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Policy Number: 037.013

Title: Coverage Determination Policy for Colony Stimulating Factors (CSF):

- **Neulasta (Pegfilgrastim); Fulphila (Pegfilgrastim-jmdb); Udenyca (Pegfilgrastim-cbqv); Ziextenzo (Pegfilgrastim-bmez); Nyvepria (Pegfilgrastim-apfg); Fylnetra (Pegfilgrastim-pbbk); Stimufend (Pegfilgrastim-fpgk); Rolvedon (Eflapegrastim- xnst); Neupogen (Filgrastim); Nivestym (Filgrastim-aafi); Zarxio (Filgrastim-sndz); Leukine (Sargramostim); Granix (Tbo-Filgrastim); Releuko (Filgrastim-ayow)**

Regions: ☒ **Texas** ☒ **New Mexico**

Impacted Areas:

☒ Network Management/Provider Services	☒ Utilization Management
☐ Member services	☐ Case management
☐ Quality Management	☐ Disease management
☐ Credentialing	☒ Claims
☐ IT	☐ Human resources
☐ Administration	☐ Finance
☐ Compliance/delegation	☒ Pharmacy
	☐ ALL

Available LCD/NCD/LCA: None

Disclaimer:
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Title: Coverage Determination Policy for Colony Stimulating Factors (CSF):

Long-acting GCSF agents	Short-acting GCSF agents
Neulasta (Pegfilgrastim)	Neupogen (Filgrastim)
Fulphila (Pegfilgrastim-jmdb)	Nivestym (Filgrastim-aafi)
Udenyca (Pegfilgrastim-cbqv)	Zarxio (Filgrastim-sndz)
Ziextenzo (Pegfilgrastim-bmez)	Leukine (Sargramostim)
Nyvepria (Pegfilgrastim-apfg)	Granix (Tbo-Filgrastim)
Fylnetra (Pegfilgrastim-pbbk)	Releuko (Filgrastim-ayow)
Stimufend (Pegfilgrastim-fpgk)	
Rolvedon (Eflapegrastim- xnst)	

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Coverage Policy Number: 037.013

Line of Business: Medicare Part B

Policy Type: Prior Authorization

Coverage Determination:

Step Therapy

This policy supplements the Medicare guidelines such as NCDs, LCDs, and other Medicare manuals for the purposes of determining coverage under the Part B medical benefits. This Step Therapy Policy is implemented to enforce a step therapy requirement for new starts only. This policy is not applicable to members continuing therapy within the past 365 days. Coverage is granted if Medicare Coverage requirements PLUS these step criteria are met.

1. **Short-Acting Colony Stimulating Factors**

   Preferred drug(s): Zarxio

   Non-preferred drug(s): Granix, Neupogen, Nivestym, Releuko

   Non-Preferred Product Step Therapy Criteria

   Granix, **Neupogen**, **Nivestym,** or **Releuko** may be covered when **ANY** of the criteria listed below in Sections **A, B, or C** are satisfied:

   - **A.** History of use of Zarxio resulting in minimal clinical response to therapy
   - **B.** History of intolerance or adverse event to Zarxio
   - **C.** Continuation of prior therapy within the past 365 days

2. **Long-Acting Colony Stimulating Factors**

   Preferred drug(s): Neulasta, Udenyca

   Non-preferred drug(s): Fulphila, Fylnetra, Nyvepria, Rolvedon, Stimufend, Ziextenzo

   Non-Preferred Product Step Therapy Criteria

   Fulphila, Fylnetra, Nyvepria, Rolvedon, Ziextenzo or Stimufend, may be covered when **ANY** of the criteria listed below in Sections **A, B, or C** are satisfied:

   - **A.** History of use of Neulasta, and Udenyca resulting in minimal clinical response to therapy
   - **B.** History of intolerance or adverse event to Neulasta and Udenyca
   - **C.** Continuation of prior therapy within the past 365 days

Initial/New Requests

1. WellMed Medical Management will cover **Neupogen (Filgrastim), Nivestym (Filgrastim-aafi), Releuko (Filgrastim-ayow), and Zarxio (Filgrastim-sndz)** as medically necessary and appropriate based on the following indication-specific criteria for the following uses:

Bone Marrow/Stem Cell Transplantation when **ONE** of the following criteria are met:

A. Patient has non-myeloid malignancies and is undergoing myeloablative chemotherapy followed by autologous or allogeneic bone marrow transplant (BMT)

B. Used for mobilization of hematopoietic progenitor cells into the peripheral blood for collection by leukapheresis

C. Patient has had a peripheral stem cell transplant (PSCT) and have received myeloablative chemotherapy

Acute Myeloid Leukemia receiving induction or consolidation chemotherapy when **ALL** of the following criteria are met:

A. Diagnosis of AML

B. **ONE** of the following:

i. Patient achieved complete remission after induction therapy

ii. Patient is receiving consolidation chemotherapy

iii. Patient is receiving fludarabine, cytarabine with or without idarubicin for relapsed or refractory disease

iv. Patient is receiving cladribine, cytarabine with or without mitoxantrone or idarubicin for relapsed or refractory disease

Primary Prophylaxis of Chemotherapy-Induced Febrile Neutropenia (FN) when **ONE** of the following criteria are met:

