), Udenyca (pegfilgrastim-cbqv), Ziextenzo (pegfilgrastim-bmez)and Nyvepria (pegfilgrastim-apgf) are leukocyte growth factors 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.

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; 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).

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

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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).

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]

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-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.

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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, Nyvepria
Neupogen	Nivestym, Zarxio

2. Coverage Criteria:

A. <u>Bone Marrow/Stem Cell Transplant</u>

1. **Leukine** or **Zarxio** will be approved based on **<u>all</u>** of the following criteria:

a. **<u>One</u>** 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 has received myeloablative chemotherapy

-AND-

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

Authorization will be issued for 3 months or duration of therapy.

2. **Neupogen or Nivestym** will be approved based on **<u>all</u>** of the following criteria:

a. **<u>One</u>** of the following:

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(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 has received myeloablative chemotherapy

-AND-

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

-AND-

c. **One** of the following:

(1) **Both** of the following:

(a) Patient has a history of failure, contraindication, or intolerance to Zarxio
(b) Physician attestation that in their clinical opinion the clinical response would be expected to be superior with Neupogen or Nivestym than experienced with Zarxio

-OR-

(2) **Neupogen vial or Nivestym vial** will be approved if the requested dose is less than 0.3mL

Authorization will be issued for 3 months or duration of therapy.

B. AML Induction or Consolidation Therapy

1. **Leukine** or **Zarxio** will be approved based on **all** of the following criteria:

a. Diagnosis of acute myeloid leukemia (AML)

-AND-

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b. Patient has completed either induction or consolidation chemotherapy

-AND-

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

Authorization will be issued for 3 months or duration of therapy.

2. **Neupogen or Nivestym** will be approved based on **all** of the following criteria:

a. Diagnosis of acute myeloid leukemia (AML)

-AND-

b. Patient has completed either induction or consolidation chemotherapy

-AND-

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

-AND-

d. **One** of the following:

(1) **Both** of the following:

(a) Patient has a history of failure, contraindication, or intolerance to Zarxio
(b) Physician attestation that in their clinical opinion the clinical response would be expected to be superior with Neupogen or Nivestym than experienced with Zarxio

-OR-

(2) **Neupogen vial or Nivestym vial** will be approved if the requested dose is less than 0.3mL

Authorization will be issued for 3 months or duration of therapy.

C. Primary Prophylaxis of Chemotherapy-Induced Febrile Neutropenia (FN)

1. **Leukine, Neulasta, Neulasta Onpro, or Zarxio** will be approved based on **all** of the following criteria:

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a. **One** of the following:

(1) Patient is receiving chemotherapy regimen(s) associated with greater than 20% incidence of FN; **or**
(2) Patient is receiving dose dense MVAC (methotrexate, vinblastine, doxorubicin, cisplatin) for bladder cancer; **or**
(3) Patient is receiving dose dense AC (doxorubicin, cyclophosphamide) followed by dose-dense paclitaxel for breast cancer

-OR-

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 for chemotherapy-induced febrile neutropenia:
- Persistent neutropenia due to prior chemotherapy, radiation therapy or bone marrow involvement by tumor (ANC <1500 neutrophils/mcL50)
- Liver dysfunction (bilirubin>2.0)
- Renal dysfunction (creatinine clearance <50)
- Age >65 years receiving full chemotherapy dose intensity

-AND-

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

Authorization will be issued for 3 months or duration of therapy.

2. **Granix, Neupogen, or Nivestym** will be approved based on **all** of the following criteria:

a. **One** of the following:

(1) Patient is receiving chemotherapy regimen(s) associated with greater than 20% incidence of FN; **or**
(2) Patient is receiving dose dense MVAC (methotrexate, vinblastine, doxorubicin, cisplatin) for bladder cancer**; or**
(3) Patient is receiving dose dense AC (doxorubicin, cyclophosphamide) followed by dose-dense paclitaxel for breast cancer

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-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 for chemotherapy-induced febrile neutropenia:
- Persistent neutropenia due to prior chemotherapy, radiation therapy or bone marrow involvement by tumor (ANC <1500 neutrophils/mcL50)
- Liver dysfunction (bilirubin>2.0)
- Renal dysfunction (creatinine clearance <50)
- Age >65 years receiving full chemotherapy dose intensity

-AND-

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

-AND-

c. **One** of the following:

(1) **Both** of the following:

(a) Patient has a history of failure, contraindication, or intolerance to Zarxio
(b) Physician attestation that in their clinical opinion the clinical response would be expected to be superior with Granix, Neupogen, or Nivestym than experienced with Zarxio

-OR-

(2) **Granix vial, Neupogen vial, or Nivestym vial** will be approved if the requested dose is less than 0.3mL

Authorization will be issued for 3 months or duration of therapy.

