Overview

This document addresses the use of white blood cell growth factors, also known as colony stimulating factors (CSF). There are two types of CSFs, granulocyte and granulocyte-macrophage. Granulocyte colony stimulating factors (G-CSF) are glycoproteins which exert major control over the reproduction and maturation of certain white blood cells. Granulocyte-macrophage colony stimulating factor (GM-CSF) is a hematopoietic growth factor which stimulates proliferation and differentiation of hematopoietic progenitor cells.

The following agents are included in the class

- **G-CSF:**
  - Neupogen (filgrastim) and Biosimilars
    - Zarxio (filgrastim-sndz)
    - Nivestym (filgrastim-aafi)
  - Neulasta (pegfilgrastim) and Biosimilars
    - Fulphila (pegfilgrastim-jmdb)
    - Udencya (pegfilgrastim-cbqv)
  - Granix (tbo-filgrastim)

- **GM-CSF**
  - Leukine (sargramostim)

The use of myeloid growth factors in the prophylaxis of febrile neutropenia is based on an assessment of both the chemotherapy regimen and patient specific risk factors. Guidance from the NCCN Myeloid Growth Factors provides various chemotherapy regimens and their risk of causing febrile neutropenia. While patient risk factors for the development of febrile neutropenia include but are not limited to (NCCN Guidelines Version 2.2019):

  a. Age greater than 65 years; OR
  b. Poor performance status (Eastern Cooperative Oncology Group 3 or 4) or HIV infection (in particular, those with low CD4 counts); OR
  c. Prior chemotherapy or radiation therapy; OR
  d. Bone marrow involvement by tumor producing cytopenias; OR
  e. Persistent neutropenia (absolute neutrophil count [ANC] less than 1500mm$^3$); OR
  f. Poor renal function (glomerular filtration rate [GFR] less than 60mL/min); OR
  g. Liver dysfunction (liver function tests at least 2X upper limit of normal); OR
  h. Recent surgery and/or the presence of open wounds

Other uses

*Use of G-CSF agents in damaged myocardium*

The use of G-CSF has been proposed as an adjunct to standard therapies to promote mobilization of stem cells and progenitor cells from the bone marrow into the circulating blood to improve repair of the damaged myocardium. The benefits of G-CSF in other fields,
such as oncology, has led to research assessing the potential of G-CSF in repairing myocardial tissue and improving clinical outcomes in those with damaged hearts. To date, the published evidence regarding the safety and efficacy of G-CSF has been lacking.

**Definitions and Measures**

Absolute neutrophil count (ANC): A measure of the number of neutrophils (a type of white blood cell) in the blood.

Acute Radiation Syndrome (ARS): Also known as radiation sickness.

Adjuvant or adjunctive treatment: Treatment given after the primary treatment to increase the chances of a cure and may include chemotherapy, radiation, hormone or biological therapy.

Febrile neutropenia: Febrile neutropenia can occur as a result of severe neutropenia; defined as the occurrence of fever (greater than or equal to 38.3°C for more than 1 hour) in association with an ANC less than 0.5 x 10⁹/L or ANC less than 1.0 x 10⁹/L and a predicted decline to less than or equal to 0.5 x 10⁹/L over the subsequent 48 hours.

ECOG or Eastern Cooperative Oncology Group Performance Status: A scale and criteria used by doctors and researchers to assess how an individual’s disease is progressing, assess how the disease affects the daily living abilities of the individual, and determine appropriate treatment and prognosis. This scale may also be referred to as the WHO (World Health Organization) or Zubrod score which is based on the following scale:

- 0 = Fully active, able to carry on all pre-disease performance without restriction
- 1 = Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, for example, light house work, office work
- 2 = Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours
- 3 = Capable of only limited self-care, confined to bed or chair more than 50% of waking hours
- 4 = Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair
- 5 = Dead

Neutropenia: A decrease in the number of neutrophils (white blood cells that respond quickly to infection) in the blood. Neutrophils less than 1,500/mm³ is considered to be neutropenic and at risk for infection. Neutrophils fewer than 500 cells/mm³ is considered at high risk of infection.

Neutrophil: A type of white blood cell that helps fight infection.

Primary prophylaxis: Prevention of febrile neutropenia with the first cycle of a specified chemotherapy regimen.

Secondary prophylaxis: Prevention of febrile neutropenia given with the second and/or subsequent cycle of a given regimen of chemotherapy for individuals who had a neutropenic complication from the preceding cycle of chemotherapy and there is no plan to reduce the dose intensity.