A. Patient is receiving dose dense MVAC (methotrexate, vinblastine, doxorubicin, cisplatin) for bladder cancer
B. Patient is receiving dose dense AC (doxorubicin, cyclophosphamide) followed by dose-dense paclitaxel for breast cancer
C. Patient is receiving chemotherapy regimen(s) associated with > 20% incidence of FN
D. **BOTH** of the following:
    i. Patient is receiving chemotherapy regimen(s) associated with 10- 20% incidence of FN
    ii. Patient has **ONE** or more risk factors for chemotherapy-induced Febrile Neutropenia such as:
        a. Persistent Neutropenia due to prior chemotherapy, radiation therapy or bone marrow involvement by tumor
        (< 500 neutrophils/mcL or < 1,000 neutrophils/mcL and a predicted decline to ≤ 500 neutrophils/mcL over the next 48 hours)
        b. Liver dysfunction (bilirubin > 2.0)
        c. Renal dysfunction (creatinine clearance < 50)
        d. Age > 65 years receiving full chemotherapy dose intensity

Secondary Prophylaxis of Febrile Neutropenia when **ONE** of the following criteria are met:

A. **ONE** of the following:
   i. Patient is receiving myelosuppressive anticancer drug(s) given with a curative intent (curative chemotherapy, chemotherapy in curative adjuvant/neoadjuvant setting)
   ii. Patient is receiving myelosuppressive anticancer drug(s) given with a non-curative intent and use of secondary prophylaxis is in accordance with the United States Food and Drug Administration approved labeling
   iii. Patient is receiving myelosuppressive anticancer drug(s) for definitive therapy (bridge to stem cell transplant, organ transplant, definitive surgery for oligometastatic disease);
   iv. **ONE** of the following:
      a. Patient has a documented history of a neutropenic event (Febrile Neutropenia or low neutrophil count leading to delay of subsequent cycle) during a previous cycle of the same chemotherapy regimen at full dose for which primary prophylaxis was not received
      b. Patient has a documented history of neutropenic event from a previous course of chemotherapy

B. **BOTH** of the following:
   i. Patient is receiving myelosuppressive anticancer drug(s) given with non-curative intent
   ii. Patient has a documented history of neutropenic event (Febrile Neutropenia or low neutrophil count leading to delay of subsequent cycle) during a previous cycle of the same chemotherapy regimen after a trial of dose reduction

C. Patient is receiving myelosuppressive anticancer drug(s) where primary prophylaxis is indicated

Treatment of Febrile Neutropenia (off-label) when **ALL** of the following criteria are met:

A. Diagnosis of Febrile Neutropenia; and
B. Patient has not received long-acting prophylactic pegfilgrastim in the last 14 days
C. Patient has **ONE** or more risk factors for an infection-associated complication such as:
    i. Sepsis syndrome
    ii. Age > 65 years
    iii. Absolute Neutrophil Count (ANC) < 100/mcL
    iv. Neutropenia expected to be > 10 days in duration
    v. Pneumonia
    vi. Clinically documented infections including invasive fungal infection
    vii. Hospitalization at the time of fever
    viii. Prior episode(s) of FN

Severe Chronic Neutropenia (SCN) when **ALL** of the following criteria are met:

A. Diagnosis of SCN (i.e., congenital, cyclic, and idiopathic Neutropenias with chronic ANC ≤ 500 neutrophils/mcL)
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

Hematopoietic Syndrome of Acute Radiation Syndrome when **ALL** of the following criteria are met:

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

2. WellMed Medical Management will cover **Fulphila (Pegfilgrastim-jmdb), Fylnetra (Pegfilgrastim-pbbk), Neulasta (Pegfilgrastim), Nyvepria (Pegfilgrastim-apfg), Rolvedon (Eflapegrastim- xnst), Stimufend (Pegfilgrastim-fpgk), Udenyca (Pegfilgrastim-cbqv), and Ziextenzo (Pegfilgrastim-bmez)** as medically necessary for the following uses:

Primary Prophylaxis of Chemotherapy-Induced Febrile Neutropenia when **ONE** of the following criteria are met:

A. Patient is receiving dose dense MVAC (methotrexate, vinblastine, doxorubicin, cisplatin) for bladder cancer
B. Patient is receiving dose dense AC (doxorubicin, cyclophosphamide) followed by dose-dense paclitaxel for breast cancer
C. Patient is receiving chemotherapy regimen(s) associated with > 20% incidence of FN
D. **BOTH** of the following:
    i. Patient is receiving chemotherapy regimen(s) associated with 10- 20% incidence of FN
    ii. Patient has **ONE** or more risk factors for chemotherapy-induced Febrile Neutropenia such as:
        a. Persistent Neutropenia due to prior chemotherapy, radiation therapy or bone marrow involvement by tumor (< 500 neutrophils/mcL or < 1,000 neutrophils/mcL and a predicted decline to ≤ 500 neutrophils/mcL over the next 48 hours)
        b. Liver dysfunction (bilirubin > 2.0)
        c. Renal dysfunction (creatinine clearance < 50)
        d. Age > 65 years receiving full chemotherapy dose intensity

Secondary Prophylaxis of Febrile Neutropenia when **ONE** of the following criteria are met:

A. **ONE** of the following:
   i. Patient is receiving myelosuppressive anticancer drug(s) given with a curative intent (curative chemotherapy, chemotherapy in curative adjuvant/neoadjuvant setting)
   ii. Patient is receiving myelosuppressive anticancer drug(s) given with a non-curative intent and use of secondary prophylaxis is in accordance with the United States Food and Drug Administration approved labeling
   iii. Patient is receiving myelosuppressive anticancer drug(s) for definitive therapy (bridge to stem cell transplant, organ transplant, definitive surgery for oligometastatic disease)

