Medical Drug Clinical Criteria

Subject:	Colony Stimulating Factor Agents		
Document #:	CC-0002	**Publish Date**:	05/01/2025
Status:	Revised	**Last Review Date**:	08/16/2024

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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 that stimulates proliferation and differentiation of hematopoietic progenitor cells.

The following agents are included in the class.

- G-CSF:
  - Granix (tbo-filgrastim)
  - Neulasta Onpro/Neulasta (pegfilgrastim) and Biosimilars
    - Fulphila (pegfilgrastim- jmdb)
    - Fylnetra (pegfilgrastim-pbbk)
    - Nyvepria (pegfilgrastim-apgf)
    - Stimufend (pegfilgrastim-fpgk)
    - Udenyca/Udenyca Onbody (pegfilgrastim-cbqv)
    - Ziextenzo (pegfilgrastim-bmez)
  - Neupogen (filgrastim) and Biosimilars
    - Nivestym (filgrastim-aafi)
    - Nypozi (filgrastim-txid)
    - Releuko (filgrastim-ayow)
    - Zarxio (filgrastim-sndz)
  - Rolvedon (eflapegrastim-xnst)
  - Ryzneuta (efbemalenograstim alfa-vuxw)
- GM-CSF
  - Leukine (sargramostim)

Ryzneuta (efbemalenograstim-alfa)
Ryzneuta is a leukocyte growth factor FDA indicated to decrease the incidence of infection, as manifested by febrile neutropenia, in adult patients with non-myeloid malignancies receiving myelosuppressive anti-cancer drugs associated with a clinically significant incidence of febrile neutropenia. Ryzneuta is not indicated for the mobilization of peripheral blood progenitor cells for hematopoietic stem cell transplantation. National Comprehensive Cancer Network (NCCN) provides a 2A recommendation for the treatment of patients with radiation-induced myelosuppression following a radiologic/nuclear incident (hematopoietic acute radiation syndrome [H-ARS]).

Rolvedon (eflapegrastim-xnst)
Rolvedon is a nonbiosimilar long-acting hematopoietic growth factor consisting of a recombinant human granulocyte-colony stimulating factor (rhG-CSF) analog conjugated to a human IgG4Fc fragment. The addition of the Fc fragment extend the drug's half-life, which has been used in other marketed biologics (e.g. etanercept). Rolvedon is indicated to decrease the incidence of infection, as manifested by febrile neutropenia, in adult patients with non-myeloid malignancies receiving myelosuppressive anti-cancer drugs associated with clinically significant incidence of febrile neutropenia. Rolvedon is not indicated for the mobilization of peripheral blood progenitor cells for hematopoietic stem cell transplantation. NCCN also provides a 2A recommendation for the treatment of patients with radiation-induced myelosuppression following a radiologic/nuclear incident (hematopoietic acute radiation syndrome [H-ARS]).

Primary prophylaxis of chemotherapy-induced febrile neutropenia
Neutropenia with fever (febrile neutropenia [FN]) is a serious consequence of myelosuppressive chemotherapy that usually results in hospitalization and the need for intravenous antibiotics (Lyman 2014). FN may result in dose reductions, delays, or even discontinuation of chemotherapy, which, in turn, may compromise patient outcomes. It is important to identify which patients are at high risk for developing FN so that patients can receive optimal chemotherapy while their risk for FN is appropriately managed. There are many factors that need to be evaluated to determine a patient's risk of developing FN, which includes type of chemotherapy regimen, type of cancer being treated, and other patient-specific risk factors.
A review of the literature was performed to gain a comprehensive and updated understanding of FN risk associated with chemotherapy regimens and patient-specific FN risk factors. Studies that have analyzed FN risk factors, often have several limitations, including their retrospective nature and small sample sizes. Our assessment of the following patient risk factors and chemotherapy regimens (see appendix below) is after a review of published literature and guidelines from the American Society of Clinical Oncology (ASCO) and National Comprehensive Cancer Network (NCCN).
The patient risk factors for the development of febrile neutropenia include:

- Age greater than 65 years (Lyman 2014; Aagaard 2018); **OR**
- Poor performance status (Eastern Cooperative Oncology Group 3 or 4) or HIV infection (in particular, those with low CD4 counts (≤ 450/μL)) but chemotherapy still indicated (Lyman 2014); **OR**
- Prior radiation therapy (within previous 1 year) (Terbuch 2018) (Fujiwara 2017) (Shigeta 2015); **OR**
- Bone marrow involvement by tumor producing cytopenias (Lyman 2014); **OR**
- Persistent neutropenia (absolute neutrophil count [ANC] less than 1500mm^3) (Lyman 2014); **OR**
- Poor renal function (glomerular filtration rate [GFR] less than 60mL/min) (Lyman 2014; Aagaard 2018); **OR**
- Liver dysfunction (liver function tests (AST or ALT levels) at least 2X upper limit of normal or bilirubin > 2.0 mg/dL) (Lyman 2014; Aagaard 2018); **OR**
- Recent surgery performed as part of cancer management within previous 30 days (not to include a procedure such as port placement, drain placement, IVC filter, etc.) (Lyman 2014; Aagaard 2018); **OR**
- History of active infection within previous 60 days (Lyman 2014; Aagaard 2018); **OR**
- Current open wound and chemotherapy cannot be delayed (Lyman 2014; Aagaard 2018).

Zynteglo (betibeglogene autotemcel) Gene Therapy
Before administration of Zynteglo, hematopoietic stem cells are mobilized with granulocyte colony-stimulating factor and plerixafor, and cells are collected by apheresis. In clinical trials, up to two mobilization cycles (separated by at least 2 weeks) were performed, determined by the need to reach the cumulated target collection number needed for beti-cel manufacture or manufacturing and for rescue cells cryopreserved and stored on site. Prior to apheresis, transfusions are recommended to obtain 8 hemoglobin levels of at least 11 g per deciliter; this hemoglobin level is recommended to be maintained during mobilization and apheresis to suppress stress erythropoiesis.
Mozobil for hematopoietic Stem Cell Mobilization
NCCN provides a 2A recommendation for the use of plerixafor in the treatment for hematopoietic cell mobilization for autologous donors in combination with filgrastim, filgrastim + cyclophosphamide, sargramostim +cyclophosphamide, or pegfilgrastim. NCCN provides a 2A recommendation for the use of motixafortide in the treatment for hematopoietic cell mobilization for autologous donors with filgrastim. NCCN also provides additional use for insufficient collection of stem cells in combination with either filgrastim (tbo-filgrastim or its biosimilars) alone or filgrastim (or tbo-filgrastim/or its biosimilars) and disease-specific chemotherapy.
Consider as additional supportive care for neutropenic patients
The use of G-CSF has been suggested in the NCCN guidelines as a 2A recommendation in supportive care for Grade 1 fever in those using CAR T-cell therapy to prevent progression of cytokine release syndrome (CRS). A small retrospective analysis in diffuse large B-cell lymphoma members using G-CSF during CAR-T therapy (Gaut 2019) showed no difference in the incidence and severity of infection or incidence of developing CRS between those who received G-CSF and those that did not.
Wilms Tumor (favorable history)
NCCN recommends the use of G-CSF has been suggested for use as supportive care in Wilms Tumor (nephroblastoma) after doses of myelosuppressive agents after courses of cyclophosphamide and etoposide and cyclophosphamide, doxorubicin, and vincristine in Regimen M and Regimen I.

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 38.3ºC for more than 1 hour) in association with an ANC less than 0.5 x 10^9/L or ANC less than 1.0 x 10^9/L and a predicted decline to less than or equal to 0.5 x 10^9/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.