**Clinical Criteria**

When a drug is being reviewed for coverage under a member’s medical benefit plan or is otherwise subject to clinical review (including prior authorization), the following criteria will be used to determine whether the drug meets any applicable medical necessity requirements for the intended/prescribed purpose.

**Neulasta (pegfilgrastim), Fulphila (pegfilgrastim-jmdb) or Udenyca (pegfilgrastim-cbqv)**

Requests for Neulasta (pegfilgrastim), Fulphila (pegfilgrastim-jmdb), or Udenyca (pegfilgrastim-cbqv) may be approved if the following criteria are met:

I. Individual with nonmyeloid malignancy is using for primary prophylaxis of Febrile Neutropenia (FN); **AND**

II. Individual has a risk of FN of 20% or greater based on chemotherapy regimen (NCCN 2A);

**OR**

III. Individual with nonmyeloid malignancy is using for primary prophylaxis of FN; **AND**

IV. Individual’s risk of developing FN is greater than or equal to 10% and less than 20% based on chemotherapy regimen and individual has any risk factors (see list in Overview) for FN (NCCN 2A):
OR
V. Individual with nonmyeloid malignancy is using for secondary prophylaxis of FN; **AND**
VI. Individual has experienced a neutropenic complication from a prior cycle of chemotherapy (for which prophylaxis was not received), in which a reduced dose may compromise disease-free or overall survival or treatment outcome (NCCN 2A);

OR
VII. Individual is using as adjunctive treatment for FN; **AND**
VIII. Individual has not received prophylactic therapy with pegfilgrastim (NCCN 2A); **AND**
IX. Individual has a high risk for infection-associated complications as demonstrated by any of the following:
   A. Expected prolonged (greater than 10 days) and profound (less than 0.1 x 10^9/L) neutropenia; **OR**
   B. Age greater than 65 years; **OR**
   C. Pneumonia or other clinically documented infections; **OR**
   D. Hypotension and multi organ dysfunction (sepsis syndrome); **OR**
   E. Invasive fungal infection; **OR**
   F. Prior episode of febrile neutropenia; **OR**
   G. Hospitalized at the time of the development of fever;

OR
X. Individual has a diagnosis of acute lymphocytic leukemia (ALL); **AND**
XI. Individual is using after completion of the first few days of initial induction chemotherapy or first post-remission course of chemotherapy (AHFS, NCCN Guidelines Acute Lymphoblastic Leukemia);

OR
XII. Individual is receiving dose dense therapy (treatment given more frequently, such as every 2 weeks instead of every 3 weeks) for adjuvant treatment of breast cancer (ASCO Smith 2015);

OR
XIII. Individual is using after accidental or intentional total body radiation of myelosuppressive doses (greater than 2 Grays [Gy]) (such as Hematopoietic Syndrome of Acute Radiation Syndrome);

OR
XIV. Individual is using after a hematopoietic progenitor stem cell transplant (HPCT/HSCT) to promote myeloid reconstitution OR when engraftment is delayed or has failed (NCCN 2A).

**Neupogen (filgrastim) or Nivestym (filgrastim-aafi) or Zarxio (filgrastim-sndz)**
Requests for Neupogen (filgrastim), Nivestym (filgrastim-aafi) or Zarxio (filgrastim-sndz) may be approved if the following criteria are met:

I. Individual with nonmyeloid malignancy is using for primary prophylaxis of FN; **AND**
II. Individual has a risk of FN of 20% or greater based on chemotherapy regimen;

OR
III. Individual with nonmyeloid malignancy is using for primary prophylaxis of FN; **AND**
IV. Individual’s risk of developing FN is greater than or equal to 10% and less than 20% based on chemotherapy regimen and individual has any risk factors (see list in Overview) for FN (NCCN 2A);

OR
V. Individual with nonmyeloid malignancy is using for secondary prophylaxis of FN; **AND**
VI. Individual has experienced a neutropenic complication from a prior cycle of chemotherapy (for which prophylaxis was not received), in which a reduced dose may compromise disease-free or overall survival or treatment outcome (NCCN 2A);