AND

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

OR

B. **BOTH** of the following:
   i. snipPatient is receiving myelosuppressive anticancer drug(s) given with non-curative intent
   ii. Patient has a documented history of neutropenic event (Febrile Neutropenia or low neutrophil count leading to delay of subsequent cycle) during a previous cycle of the same chemotherapy regimen after a trial of dose reduction

OR

C. Patient is receiving myelosuppressive anticancer drug(s) where primary prophylaxis is indicated.

Treatment of Febrile Neutropenia (off-label) when **ALL** of the following criteria are met:

A. Diagnosis of Febrile Neutropenia
B. Patient has not received long-acting prophylactic pegfilgrastim in the last 14 days; and
C. Patient has **ONE** or more risk factors for an infection-associated complication such as:
    i. Sepsis syndrome
    ii. Age > 65 years
    iii. Absolute Neutrophil Count (ANC) < 100/mcL
    iv. Neutropenia expected to be > 10 days in duration
    v. Pneumonia
    vi. Clinically documented infections including invasive fungal infection
    vii. Hospitalization at the time of fever
    viii. Prior episode(s) of FN

Hematopoietic Syndrome of Acute Radiation Syndrome when **ALL** of the following criteria are met:

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

3. WellMed Medical Management will cover **Granix (Tbo-filgrastim)** as medically necessary for the following uses:

Primary Prophylaxis of Chemotherapy-Induced Febrile Neutropenia when **ONE** of the following criteria are met:

A. Patient is receiving dose dense MVAC (methotrexate, vinblastine, doxorubicin, cisplatin) for bladder cancer
B. Patient is receiving dose dense AC (doxorubicin, cyclophosphamide) followed by dose-dense paclitaxel for breast cancer
C. Patient is receiving chemotherapy regimen(s) associated with > 20% incidence of FN

OR

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

Secondary Prophylaxis of Febrile Neutropenia when **ONE** of the following criteria are met:

A. **ONE** of the following:
   i. Patient is receiving myelosuppressive anticancer drug(s) given with a curative intent (curative chemotherapy, chemotherapy in curative adjuvant/neoadjuvant setting)
   ii. Patient is receiving myelosuppressive anticancer drug(s) given with a non-curative intent and use of secondary prophylaxis is in accordance with the United States Food and Drug Administration approved labeling
   iii. Patient is receiving myelosuppressive anticancer drug(s) for definitive therapy (bridge to stem cell transplant, organ transplant, definitive surgery for oligometastatic disease)

AND

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

OR

B. **BOTH** of the following:
   i. Patient is receiving myelosuppressive anticancer drug(s) given with non-curative intent
   ii. Patient has a documented history of neutropenic event (Febrile Neutropenia or low neutrophil count leading to delay of subsequent cycle) during a previous cycle of the same chemotherapy regimen after a trial of dose reduction

OR

C. Patient is receiving myelosuppressive anticancer drug(s) where primary prophylaxis is indicated

4. WellMed Medical Management will cover **Leukine (Sargramostim)** as medically necessary for the following uses:

Bone Marrow/Stem Cell Transplantation when **ONE** of the following criteria are met:

A. Patient has non-myeloid malignancies and is undergoing myeloablative chemotherapy followed by autologous or allogeneic bone marrow transplant (BMT)
B. Used for mobilization of hematopoietic progenitor cells into the peripheral blood for collection by leukapheresis
C. Patient has had a peripheral stem cell transplant (PSCT) and have received myeloablative chemotherapy

Acute Myeloid Leukemia Receiving Induction or Consolidation Chemotherapy when **ALL** of the following criteria are met:

A. Diagnosis of AML
B. **ONE** of the following:
    i. Patient achieved complete remission after induction therapy
    ii. Patient is receiving consolidation chemotherapy
    iii. Patient is receiving fludarabine, cytarabine with or without idarubicin for relapsed or refractory disease
    iv. Patient is receiving cladribine, cytarabine with or without mitoxantrone or idarubicin for relapsed or refractory disease

Primary Prophylaxis of Chemotherapy-Induced Febrile Neutropenia when **ONE** of the following criteria are met:

A. Patient is receiving dose dense MVAC (methotrexate, vinblastine, doxorubicin, cisplatin) for bladder cancer
B. Patient is receiving dose dense AC (doxorubicin, cyclophosphamide) followed by dose-dense paclitaxel for breast cancer
C. Patient is receiving chemotherapy regimen(s) associated with > 20% incidence of FN

OR

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

Secondary Prophylaxis of Febrile Neutropenia when **ONE** of the following criteria are met:

A. **ONE** of the following:
   i. Patient is receiving myelosuppressive anticancer drug(s) given with a curative intent (curative chemotherapy, chemotherapy in curative adjuvant/neoadjuvant setting)
   ii. Patient is receiving myelosuppressive anticancer drug(s) given with a non-curative intent and use of secondary prophylaxis is in accordance with the United States Food and Drug Administration approved labeling
   iii. Patient is receiving myelosuppressive anticancer drug(s) for definitive therapy (bridge to stem cell transplant, organ transplant, definitive surgery for oligometastatic disease)

AND

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

OR

B. **BOTH** of the following:
   i. Patient is receiving myelosuppressive anticancer drug(s) given with non-curative intent
   ii. Patient has a documented history of neutropenic event (Febrile Neutropenia or low neutrophil count leading to delay of subsequent cycle) during a previous cycle of the same chemotherapy regimen after a trial of dose reduction

OR

C. Patient is receiving myelosuppressive anticancer drug(s) where primary prophylaxis is indicated

Treatment of Febrile Neutropenia (off-label) when **ALL** of the following criteria are met:

A. Diagnosis of Febrile Neutropenia
B. Patient has not received long-acting prophylactic pegfilgrastim in the last 14 days
C. Patient has **ONE** or more risk factors for an infection-associated complication such as:
    i. Sepsis syndrome
    ii. Age > 65 years
    iii. Absolute Neutrophil Count (ANC) < 100/mcL
    iv. Neutropenia expected to be > 10 days in duration
    v. Pneumonia
    vi. Clinically documented infections including invasive fungal infection
    vii. Hospitalization at the time of fever
    viii. Prior episode(s) of FN

Hematopoietic Syndrome of Acute Radiation Syndrome when **ALL** of the following criteria are met:

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

NOTE:
NCCN guideline recommends that prior to second or subsequent chemotherapy cycles, dose reduction or change in treatment regimen should be considered in patients with prior use of GCSF.

Renewal/Continuation of Therapy Requests

WellMed Medical Management **WILL COVER** renewal or continuation of therapy requests for: **Neulasta (Pegfilgrastim); Fulphila (Pegfilgrastim-jmdb); Udenyca (Pegfilgrastim-cbqv); Ziextenzo (Pegfilgrastim-bmez); Nyvepria (Pegfilgrastim-apfg); Fylnetra (Pegfilgrastim-pbbk); Stimufend (Pegfilgrastim-fpgk); Rolvedon (Eflapegrastim- xnst)**; **Neupogen (Filgrastim); Nivestym (Filgrastim-aafi); Zarxio (Filgrastim-sndz); Leukine (Sargramostim); Granix (Tbo-Filgrastim); Releuko (Filgrastim-ayow),** if the following criteria are met:

A. The patient continues to meet initial treatment criteria requirement (e.g. AML Induction or Consolidation Therapy; Secondary Prophylaxis of FN; etc)
B. The requested dosing regimen remains within the FDA recommended dosing

FDA Approved Dose and Indication

Neupogen (Filgrastim) **Nivestym (Filgrastim-aafi)** **Releuko (Filgrastim-ayow)** **Zarxio (Filgrastim-sndz)**	Febrile neutropenia, In non-myeloid malignancies, in patients undergoing myeloablative chemotherapy followed by marrow transplantation; Prophylaxis • 10 mcg/kg/day given as an IV infusion lasting no longer than 24 hours; start at least 24 hours after chemotherapy and bone marrow infusion Febrile neutropenia, In non-myeloid malignancies following myelosuppressive chemotherapy; Prophylaxis • 5 mcg/kg SUBQ or IV daily starting at least 24 hours after chemotherapy Febrile neutropenia, In patients with acute myeloid leukemia receiving chemotherapy; Prophylaxis • 5 mcg/kg SUBQ or IV daily; starting at least 24 hours after chemotherapy Harvesting of peripheral blood stem cells • 10 mcg/kg/day SUBQ given at least 4 days before first leukapheresis and continued until the last leukapheresis Hematopoietic subsyndrome of acute radiation syndrome • 10 mcg/kg SUBQ as a single daily dose, starting as soon as possible after suspected or confirmed exposure to radiation dose greater than 2 gray; do not delay administration if a CBC is unavailable; continue until absolute neutrophil count (ANC) is greater than 1000/mm(3) for 3 consecutive CBCs obtained approximately every third day or ANC is greater than 10,000/mm(3) after radiation-induced nadir Neutropenic disorder, chronic (Severe), Symptomatic • (Congenital neutropenia) 6 mcg/kg SUBQ twice daily • (Idiopathic or cyclic neutropenia) 5 mcg/kg SUBQ daily

Granix (Tbo-Filgrastim)	Neutropenia (Severe), In nonmyeloid malignancies following myelosuppressive chemotherapy; Prophylaxis • 5 mcg/kg/day subQ; give first dose no earlier than 24 hours after myelosuppressive chemotherapy; continue until the expected neutrophil count passes nadir and has recovered to normal range; do not give within 24 hours prior to chemotherapy

Leukine (Sargramostim)	Acute myeloid leukemia - Neutrophil recovery, Following induction chemotherapy • 250 mcg/m(2)/day IV over 4 hours beginning on or about day 11 or 4 days following the completion of induction chemotherapy if the day 10 bone marrow is hypoplastic (less than 5% blasts). Continue sargramostim until the absolute neutrophil count is greater than 1500 cells/mm(3) for 3 consecutive days or for a maximum of 42 days. If a second cycle of induction chemotherapy is required, administer sargramostim approximately 4 days following the completion of chemotherapy if the bone marrow is hypoplastic with less than 5% blasts. Discontinue if leukemic regrowth occurs Allogeneic bone marrow transplantation, Myeloid reconstitution • 250 mcg/m(2)/day IV over 2 hours; begin 2 to 4 hours after bone marrow infusion and continue until the ANC is greater than 1500 cells/mm(3) for 3 consecutive days; do not administer sooner than 24 hours after the last dose of chemotherapy or radiotherapy, within 24 hours before chemotherapy or radiotherapy, or until the post marrow infusion ANC is less than 500 cells/mm(3) Autologous bone marrow transplant, Myeloid reconstitution • 250 mcg/m(2)/day IV over 2 hours; begin 2 to 4 hours after bone marrow infusion and continue until the ANC is greater than 1500 cells/mm(3) for 3 consecutive days; do not administer sooner than 24 hours after the last dose of chemotherapy or radiotherapy, within 24 hours before