Rolvedon (eflapegrastim-xnst)

Requests for Rolvedon (eflapegrastim-xnst) 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) (see Appendix, Table 1);

OR

III. Individual with nonmyeloid malignancy is using for primary prophylaxis of FN; **AND**
IV. Individual has a risk of developing FN is greater than or equal to 10% and less than 20% based on chemotherapy regimen (see Appendix, Table 1) and individuals have any of the following risk factors for FN:

   A. Age greater than 65 years (Lyman 2014; Aagaard 2018); **OR**
   B. Poor performance status (Eastern Cooperative Oncology Group 3 or 4) or HIV infection (in particular, those with low CD4 counts (≤ 450/µL)) but chemotherapy still indicated (Lyman 2014); **OR**
   C. Prior radiation therapy (within previous 1 year) (Terbuch 2018) (Fujiwara 2017) (Shigeta 2015); **OR**
   D. Bone marrow involvement by tumor producing cytopenias (Lyman 2014); **OR**
   E. Persistent neutropenia (absolute neutrophil count [ANC] less than 1500mm^3) (Lyman 2014); **OR**
   F. Poor renal function (glomerular filtration rate [GFR] less than 60mL/min) (Lyman 2014; Aagaard 2018); **OR**
   G. Liver dysfunction (liver function tests (AST or ALT levels) at least 2X upper limit of normal or bilirubin > 2.0 mg/dL) (Lyman 2014) (Aagaard 2018); **OR**
   H. Recent surgery performed as part of cancer management within previous 30 days (not to include a procedure such as port placement, drain placement, IVC filter, etc.) (Lyman 2014; Aagaard 2018); **OR**
   I. History of active infection within previous 60 days (Lyman 2014; Aagaard 2018); **OR**
   J. Current open wound and chemotherapy cannot be delayed (Lyman 2014; Aagaard 2018).

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 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) (NCCN 2A).

Ryzneuta (efbemalenograstim alfa-vuxw)

Requests for Ryzneuta (efbemalenograstim alfa-vuxw) 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) (see Appendix, Table 1);

OR

III. Individual with nonmyeloid malignancy is using for primary prophylaxis of FN; **AND**
IV. Individual has a risk of developing FN is greater than or equal to 10% and less than 20% based on chemotherapy regimen (see Appendix, Table 1) and individuals have any of the following risk factors for FN:
   A. Age greater than 65 years (Lyman 2014; Aagaard 2018); **OR**
   B. Poor performance status (Eastern Cooperative Oncology Group 3 or 4) or HIV infection (in particular, those with low CD4 counts (≤ 450/μL)) but chemotherapy still indicated (Lyman 2014); **OR**
   C. Prior radiation therapy (within previous 1 year) (Terbuch 2018) (Fujiwara 2017) (Shigeta 2015); **OR**
   D. Bone marrow involvement by tumor producing cytopenias (Lyman 2014); **OR**
   E. Persistent neutropenia (absolute neutrophil count [ANC] less than 1500mm^3) (Lyman 2014); **OR**
   F. Poor renal function (glomerular filtration rate [GFR] less than 60mL/min) (Lyman 2014; Aagaard 2018); **OR**
   G. Liver dysfunction (liver function tests at least (AST or ALT levels) 2X upper limit of normal or bilirubin > 2.0 mg/dL) (Lyman 2014) (Aagaard 2018); **OR**
   H. Recent surgery performed as part of cancer management within previous 30 days (not to include a procedure such as port placement, drain placement, IVC filter, etc.) (Lyman 2014; Aagaard 2018); **OR**
   I. History of active infection within previous 60 days (Lyman 2014; Aagaard 2018); **OR**
   J. Current open wound and chemotherapy cannot be delayed (Lyman 2014; Aagaard 2018).

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 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) (NCCN 2A).