OR
VII. Individual is using as adjunctive treatment for FN; **AND**
VIII. Individual has been on prophylactic therapy with filgrastim; **OR**
IX. Individual has not received prophylactic therapy with a granulocyte colony stimulating factor (NCCN Guidelines Myeloid Growth Factors); **AND**
X. Individual has a high risk for infection-associated complications as demonstrated by any of the following (NCCN 2A):
   A. Expected prolonged (greater than 10 days) and profound (less than 0.1 x 10^9/L) neutropenia; **OR**
   B. Age greater than 65 years; **OR**
   C. Pneumonia or other clinically documented infections; **OR**
D. Hypotension and multi organ dysfunction (sepsis syndrome); OR
E. Invasive fungal infection; OR
F. Prior episode of febrile neutropenia; OR
G. Hospitalized at the time of the development of fever;

OR
XI. Individual has a diagnosis of acute lymphocytic leukemia (ALL); AND
XII. Individual is using after completion of the first few days of initial induction chemotherapy or first post-remission course of chemotherapy (AHFS, NCCN Guidelines Acute Lymphoblastic Leukemia);

OR
XIII. Individual is 18 years of age or older and has a diagnosis of acute myeloid leukemia (AML); AND
XIV. Individual is using shortly after the completion of induction or repeat induction chemotherapy, or after the completion of consolidation chemotherapy for AML;

OR
XV. Individual has a diagnosis of hairy cell leukemia with severe neutropenia (AHFS, NCCN Guidelines Hairy Cell Leukemia);

OR
XVI. Individual has a diagnosis of myelodysplastic syndrome (MDS) (NCCN 2A); AND
XVII. Individual has severe neutropenia (ANC less than or equal to 500/mm³) or experiencing recurrent or resistant infections;

OR
XVIII. Individual is receiving dose dense therapy (treatment given more frequently, such as every 2 weeks instead of every 3 weeks) for adjuvant treatment of breast cancer (ASCO Smith 2015);

OR
XIX. Individual is using for chronic administration to reduce the incidence and duration of sequelae of neutropenia (for example, fever, infections, oropharyngeal ulcers) in symptomatic individuals with congenital neutropenia, cyclic neutropenia, or idiopathic neutropenia;

OR
XX. Individual is using for the treatment of (non-chemotherapy) drug-induced neutropenia (AHFS);

OR
XXI. Individual is less than 21 years of age and is diagnosed with glycogen storage disease type 1b; AND
XXII. Individual is using for the treatment of low neutrophil counts (AHFS);

OR
XXIII. Individual is using for the treatment of neutropenia associated with human immunodeficiency virus infection and antiretroviral therapy (AHFS);

OR
XXIV. Individual is using after accidental or intentional total body radiation of myelosuppressive doses (greater than 2 Grays [Gy]) (such as Hematopoietic Syndrome of Acute Radiation Syndrome);

OR
XXV. Individual is using after a hematopoietic progenitor stem cell transplant (HPCT/HSCT) to promote myeloid reconstitution or when engraftment is delayed or has failed (NCCN 2A);

OR
XXVI. Individual is using to mobilize progenitor cells into peripheral blood for collection by leukapheresis, as an adjunct to peripheral blood/hematopoietic stem cell transplantation (PBSCT/PHSCT);

OR
XXVII. Individual is using as an alternate or adjunct to donor leukocyte infusions (DLI) in those with leukemic relapse after an allogenic hematopoietic stem cell transplant (DrugsPoints B IIa);

OR
XXVIII. Individual is using to reduce the duration of neutropenia and neutropenia related clinical sequelae in those with nonmyeloid malignancies undergoing myeloblastic chemotherapy followed by bone marrow transplant (BMT).
Leukine (Sargramostim)

Requests for Leukine (sargramostim) may be approved if the following criteria are met:

I. Individual is using as adjunctive treatment for FN; **AND**
II. Individual has not previously received prophylactic granulocyte colony-stimulating factors (NCCN 2A); **AND**
III. Individual has a high risk for infection-associated complications as demonstrated by any of the following (NCCN 2A):
   A. Expected prolonged (greater than 10 days) and profound (less than 0.1 x 10^9/L) neutropenia; **OR**
   B. Age greater than 65 years; **OR**
   C. Pneumonia or other clinically documented infections; **OR**
   D. Hypotension and multi organ dysfunction (sepsis syndrome); **OR**
   E. Invasive fungal infection; **OR**
   F. Prior episode of febrile neutropenia; **OR**
   G. Hospitalized at the time of the development of fever; **OR**