	chemotherapy or radiotherapy, or until the post marrow infusion ANC is less than 500 cells/mm(3) Bone marrow transplant, Delay or failure of myeloid engraftment • 250 mcg/m(2)/day IV over 2 hours for 14 days; may repeat after 7 days off therapy if neutrophil recovery has not occurred; after an additional 7 days, may administer a third course of 500 mcg/m(2)/day for 14 days. If there is still no improvement, it is unlikely that further dose escalation will be beneficial. Discontinue if blast cells appear or disease progression occurs Hematopoietic subsyndrome of acute radiation syndrome • Prior to initiation, obtain baseline CBC with differential and serial CBCs approximately every third day; estimate absorbed radiation dose; do not delay administration if CBC not available. • (Greater than 40 kg) 7 mcg/kg subQ once daily as soon as possible following suspected or confirmed radiation exposure greater than 2 gray (Gy); continue therapy until ANC is greater than 1000/mm(3) for 3 consecutive CBCs or exceeds 10,000/mm(3) after radiation-induced nadir Mobilization, Of hematopoietic progenitor cells into peripheral blood for collection by leukapheresis 250 mcg/m(2)/day IV over 24 hours or subQ once daily; continue through the peripheral blood progenitor cell collection period; collection usually began by day 5 in studies; consider other mobilization therapy if an adequate number of progenitor cells are not collected
Fulphila (Pegfilgrastim-jmdb) **Fylnetra (Pegfilgrastim-pbbk)** **Neulasta (Pegfilgrastim)** **Nyvepria (Pegfilgrastim-apfg)** **Stimufend (Pegfilgrastim-fpgk)** **Udenyca (Pegfilgrastim-cbqv)** **Ziextenzo (Pegfilgrastim-bmez)**	Febrile neutropenia, In patients with non-myeloid malignancies receiving myelosuppressive anti-cancer drugs; Prophylaxis • 6 mg subQ once per chemotherapy cycle; do not administer between 14 days prior to and 24 hours after the administration of chemotherapy Hematopoietic subsyndrome of acute radiation syndrome • Prior to initiation, obtain CBC and estimate absorbed radiation dose; however, do not delay administration if CBC not available

	• 6 mg subQ administered 1 week apart for 2 doses; initiate treatment immediately
Rolvedon (Eflapegrastim- xnst)	Febrile neutropenia, In patients with non-myeloid malignancies receiving myelosuppressive anti-cancer drugs; Prophylaxis • 13.2 mg subQ once per chemotherapy cycle; do not administer between 14 days prior to and 24 hours after the administration of chemotherapy Hematopoietic subsyndrome of acute radiation syndrome • Prior to initiation, obtain CBC and estimate absorbed radiation dose; however, do not delay administration if CBC not available • 13.2 mg subQ administered 1 week apart for 2 doses; initiate treatment immediately

General Background

Colony Stimulating Factors (CSF) are hematopoietic growth factors, which act on progenitor cells capable of forming either single differentiated (lineage-specific) cell types, such as the neutrophilic granulocyte, or forming several differentiated cell types (i.e., non-lineage-specific). G-CSFs regulate the production of neutrophils in the bone marrow. Neutrophils are essential in the body's fight against infections.

Pegfilgrastim (Neulasta) is the pegylated form of recombinant methionyl human G-CSF (filgrastim) and is a colony-stimulating factor that acts on hematopoietic cells by binding to specific cell surface receptors, thereby stimulating proliferation, differentiation, commitment, and end cell functional activation.

Pegfilgrastim-jmdb (Fulphila), Pegfilgrastim-cbqv (Udenyca), Pegfilgrastim-bmez (Ziextenzo), Pegfilgrastim-apfg (Nyvepria), Pegfilgrastim-pbbk (Fylnetra), and Pegfilgrastim-fpgk (Stimufend), are biologic products approved by the United States Food and Drug Administration as biosimilars to pegfilgrastim.

Biosimilars are approved based on data demonstrating that it is highly similar to an FDA-approved biological product, known as a reference product, and that there are no clinically meaningful differences between the biosimilar product and the reference product.

Eflapegrastim-xnst (Rolvedon) is a recombinant human granulocyte growth factor that binds to G-CSF receptors on myeloid progenitor cells and neutrophils, triggering signaling pathways that control cell differentiation, proliferation, migration and survival.

Filgrastim (Neupogen) is a human granulocyte colony-stimulating factor (G-CSF) which acts on hematopoietic cells by binding to specific cell surface receptors and regulating neutrophil production, progenitor proliferation, and differentiation. It also affects some end-cell functional activation including phagocytic activity, cellular metabolism, and antibody-dependent killing.

Filgrastim-aafi (Nivestym), Filgrastim-sndz (Zarxio), and Filgrastim-ayow (Releuko) are biologic products approved by the United States Food and Drug Administration as biosimilars to filgrastim.

Sargramostim (Leukine) is a recombinant human granulocyte-macrophage colony-stimulating factor that triggers proliferation and differentiation of hematopoietic progenitor cells, primarily neutrophils, monocytes/macrophages, and myeloid-derived dendritic cells. Sargramostim can promote various cellular responses (i.e., division, maturation, activation) by binding to specific receptors found on the cell surface of target cells and may also stimulate polymorphonuclear neutrophils to block the growth of tumor cells and increase the cytotoxic activity of monocytes against certain types of neoplastic cells.

Tbo-Filgrastim (Granix) is a granulocyte colony-stimulating factor (G-CSF) that increases neutrophil counts and activity by binding to G-CSF receptors and stimulating differentiation commitment and some end-cell functional activation.