Neulasta/Neulasta Onpro (pegfilgrastim), Fulphila (pegfilgrastim-jmdb), Fylnetra (pegfilgrastim-pbbk), Nyvepria (pegfilgrastim-apgf), Stimufend (pegfilgrastim-fpgk), Udenyca/Udenyca Onbody (pegfilgrastim-cbqv), or Ziextenzo (pegfilgrastim-bmez)

Requests for Neulasta/Neulasta Onpro (pegfilgrastim), Fulphila (pegfilgrastim-jmdb), Fylnetra (pegfilgrastim-pbbk), Nyvepria (pegfilgrastim-apgf), Udencya/Udenyca Onbody (pegfilgrastim-cbqv), or Ziextnzo (pegfilgrastim-bmez) 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 (see Appendix, Table 1);

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 (see Appendix, Table 1) and individual has any of the following risk factors for FN:
    A. Age greater than 65 years (Lyman 2014; Aagaard 2018); **OR**
    B. Poor performance status (Eastern Cooperative Oncology Group 3 or 4) or HIV infection (in particular, those with low CD4 counts (≤ 450/μL)) but chemotherapy still indicated (Lyman 2014); **OR**
    C. Prior radiation therapy (within previous 1 year) (Terbuch 2018) (Fujiwara 2017) (Shigeta 2015); **OR**
    D. Bone marrow involvement by tumor producing cytopenias (Lyman 2014); **OR**
    E. Persistent neutropenia (absolute neutrophil count [ANC] less than 1500mm^3) (Lyman 2014); **OR**
    F. Poor renal function (glomerular filtration rate [GFR] less than 60mL/min) (Lyman 2014; Aagaard 2018); **OR**
    G. Liver dysfunction (liver function tests (AST or ALT levels) at least 2X upper limit of normal or bilirubin > 2.0 mg/dL) (Lyman 2014) (Aagaard 2018); **OR**
    H. Recent surgery performed as part of cancer management within previous 30 days (not to include a procedure such as port placement, drain placement, IVC filter, etc) (Lyman 2014; Aagaard 2018); **OR**
    I. History of active infection within previous 60 days (Lyman 2014; Aagaard 2018); **OR**
    J. Current open wound and chemotherapy cannot be delayed (Lyman 2014; Aagaard 2018);

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 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

XI. 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) (Label, NCCN 2A);

OR

XII. 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

XIII. Individual is using for treatment of hematopoietic cell mobilization in combination with plerixafor (NCCN 2A);

OR

XIV. Individual is using for Wilms Tumor (Nephroblastoma) (NCCN 2A); **AND**

XV. Using with Regimen M and Regimen I for one of the following courses:
    A. Cyclophosphamide and etoposide; **OR**
    B. Cyclophosphamide, doxorubicin, and vincristine;

OR

XVI. Individual is using for autologous hematopoietic stem cell (HSC) mobilization as part of the development of an FDA-approved ex vivo gene therapy (e.g. Zynteglo (betibeglogene autoemcel)).

Neupogen (filgrastim), Nivestym (filgrastim-aafi), Nypozi (filgrastim-txid), Releuko (filgrastim-ayow), or Zarxio (filgrastim-sndz)

Requests for Neupogen (filgrastim), Nivestym (filgrastim-aafi), Nypozi (filgrastim-txid), Releuko (filgrastim-ayow), 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 (see Appendix, Table 1);

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 (see Appendix, Table 1) and individual has any risk factors for FN:
    A. Age greater than 65 years (Lyman 2014; Aagaard 2018); **OR**
    B. Poor performance status (Eastern Cooperative Oncology Group 3 or 4) or HIV infection (in particular, those with low CD4 counts (≤ 450/μL) but chemotherapy still indicated (Lyman 2014); **OR**
    C. Prior radiation therapy (within previous 1 year) (Terbuch 2018) (Fujiwara 2017) (Shigeta 2015); **OR**
    D. Bone marrow involvement by tumor producing cytopenias (Lyman 2014); **OR**
    E. Persistent neutropenia (absolute neutrophil count [ANC] less than 1500mm^3) (Lyman 2014); **OR**
    F. Poor renal function (glomerular filtration rate [GFR] less than 60mL/min) (Lyman 2014) (Aagaard 2018); **OR**
    G. Liver dysfunction (liver function tests (AST or ALT levels) at least 2X upper limit of normal or bilirubin > 2.0 mg/dL) (Lyman 2014; Aagaard 2018); **OR**
    H. Recent surgery performed as part of cancer management within previous 30 days (not to include a procedure such as port placement, drain placement, IVC filter, etc) (Lyman 2014; Aagaard 2018); **OR**
    I. History of active infection within previous 60 days (Lyman 2014; Aagaard 2018); **OR**
    J. Current open wound and chemotherapy cannot be delayed (Lyman 2014; Aagaard 2018);