IV. Individual is receiving dose dense therapy (treatment given more frequently, such as every 2 weeks instead of every 3 weeks) for adjuvant treatment of breast cancer (ASCO Smith 2015); **OR**
V. Individual has a diagnosis of acute myeloid leukemia (AML); **AND**
VI. Individual is 55 years and older; **AND**
VII. Individual is using shortly after the completion of induction or repeat induction chemotherapy of AML; **OR**
VIII. Individual has a diagnosis of myelodysplastic syndrome (MDS); **AND**
IX. Individual has severe neutropenia (ANC less than or equal to 500/mm^3) or experiencing recurrent or resistant infections (NCCN Guidelines Myelodysplastic Syndromes; AHFS); **OR**
X. Individual is 18 years or older; **AND**
XI. Individual is using for the mobilization of hematopoietic progenitor cells into peripheral blood for collection by leukapheresis and autologous transplantation **OR**
XII. Individual is 2 years of age and older; **AND**
XIII. Individual is using for the acceleration of myeloid reconstitution following autologous or allogenic bone marrow transplantation or peripheral blood progenitor cell transplantation; **OR**
XIV. Individual is 2 years of age and older; **AND**
XV. Individual is using for the treatment of delayed neutrophil recovery or graft failure after autologous or allogenic bone marrow transplantation; **OR**
XVI. Individual is using to increase survival in adult and pediatric individuals (from birth to 17 years of age) acutely exposed to myelosuppressive doses of radiation (such as Hematopoietic Syndrome of Acute Radiation Syndrome (H-ARS)).

Granix (Tbo-Filgrastim)

Requests for Granix (Tbo-Filgrastim) may be approved if the following criteria are met:

I. Individual with non-myeloid malignancy is using for primary prophylaxis of Febrile Neutropenia (FN); **AND**
II. Individual has a risk of FN of 20% or greater based on chemotherapy regimen; **OR**
III. Individual with nonmyeloid malignancy is using for primary prophylaxis of FN; **AND**
IV. Individual’s risk of developing FN is greater than or equal to 10% and less than 20% based on chemotherapy regimen and individual has any risk factors (see list in Overview) for FN (NCCN 2A); **OR**
V. Individual with nonmyeloid malignancy is using for secondary prophylaxis of FN; **AND**
VI. Individual has experienced a neutropenic complication from a prior cycle of chemotherapy (for which prophylaxis was not received), in which a reduced dose may compromise disease-free or overall survival or treatment outcome (NCCN 2A);
OR
VII. Individual is using as an adjunctive treatment for FN; AND
VIII. Individual was previously using Granix (tbo-filgrastim) prophylactically (NCCN 2A);
OR
IX. Individual has not received prophylactic therapy with a granulocyte colony stimulating factor (NCCN Guidelines Myeloid Growth Factors);
AND
X. Individual has a high risk for infection-associated complications as demonstrated by any of the following:
   A. Expected prolonged (greater than 10 days) and profound (less than 0.1 x 10^9/L) neutropenia (NCCN 2A); OR
   B. Age greater than 65 years; OR
   C. Pneumonia or other clinically documented infections; OR
   D. Hypotension and multi organ dysfunction (sepsis syndrome); OR
   E. Invasive fungal infection; OR
   F. Prior episode of febrile neutropenia; OR
   G. Hospitalized at the time of the development of fever;
OR
XI. Individual is using after a hematopoietic progenitor stem cell transplant (HPCT/HSCT) to promote myeloid reconstitution or when engraftment is delayed or has failed (NCCN 2A);
OR
XII. Individual has a diagnosis of myelodysplastic syndrome (MDS); AND
XIII. Individual has severe neutropenia (ANC less than or equal to 500/mm^3) or experiencing recurrent or resistant infections (NCCN 2A);
OR
XIV. Individual is using to mobilize progenitor cells into peripheral blood for collection by leukapheresis, as an adjunct to peripheral blood/hematopoietic stem cell transplantation (PBSCT/PHSCT) (AHFS).

Colony Stimulating Factors (filgrastim, pegfilgrastim, sargramostim, and tbo-filgrastim) may not be approved for any of the following:

I. Individual is using as prophylaxis for febrile neutropenia, except when above criteria are met; OR
II. Individual using as treatment for neutropenia in those who are afebrile, except when above criteria are met; OR
III. Individual is using as adjunctive therapy in those with uncomplicated febrile neutropenia, defined as a fever less than 10 days duration, no evidence of pneumonia, cellulitis, abscess, sinusitis, hypotension, multi-organ dysfunction, or invasive fungal infection, and no uncontrolled malignancies; OR
IV. Individual is using for chemosensitization of myeloid leukemias; OR
V. Individual is using for prophylaxis of FN during concomitant chemotherapy and radiation therapy; OR
VI. Individual is continuing use if no response is seen within 28-42 days (individuals who have failed to respond within this time frame are considered non-responders); OR
VII. Individual is using as a technique to increase the numbers of circulating hematopoietic stem cells as treatment of damaged myocardium.