Clinical Evidence

National Comprehensive Cancer Network®

NCCN Guidelines Version 1.2024
Hematopoietic Growth Factors

NCCN Guidelines Index
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Discussion

EXAMPLES OF DISEASE SETTINGS AND CHEMOTHERAPY REGIMENS WITH A HIGH RISK FOR FEBRILE NEUTROPENIA (>20%)[a]

- ***This list is not comprehensive***; there are other agents/regimens that have a high risk for the development of febrile neutropenia. Regimens recommended in the NCCN Guidelines for Treatment by Cancer Type are considered when updating this list of examples.
- The type of chemotherapy regimen is only one component of the risk assessment (Patient Risk Factors for Developing Febrile Neutropenia, MGF-2).
- The exact risk includes agent, dose, and the treatment setting (ie, treatment naive vs. heavily pretreated patients) (MGF-1).
- In general, dose-dense regimens require MGF support to maintain dose intensity and schedule.

Acute Lymphoblastic Leukemia (ALL)
- Select ALL regimens as directed by treatment protocol (NCCN Guidelines for ALL)

Bladder Cancer
- Dose-dense MVAC (methotrexate, vinblastine, doxorubicin, cisplatin)[1]

Bone Cancer
- VAIA (vincristine, doxorubicin, ifosfamide, and dactinomycin)[2]
- VDC-IE (vincristine, doxorubicin or dactinomycin, and cyclophosphamide alternating with ifosfamide and etoposide)[3]
- Cisplatin/doxorubicin[4]
- VDC (cyclophosphamide, vincristine, doxorubicin or dactinomycin)[5]
- VIDE (vincristine, ifosfamide, doxorubicin or dactinomycin, etoposide)[6]

Breast Cancer
- Dose-dense AC followed by dose-dense paclitaxel (doxorubicin, cyclophosphamide, paclitaxel)[7,b]
- TAC (docetaxel, doxorubicin, cyclophosphamide)[8]
- TC[a,c] (docetaxel, cyclophosphamide)[9]
- TCH[a] (docetaxel, carboplatin, trastuzumab)[10]

Head and Neck Squamous Cell Carcinoma
- TPF (docetaxel, cisplatin, 5-fluorouracil)[11-13]

Hodgkin Lymphoma
- Brentuximab vedotin + AVD (doxorubicin, vinblastine, dacarbazine)[14]
- Escalated BEACOPP[d] (bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, prednisone)[15]

Kidney Cancer
- Doxorubicin/gemcitabine[16]

Non-Hodgkin Lymphomas
- CHP (cyclophosphamide, doxorubicin, prednisone) + brentuximab vedotin
- Dose-adjusted EPOCH[a] (etoposide, prednisone, vincristine, cyclophosphamide, doxorubicin)[17]
- ICE (ifosfamide, carboplatin, etoposide)[a,18,19]
- Dose-dense CHOP-14[a] (cyclophosphamide, doxorubicin, vincristine, prednisone)[20,21]
- MINE[a] (mesna, ifosfamide, mitoxantrone, etoposide)[22]
- DHAP[a] (dexamethasone, cisplatin, cytarabine)[23]
- ESHAP[a] (etoposide, methylprednisolone, cisplatin, cytarabine)[24]
- HyperCVAD[a] (cyclophosphamide, vincristine, doxorubicin, dexamethasone)[25,26]
- Pola-R-CHP (polatuzumab vedotin-piiq, rituximab, cyclophosphamide, doxorubicin, prednisone)[27]

Melanoma
- Dacarbazine-based combination with IL-2, interferon alfa (dacarbazine, cisplatin, vinblastine, IL-2, interferon alfa)[28]

Multiple Myeloma
- DT-PACE (dexamethasone/thalidomide/cisplatin/doxorubicin/cyclophosphamide/etoposide)[29] ± bortezomib (VTD-PACE)[30]

Ovarian Cancer
- Topotecan[a,31]
- Docetaxel[32]

Soft Tissue Sarcoma
- MAID (mesna, doxorubicin, ifosfamide, dacarbazine)[33]
- Doxorubicin[a,34]
- Ifosfamide/doxorubicin[35]

Small Cell Lung Cancer[e]
- Topotecan[36]

Testicular Cancer
- VeIP (vinblastine, ifosfamide, cisplatin)[37]
- VIP (etoposide, ifosfamide, cisplatin)
- TIP (paclitaxel, ifosfamide, cisplatin)[38]

Disease Settings and Chemotherapy Regimens with an Intermediate Risk for Febrile Neutropenia, MGF-A (2 of 5)

[a] Guidelines apply to chemotherapy regimens with or without monoclonal antibodies (eg, trastuzumab, rituximab). There is the potential for increased neutropenia risk with the addition of monoclonal antibodies. Rituximab has been associated with prolonged neutropenia with or without chemotherapy. For details on when monoclonal antibodies are recommended with the regimens listed above in clinical practice, see NCCN Guidelines for Treatment by Cancer Type.

[b] Growth factor support may not be needed during the paclitaxel portion and can be safely avoided in a large percentage of patients.

[c] Risk for febrile neutropenia has been reported variably as intermediate risk or high risk depending on the study.

[d] Risk of bleomycin-induced pulmonary toxicity may be increased in patients treated with G-CSFs. See Toxicity Risks with MGFs (MGF-C).

[e] Trilaciclib may be used as a prophylactic option to decrease the incidence of chemotherapy-induced myelosuppression when administered before (prophylactic G-CSF may be administered after cycle 1) platinum/etoposide ± immune checkpoint inhibitor-containing regimens or a topotecan-containing regimen for extensive-stage small cell lung cancer (ES-SCLC).