3. **Fulphila, Udenyca, Ziextenzo, or Nyvepria** will be approved based on **all** of the following criteria:

a. **One** of the following:

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(1) Patient is receiving chemotherapy regimen(s) associated with greater than 20% incidence of FN; **or**
(2) Patient is receiving dose dense MVAC (methotrexate, vinblastine, doxorubicin, cisplatin) for bladder cancer; **or**
(3) Patient is receiving dose dense AC (doxorubicin, cyclophosphamide) followed by dose-dense paclitaxel for breast cancer

-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 for chemotherapy-induced febrile neutropenia:
- Persistent neutropenia due to prior chemotherapy, radiation therapy or bone marrow involvement by tumor (ANC <1500 neutrophils/mcL50)
- Liver dysfunction (bilirubin>2.0)
- Renal dysfunction (creatinine clearance <50)
- Age >65 years receiving full chemotherapy dose intensity

-AND-

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

-AND-

c. **Both** of the following:

(1) Patient has a history of failure, contraindication, or intolerance to Neulasta
(2) Physician attestation that in their clinical opinion the clinical response would be expected to be superior with Fulphila, Udenyca, Ziextenzo, or Nyvepria than experienced with Neulasta

Authorization will be issued for 3 months or duration of therapy.

Note: Chemotherapy regimen associated incidence of febrile neutropenia will be based on the clinical trial(s) with the highest level of evidence according to the GRADE criteria.

D. Secondary Prophylaxis of Febrile Neutropenia (FN)

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1. **Leukine, Neulasta, Neulasta Onpro, or Zarxio** will be approved based on **all** of the following criteria:

a. Patient is receiving myelosuppressive anti-cancer drugs associated with neutropenia (ANC less than or equal to 1500 neutrophils/mcL[50])

-AND-

b. A documented history of febrile neutropenia during a previous course of chemotherapy

-AND-

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

Authorization will be issued for 3 months or duration of therapy.

2. **Granix, Neupogen, or Nivestym** will be approved based on **all** of the following criteria:

a. Patient is receiving myelosuppressive anti-cancer drugs associated with neutropenia (ANC less than or equal to 1500 neutrophils/mcL[50])

-AND-

b. A documented history of febrile neutropenia during a previous course of chemotherapy

-AND-

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

-AND-

d. **One** of the following:

(1) **Both** of the following:

(a) Patient has a history of failure, contraindication, or intolerance to Zarxio
(b) Physician attestation that in their clinical opinion the clinical response would be expected to be superior with Granix, Neupogen, or Nivestym than experienced with Zarxio

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-OR-

(2) **Granix vial, Neupogen vial, or Nivestym vial** will be approved if the requested dose is less than 0.3mL

Authorization will be issued for 3 months or duration of therapy.

3. **Fulphila, Udenyca, Ziextenzo, or Nyvepria** will be approved based on **all** of the following criteria:

a. Patient is receiving myelosuppressive anti-cancer drugs associated with neutropenia (ANC less than or equal to 1500 neutrophils/mcL[50])

-AND-

b. A documented history of febrile neutropenia during a previous course of chemotherapy

-AND-

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

-AND-

d. **Both** of the following:

(1) Patient has a history of failure, contraindication, or intolerance to Neulasta
(2) Physician attestation that in their clinical opinion the clinical response would be expected to be superior with Fulphila, Udenyca, Ziextenzo, and Nyvepria than experienced with Neulasta

Authorization will be issued for 3 months or duration of therapy.