**Step Therapy**

**Note:** When a white blood cell growth factor, also known as a colony stimulating factor (CSF) is deemed approvable based on the clinical criteria above, the benefit plan may have additional criteria requiring the use of a preferred agent or agents.

A benefit plan may select any one or more of the following as long-acting preferred white blood cell growth factors: pegfilgrastim (Neulasta), pegfilgrastim-jmdb (Fulphila), pegfilgrastim-cbqv (Udenyca).

Currently step therapy does not apply under the medical benefit.

**Non-Preferred Long-acting Colony Stimulating Factor (CSF) Agents Step Therapy**

Requests for a non-preferred Long-acting CSF agent may be approved when the following criteria are met:

I. Individual has had a trial and inadequate response or intolerance to one preferred Long-acting CSF agent.
A benefit plan may select any one or more of the following as short-acting preferred white blood cell growth factors: tbo-filgrastim (Granix), filgrastim (Neupogen), filgrastim-aafi (Nivestym), and filgrastim-sndz (Zarxio). A list of short-acting the preferred white blood cell growth factors is available here.

Non-Preferred Short-acting Colony Stimulating Factor (CSF) Agents Step Therapy

Requests for a non-preferred Short-acting CSF agent may be approved when the following criteria are met:

I. Individual has had a trial and inadequate response or intolerance to one preferred Short-acting CSF agent:

   OR

II. The preferred agent is not FDA-approved for the prescribed indication and the requested non-preferred agent is.

Preferred, as used herein, refers to agents that were deemed to be clinically comparable to other agents in the same class or disease category but are preferred based upon clinical evidence and cost effectiveness.

Coding

The following codes for treatments and procedures applicable to this document are included below for informational purposes. Inclusion or exclusion of a procedure, diagnosis or device code(s) does not constitute or imply member coverage or provider reimbursement policy. Please refer to the member’s contract benefits in effect at the time of service to determine coverage or non-coverage of these services as it applies to an individual member.

**CPT**

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<td>96377</td>
<td>Application of on-body injector (includes cannula insertion) for timed subcutaneous injection [Neulasta OnPro injector]</td>
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**HCPCS**

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<td>Injection, tbo-filgrastim, 1 microgram [Granix]</td>
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<td>J2505</td>
<td>Injection, pegfilgrastim, 6 mg [Neulasta]</td>
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<td>J2820</td>
<td>Injection, sargramostim (GM-CSF), 50 mcg [Leukine, Prokine]</td>
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<td>Injection, filgrastim-sndz, biosimilar, (Zarxio), 1 microgram</td>
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<td>Injection, pegfilgrastim-cbqv, biosimilar, (Udenyca), 0.5 mg</td>
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<td>Home therapy; hematopoietic hormone injection therapy (e.g., erythropoietin, G-CSF, GM-CSF); per diem [when specified as G_CS, GM-CSF]</td>
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**ICD-10 Diagnosis**

All diagnoses

Document History

Revised: 11/15/2019

Document History:

- 11/15/2019 – Select Review: Update May not be approved section to add criteria in use of granulocyte-colony stimulating factor agents in the treatment of damaged myocardium. Coding reviewed: No changes
- 12/20/2018 – HCPCS changes; added Q5111.
• 09/10/2018 – Annual Review: Archive Colony Stimulating Factor NP ST. Replace with 2 new NP ST, one for short acting agents and the other for long-acting agents.
• 08/17/2018 – Annual Review: Update all PAs according to FDA label and off-label compendia -- AHFS, DrugPoints, and NCCN 2A off-label updates. Included biosimilars Nivestym and Fulphila within Overview table of products, the PA policies, and within the NP CSF Step therapy.

References


Federal and state laws or requirements, contract language, and Plan utilization management programs or polices may take precedence over the application of this clinical criteria.

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### Commercial Medical Benefit

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### Medicaid Medical Benefit

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### Medicare Medical Benefit

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