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

References

EXAMPLES OF DISEASE SETTINGS AND CHEMOTHERAPY REGIMENS WITH AN INTERMEDIATE RISK FOR FEBRILE NEUTROPENIA (10%–20%)[a]

- ***This list is not comprehensive***; **there are other agents/regimens that have an intermediate risk for the development of febrile neutropenia. Regimens recommended in the NCCN Guidelines for Treatment by Cancer Type are considered when updating this list of examples.**
- **The type of chemotherapy regimen is only one component of the Risk Assessment. See Patient Risk Factors for Developing Febrile Neutropenia (MGF-2).**
- **The exact risk includes agent, dose, and the treatment setting (ie, treatment naive vs. heavily pretreated patients) (MGF-1).**
- **In general, dose-dense regimens require MGF support to maintain dose intensity and schedule.**

Occult Primary - Adenocarcinoma
- Gemcitabine/docetaxel[41]

Breast Cancer
- Docetaxel[a,42,43]
- AC (doxorubicin, cyclophosphamide) + sequential docetaxel (taxane portion only)[a,44]
- Paclitaxel every 21 days[a,45]

Cervical Cancer
- Cisplatin/topotecan[46,47]
- Paclitaxel/cisplatin[a,46]
- Topotecan[48]
- Irinotecan[49]

Colorectal Cancer
- FOLFIRINOX (fluorouracil, leucovorin, oxaliplatin, irinotecan)[f,50-52]

Esophageal and Gastric Cancers
- Irinotecan/cisplatin[a,53]

Non-Hodgkin Lymphomas
- GDP (gemcitabine, dexamethasone, cisplatin/carboplatin)[a,54]
- CHOP[a] (cyclophosphamide, doxorubicin, vincristine, prednisone)[55,56] including regimens with pegylated liposomal doxorubicin[57,58]
- Bendamustine[a]

Non-Small Cell Lung Cancer
- Cisplatin/paclitaxel[59]
- Cisplatin/vinorelbine[60]
- Cisplatin/docetaxel[59,61]
- Cisplatin/etoposide[62]
- Carboplatin/paclitaxel[a,g,63]
- Docetaxel[61]

Ovarian Cancer
- Carboplatin/docetaxel[64]

Pancreatic Cancer
- FOLFIRINOX[h] (fluorouracil, leucovorin, irinotecan, oxaliplatin)

Prostate Cancer
- Cabazitaxel[i,65]

Small Cell Lung Cancer[e]
- Etoposide/carboplatin[66]

Testicular Cancer
- BEP[d] (bleomycin, etoposide, cisplatin)[67-69]
- Etoposide/cisplatin[70]

Uterine Sarcoma
- Docetaxel[71]

[a] Guidelines apply to chemotherapy regimens with or without monoclonal antibodies (eg, trastuzumab, rituximab). There is the potential for increased neutropenia risk with the addition of monoclonal antibodies. Rituximab has been associated with prolonged neutropenia with or without chemotherapy. For details on when monoclonal antibodies are recommended with the regimens listed above in clinical practice, see NCCN Guidelines for Treatment by Cancer Type.

[d] Risk of bleomycin-induced pulmonary toxicity may be increased in patients treated with G-CSFs. See Toxicity Risks with MGFs (MGF-C).

[e] Trilaciclib may be used as a prophylactic option to decrease the incidence of chemotherapy-induced myelosuppression when administered before (prophylactic G-CSF may be administered after cycle 1) platinum/etoposide ± immune checkpoint inhibitor-containing regimens or a topotecan-containing regimen for ES-SCLC.

[f] There are many factors that need to be evaluated to determine a patient's risk categorization; these include type of chemotherapy regimen (MGF-A) and patient risk factors (MGF-2).

[g] If carboplatin dose is area under the curve ≥6 and/or patient is of Japanese ancestry.

[h] A small retrospective trial had a 17% risk of febrile neutropenia in the neoadjuvant setting[39] and a randomized trial had a 5.4% risk in the metastatic setting (G-CSFs were administered to 42.5% of patients who received FOLFIRINOX).[40] While G-CSF was not recommended as primary prophylaxis, it may be considered in patients with high-risk clinical features.

[i] The published results for cabazitaxel have an 8% rate of febrile neutropenia but neutropenic deaths were reported. Primary prophylaxis with G-CSFs is recommended in patients with high-risk clinical features, and should be considered in all patients receiving a dose of 25 mg/m².

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

References

Cytotoxic chemotherapy can cause profound and sometimes prolonged neutropenia, which may result in hospitalization for treatment of fever or cause a potentially fatal infection. In an attempt to decrease infectious complications, recombinant human granulocyte colony-stimulating factor (G-CSF) has been used to reduce the duration and degree of neutropenia. These myeloid growth factors (MGF's) are a class of biologic agents that regulate the proliferation, differentiation, survival, and activation of cells in the myeloid lineage. In cancer patients receiving myelosuppressive chemotherapy, MGF's are primarily used to reduce the incidence of neutropenia. Neutropenia is defined as an absolute neutrophil count (ANC) of less than 500 neutrophils/mcL or an ANC of less than 1000 neutrophils/mcL and a predicted decline to less than or equal to 500 neutrophils/mcL over the next 48 hours. Fever in a neutropenic patient is usually defined as a single temperature >38.3 degrees C (101.3 degrees F) or a temperature >38 degrees C (100.4 degrees F) sustained for more than one hour. A review by Dale et al showed that about 25% to 40% of treatment-naïve patients develop febrile neutropenia with common chemotherapy regimens. Development of febrile neutropenia increases diagnostic and treatment costs and often leads to longer hospital stays. The risk of febrile neutropenia is usually based on the treatment regimen and delivered dose intensity.