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 (NCCN 2A); **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 is 18 years of age or older and has a diagnosis of acute myeloid leukemia (AML); **AND**
XII. Individual is using shortly after the completion of induction or repeat induction chemotherapy, or after the completion of consolidation chemotherapy for AML (Label, NCCN 2A);

OR

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

OR

XIV. Individual has a diagnosis of myelodysplastic syndrome (MDS) (NCCN 2A); **AND**
XV. Individual has severe neutropenia (ANC less than or equal to 500mm^3) or experiencing recurrent or resistant infections;

OR

XVI. Individual has a diagnosis of myelodysplastic syndrome with ring sideroblasts (MDS-RS) or MDS/MPN-RS-T; **AND**
XVII. Individual is using in combination with Reblozyl (Reblozyl Label);

OR

XVIII. Individual has IPSS-R (Very Low, Low, Intermediate) risk myelodysplastic syndrome associated with symptomatic anemia (NCCN 2A); **AND**
XIX. Individual does not have a del(5q) chromosomal abnormality; **AND**
XX. Individual has serum erythropoietin ≤ 500 mU/ML; **AND**
XXI. Individual will use in combination with an erythropoiesis-stimulating agent (ESA) following no response to either an ESA alone or luspatercept-aamt (Reblozyl);

OR

XXII. 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

XXIII. 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

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

OR

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

OR

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

OR

XXVIII. 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

XXIX. 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

XXX. 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

XXXI. 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 (DrugPoints B Iia);

OR

XXXII. Individual is using to reduce the duration of neutropenia and neutropenia related clinical sequelae in those with nonmyeloid malignancies undergoing myeloblative chemotherapy followed by bone marrow transplant (BMT) (Label);

OR

XXXIII. Individual is using for treatment of hematopoietic cell mobilization for autologous donors (NCCN 2A);

OR

XXXIV. Individual is using for additional therapy for insufficient collection of stem cells in combination with plerixafor following treatment with filgrastim alone (or its biosimilars) or filgrastim (or its biosimilars) and disease-specific chemotherapy (NCCN 2A);

OR

XXXV. Individual is using for Wilms Tumor (Nephroblastoma) (NCCN 2A); **AND**

XXXVI. Using with Regimen M and Regimen I for one of the following courses:

A. Cyclophosphamide and etoposide; **OR**
B. Cyclophosphamide, doxorubicin, and vincristine;

OR

XXXVII. Individual is using for autologous hematopoietic stem cell (HSC) mobilization as part of the development of an FDA-approved ex vivo gene therapy (e.g. Zynteglo (betibeglogene autoemcel)) (NCCN 2A);

OR

XXXVIII. Individual is using for hematopoietic cell mobilization for allogenic donors as a single agent (NCCN 2A);

OR

XXXIX. Individual is using as supportive management of neutropenic events due to immunotherapy related toxicities from CAR T-cell therapy (NCCN 2A).