E. Treatment of Febrile Neutropenia (FN) (off-label)

1. **Leukine, Neulasta, Neulasta Onpro, or Zarxio** will be approved based on **all** of the following criteria:

a. Diagnosis of febrile neutropenia; **and**

b. Patient is considered high risk for infection-associated complications; (e.g. hypotension, acute renal, respiratory, heart failure) with the score of < 21 on Multinational Association of Supportive Care in Cancer

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(MASCC) Scoring system in patients with cancer and febrile neutropenia

-AND-

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

Authorization will be issued for 1 month.

2. **Neupogen or Nivestym** will be approved based on **all** of the following criteria:

a. Diagnosis of febrile neutropenia; **and**

b. Patient is considered high risk for infection-associated complications; (e.g. hypotension, acute renal, respiratory, heart failure) with the score of < 21 on Multinational Association of Supportive Care in Cancer (MASCC) Scoring system in patients with cancer and febrile neutropenia

-AND-

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

-AND-

d. **One** of the following:

(1) **Both** of the following:

(a) Patient has a history of failure, contraindication, or intolerance to Zarxio
(b) Physician attestation that in their clinical opinion the clinical response would be expected to be superior with Neupogen or Nivestym than experienced with Zarxio

-OR-

(2) **Neupogen vial or Nivestym vial** will be approved if the requested dose is less than 0.3mL

Authorization will be issued for 1 month.

3. **Fulphila, Udenyca, Ziextenzo, or Nyvepria** will be approved based on **all** of the following criteria:

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a Diagnosis of febrile neutropenia; **and**

b. Patient is considered high risk for infection-associated complications; (e.g. hypotension, acute renal, respiratory, heart failure) with the score of < 21 on Multinational Association of Supportive Care in Cancer (MASCC) Scoring system in patients with cancer and febrile neutropenia

-AND-

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

-AND-

d. **Both** of the following:

(1) Patient has a history of failure, contraindication, or intolerance to Neulasta
(2) Physician attestation that in their clinical opinion the clinical response would be expected to be superior with Fulphila, Udenyca, Ziextenzo, or Nyvepria than experienced with Neulasta

Authorization will be issued for 1 month.

F. Severe Chronic Neutropenia (SCN)

1. **Zarxio** will be approved based on **all** of the following criteria:

a. Diagnosis of SCN (i.e., congenital, cyclic, and idiopathic neutropenias with chronic ANC less than or equal to 500 neutrophils/mcL[50])

-AND-

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

Authorization will be issued for 12 months.

2. **Neupogen or Nivestym** will be approved based on **all** of the following criteria:

a. Diagnosis of SCN (i.e., congenital, cyclic, and idiopathic neutropenias with chronic ANC less than or equal to 500 neutrophils/mcL[50])

-AND-

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

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-AND-

c. **One** of the following:

(1) **Both** of the following:
(a) Patient has a history of failure, contraindication, or intolerance to Zarxio
(b) Physician attestation that in their clinical opinion the clinical response would be expected to be superior with Neupogen or Nivestym than experienced with Zarxio

-OR-

(2) **Neupogen vial or Nivestym vial** will be approved if the requested dose is less than 0.3mL

Authorization will be issued for 12 months.

G.

I. Hematopoietic Syndrome of Acute Radiation Syndrome

1. **Leukine, Neulasta, or Zarxio** will be approved based on **all** of the following criteria:

a. Patient has been acutely exposed to myelosuppressive doses of radiation

-AND-

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

Authorization will be issued for 3 months or duration of therapy.

2. **Neupogen or Nivestym** will be approved based on **all** of the following criteria:

a. Patient has been acutely exposed to myelosuppressive doses of radiation

-AND-

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

-AND-

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c. **One** of the following:

(1) **Both** of the following:

(a) Patient has a history of failure, contraindication, or intolerance to Zarxio
(b) Physician attestation that in their clinical opinion the clinical response would be expected to be superior with Neupogen or Nivestym than experienced with Zarxio

-OR-

(2) **Neupogen vial or Nivestym vial** will be approved if the requested dose is less than 0.3mL

Authorization will be issued for 3 months or duration of therapy.