The risk of febrile neutropenia (FN) involves varied components including disease type, chemotherapeutic regimen (high-dose, dose-dense, or standard-dose therapy), patient risk

factors, and treatment intent. 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). It should be emphasized that the type of chemotherapy regimen is only one component of the risk assessment and needs to be combined with patient risk factor for an estimation of the overall risk for FN.

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. NCCN guidelines recommend prophylactic CSF if the risk of FN is greater than 20%. For those patients at Intermediate risk for FN, the NCCN recommends individualized consideration of CSF use based on physician-patient discussion of the risk-benefit ratio with respect to the likelihood of developing FN, the potential consequences of a neutropenic event, and the implications of reduced chemotherapy dose delivery. For low-risk patients, as defined by risk less than 10%, routine use of CSF's is not recommended (but may be considered for patients with risk factors) as an alternative treatment option may be more appropriate. After the first cycle of chemotherapy, patient evaluation should be performed prior to each subsequent cycle to determine the risk categorization and treatment intent.

The NCCN Panel identifies possible patient risk factors for febrile neutropenia. According to the NCCN panel, risk factors may include:

- Prior chemotherapy or radiation therapy
- Persistent neutropenia
- Bone marrow involvement by tumor
- 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 GCSF
- For patients who have not received prophylactic MGFs, the NCCN Panel recommends an evaluation for risk factors for infection-related complications or poor clinical outcome
- The NCCN Panel recommends administration of filgrastim, filgrastim-sndz, tbo-filgrastim, or filgrastim-aafi as a single agent or as part of a chemo-mobilization regimen, starting on the day after completion of chemotherapy
- The NCCN Panel recommends single-agent filgrastim, filgrastim-sndz, or tbo-filgrastim for allogeneic

hematopoietic cell mobilization and for granulocyte transfusion
• The NCCN Panel recommends consideration of MGFs in the supportive care setting post-autologous hematopoietic cell transplant. Filgrastim, filgrastim-sndz, tbo-filgrastim, filgrastim-aafi, and pegfilgrastimcan be considered in the supportive care setting

Additionally, the prophylactic use of CSF's in patients given concurrent chemotherapy and radiation has not been evaluated and is therefore not recommended according to the NCCN.

Medicare does not have a National Coverage Determination (NCD) for Colony Stimulating Factors (CSF). Local Coverage Determinations (LCDs) for Texas and New Mexico do not exist at this time.

HCPCS Code

HCPCS codes	Available Dosage Form	Route of Administration
J2506: Pegfilgrastim (Neulasta, Neulasta Onpro)	Sub-cut Solution: 6 MG/0.6 ML	Subcutaneous
Q5108: Fulphila (Pegfilgrastim-jmdb)	Sub-cut Solution: 6 MG/0.6 ML	Subcutaneous
Q5111: Udenyca (Pegfilgrastim-cbqv)	Sub-cut Solution: 6 MG/0.6 ML	Subcutaneous
Q5120: Ziextenzo (Pegfilgrastim-bmez)	Sub-cut Solution: 6 MG/0.6 ML	Subcutaneous
Q5122: Nyvepria (Pegfilgrastim-apfg)	Sub-cut Solution: 6 MG/0.6 ML	Subcutaneous
Q5130: Fylnetra (Pegfilgrastim-pbbk)	Sub-cut Solution: 6 MG/0.6 ML	Subcutaneous
Q5127: Stimufend (Pegfilgrastim-fpgk)	Sub-cut Solution: 6 MG/0.6 ML	Subcutaneous
J1449: Rolvedon (Eflapegrastim- xnst)	Sub-cut Solution: 13.2 MG/0.6 ML	Subcutaneous
J1442: Neupogen (Filgrastim)	Injection Solution: 300 MCG/1 ML, 480MCG/1.6 ML, 480 MCG/0.8 ML, 300 MCG/0.5 ML	Intravenous and Subcutaneous
Q5110: Nivestym (Filgrastim-aafi)	Injection Solution: 300 MCG/1 ML, 300 MCG/0.5 ML, 480 MCG/0.8 ML	Intravenous and Subcutaneous
Q5101: Zarxio (Filgrastim-sndz)	Injection Solution: 480 MCG/0.8 ML, 300 MCG/0.5 ML	Intravenous and Subcutaneous
J1447: Granix (Tbo-Filgrastim)	Sub-cut Solution: 480 MCG/1.6 ML, 300 MCG/1 ML, 480 MCG/0.8 ML, 300 MCG/0.5 ML	Subcutaneous
J2820: Leukine (Sargramostim)	Injection Powder for Solution: 250 MCG	Intravenous
Q5125: Releuko (Filgrastim-ayow)	Injection Solution: 480 MCG/1.6 ML, 300 MCG/1 ML Sub-cut Solution: 480 MCG/0.8 ML, 300 MCG/0.5 ML	Intravenous and Subcutaneous

Acronyms

FDA = Food and Drug Administration

G-CSF = Granulocyte colony-stimulating factor

MGF = Myeloid growth factors

ANC = Absolute neutrophil count

FN = Febrile neutropenia

NCCN = National Comprehensive Cancer Network

SCN = Severe Chronic Neutropenia

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