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 500mm^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 for treatment of hematopoietic cell mobilization for autologous donors (NCCN 2A);

OR

XVII. 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));

OR

XVIII. Individual is 18 years of age or younger; **AND**
XIX. Individual is diagnosed with relapsed/refractory high-risk neuroblastoma; **AND**
XX. Individual is using in a regiment with dinutuximab (Unituxin) (NCCN 1, 2A); **AND**
XXI. Individual achieved a partial response to first-line multi-agent, multi-modality therapy (i.e. induction combination chemotherapy, or myeloablative consolidation chemotherapy followed by autologous stem cell transplant);

OR

XXII. Individual is diagnosed with relapsed/refractory high-risk neuroblastoma; **AND**
XXIII. Individual is using in combination with Danyelza (naxitamab-gqgk).

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 (see Appendix, Table 1);

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 (see Appendix, Table 1) and individual has any risk factors for FN:
   A. Age greater than 65 years (Lyman 2014; Aagaard 2018); **OR**
   B. Poor performance status (Eastern Cooperative Oncology Group 3 or 4) or HIV infection (in particular, those with low CD4 counts (≤ 450/µL)) but chemotherapy still indicated (Lyman 2014); **OR**
   C. Prior radiation therapy (within previous 1 year) (Terbuch 2018) (Fujiwara 2017) (Shigeta 2015); **OR**
   D. Bone marrow involvement by tumor producing cytopenias (Lyman 2014); **OR**
   E. Persistent neutropenia (absolute neutrophil count [ANC] less than 1500mm^3) (Lyman 2014); **OR**
   F. Poor renal function (glomerular filtration rate [GFR] less than 60mL/min) (Lyman 2014; Aagaard 2018); **OR**
   G. Liver dysfunction (liver function tests (AST or ALT levels) at least 2X upper limit of normal or bilirubin > 2.0 mg/dL) (Lyman 2014; Aagaard 2018); **OR**
   H. Recent surgery performed as part of cancer management within previous 30 days (not to include a procedure such as port placement, drain placement, IVC filter, etc.) (Lyman 2014; Aagaard 2018); **OR**
   I. History of active infection within previous 60 days (Lyman 2014; Aagaard 2018); **OR**
   J. Current open wound and chemotherapy cannot be delayed (Lyman 2014; Aagaard 2018);

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 500mm^3) or experiencing recurrent or resistant infections (NCCN 2A);

OR

XIV. Individual has a diagnosis of myelodysplastic syndrome with ring sideroblasts (MDS-RS) or MDS/MPN-RS-T; **AND**
XV. Individual is using in combination with Reblozyl;

OR

XVI. Individual has IPSS-R (Very Low, Low, Intermediate) risk myelodysplastic syndrome associated with symptomatic anemia (NCCN 2A); **AND**
XVII. Individual does not have a del(5q) chromosomal abnormality; **AND**
XVIII. Individual has serum erythropoietin ≤ 500 mU/ML; **AND**
XIX. Individual will use in combination with an erythropoiesis-stimulating agent (ESA) following no response to either an ESA alone or luspatercept-aamt (Reblozyl);

OR

XX. 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);

OR

XXI. Individual is using for treatment of hematopoietic cell mobilization for autologous donors (NCCN 2A);

OR

XXII. Individual is using for additional therapy for insufficient collection of stem cells in combination with plerixafor following treatment with tbo-filgrastim alone or tbo-filgrastim and disease-specific chemotherapy (NCCN 2A);

OR

XXIII. Individual is using for autologous hematopoietic stem cell (HSC) mobilization as part of the development of an FDA-approved ex vivo gene therapy (e.g. Zynteglo (betibeglogene autoemcel));

OR

XXIV. Individual is using for hematopoietic cell mobilization for autologous donors in combination with Aphexda (motixafortide) (Aphexda Label).

Colony Stimulating Factors (filgrastim and their biosimilars, pegfilgrastim and their biosimilars, 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 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**
VI. 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[1] agent or agents.

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

A list of long-acting preferred white blood cell growth factors is available here.

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.

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

A list of short-acting preferred white blood cell growth factors is available here.

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.