3. **Fulphila, Udenyca, Ziextenzo, or Nyvepria** will be approved based on **all** of the following criteria:

a. Patient has been acutely exposed to myelosuppressive doses of radiation

-AND-

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

-AND-

c. **Both** of the following:

(1) Patient has a history of failure, contraindication, or intolerance to Neulasta
(2) Physician attestation that in their clinical opinion the clinical response would be expected to be superior with Fulphila, Udenyca, Ziextenzo, or Nyvepria than experienced with Neulasta

Authorization will be issued for 3 months or duration of therapy.

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,

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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

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." 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

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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.)

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• 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

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o 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

o 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.

o 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

o 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

o 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

o 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.

3. Additional Clinical Rules:

- Notwithstanding Coverage Criteria, UnitedHealthcare may approve initial and re-authorization based solely on previous claim/medication history, diagnosis codes (ICD-10) and/or claim logic. Use of automated approval and re-approval processes varies by program and/or therapeutic class.
- Supply limits may be in place.

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Program	Prior Authorization
Change Control	
Date	Change

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12/2009	Criteria were taken from previously approved AmeriChoice Growth Hormone policy and Unison's RX06 Colony Stimulating Factors policy. Policy was updated and reformatted.
2/2010	Addition of intermediate or high-risk chemotherapy regimens as a risk factor for febrile neutropenia under Primary Prophylaxis of Chemotherapy Induced Febrile Neutropenia. Addition of coverage for Myelodysplastic Syndromes (off-label).
12/2011	Annual Review • Updated authorization period for bone marrow/stem cell transplant • Updated authorization period for AML Induction or Consolidation Therapy • Added Dose Dense Chemotherapy criteria to the Neutropenia Associated with Cancer Chemotherapy section. Added table 1 as a reference for Intergroup C9741 Protocol • Updated authorization period for Severe Chronic Neutropenia (SCN) • Updated Hepatitis-C Treatment Related Neutropenia (Off-label) criteria
12/2012	• Added prescriber requirements. • Separated criteria for each individual drug (Neupogen, Neulasta, and Luekine) instead of combining criteria for each drug at each section of the guideline (where necessary). • Updated clinical requirements for each section to align with national UHC guideline.
3/2013	• Revised background (formatting, references, treatment guidelines); made notes into endnotes; made examples into endnotes to match Medicare; added prescriber requirement for Neupogen to match Medicare • Removed unnecessary HIV-related neutropenia criteria for pts • with risk factors since it can be approved for pts with or without • risk factors; addition of infectious disease specialist for HIV related neutropenia
5/2013	• Added additional prescribers for neutropenia related to hepatitis C: gastroenterologist and infectious disease specialist.
6/2014	• Added Granix to the product list for the following indications: primary prophylaxis of chemotherapy-induced febrile neutropenia and secondary prophylaxis of febrile neutropenia. • Background and references updated. • Template updated to align across UHC enterprise

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9/2015	Added Zarxio to product list and reference list Removed Neupogen as a preferred product in all applicable criteria sections and replaced with Zarxio and Granix
9/2016	Removed Granix as a preferred product in all applicable criteria sections. Added non-preferred products section. Updated policy template.
12/2016	Added criteria to allow for approval of Neupogen if the requested dose is less than 0.3mL
12/2017	Added Neulasta Onpro to medications section and throughout criteria as a preferred product. Updated references.
8/2018	Added Fulphila and Nivestym to the policy. Updated background and minor changes to criteria to align with medical policy. Updated references.
10/2018	Added review criteria for Hematopoietic Syndrome of Acute Radiation Syndrome. Updated background and references.
1/2019	Added Udenyca to program. Revised step therapy criteria based on changes in preferred pegfilgrastim products. Added non-preferred product review to each section to clarify intent. Updated references.
4/2019	Revised step therapy medications due to changes in preferred products. Added information on biosimilars to the background.
1/2020	Added Ziextenzo to the program. Updated background and references.
1/2021	Annual review. Revised clinical criteria removing Neutropenia Associated with Cancer Chemotherapy and adding dose dense chemotherapy under Primary Prophylaxis of Chemotherapy-Induced Febrile Neutropenia (FN). Added specific criteria under risk factors for chemotherapy-induced febrile neutropenia in patients receiving chemotherapy regimen(s) associated with 10 – 20% incidence of febrile neutropenia. Removed criteria for HIV and Hepatitis C related neutropenia. Added Nyvepria to the program. Updated background and references

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