[1]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	
96377	Application of on-body injector (includes cannula insertion) for timed subcutaneous injection [Neulasta OnPro injector]
HCPCS	
C9173	Injection, filgrastim-txid (nypozi), biosimilar, 1 microgram [Nypozi]
J1442	Injection, filgrastim (G-CSF), excludes biosimilars, 1 mcg [Neupogen]
J1447	Injection, tbo-filgrastim, 1 mcg [Granix]
J1449	Injection, eflapegrastim-xnst, 0.1 mg [Rolvedon]
J2506	Injection, pegfilgrastim, excludes biosimilar, 0.5 mg [Neulasta]
J2820	Injection, sargramostim (GM-CSF), 50 mcg [Leukine]
J9361	Injection, efbemalenograstim alfa-vuxw, 0.5 mg [Ryzneuta]
Q5101	Injection, filgrastim-sndz, biosimilar, (Zarxio), 1 mcg
Q5108	Injection, pegfilgrastim-jmdb (Fulphila), biosimilar, 0.5 mg
Q5110	Injection, filgrastim-aafi, biosimilar, (Nivestym), 1 mcg
Q5111	Injection, pegfilgrastim-cbqv, biosimilar, (Udenyca), 0.5 mg, [Udenyca, Udenyca Onbody]
Q5120	Injection, pegfilgrastim-bmez (ZIEXTENZO), biosimilar, 0.5 mg
Q5122	Injection, pegfilgrastim-apgf (Nyvepria), biosimilar, 0.5 mg
Q5125	Injection, filgrastim-ayow, biosimilar, (Releuko), 1 mcg
Q5127	Injection, pegfilgrastim-fpgk (Stimufend), biosimilar, 0.5 mg
Q5130	Injection, pegfilgrastim-pbbk (Fylnetra), biosimilar, 0.5 mg
Q5148	Injection, filgrastim-txid (Nypozi), biosimilar, 1 microgram
ICD-10 Diagnosis	
	All diagnosis

Document History

Revised: 09/09/2024
Document History:

- 05/01/2025 – Step therapy table updates.
- 04/01/2025 – Adjusted coding to numeric order. Step therapy table updates.
- 03/04/2025 - Coding Update: Removed HCPCS NOC J3590 and added Q5148 for Nypozi effective 4/1/25.
- 09/09/2024 – Select Review: Update existing criteria for use with plerixafor within Leukine (Sargramostim) and Granix (tbo-filgrastim) criteria. Step therapy table updates. Coding Reviewed: No changes. Add HCPCS C9173 effective 1/1/2025 for Nypozi and delete C9399.
- 08/16/2024 – Select Review: Add new biosimilar agent Nypozi to Neupogen criteria. Coding Reviewed: Add HCPCS C9399 and J3590 for Nypozi.
- 05/17/2024 – Annual Review: Add criteria to stipulate liver dysfunction risk factor for febrile neutropenia can be 2X ULN for either AST or ALT levels Rolvedon and Ryzneuta: Add NCCN criteria for use in Hematopoietic Syndrome of Acute Radiation Syndrome. Neupogen: Add criteria for use in IPSS-R risk myelodysplastic syndrome associated with symptomatic anemia. Clarify criteria for use in hematopoietic cell mobilization. Add criteria for use in combination with plerixafor when used for insufficient collection of stem cells following prior filgrastim therapy (alone or in combination). Add criteria for use in hematopoietic cell mobilization for allogenic donors as a single agent. Add criteria for use as supportive management of neutropenic events due to immunotherapy related toxicities from CAR-T cell therapy. Leukine: Add criteria for use in hematopoietic cell mobilization in combination with cyclophosphamide with or without plerixafor. Clarify existing criteria for use in r/r high-risk neuroblastoma in combination with Unituxin (dinutuximab). Granix: Add criteria for use in IPSS-R risk myelodysplastic syndrome associated with symptomatic anemia. Add definition for “older adult” in FN Risk table for use in Breast cancer for adjuvant TC. Coding Reviewed: Minor updates to HCPCS code descriptions. Removed Prokine from HCPCS J2820. Effective 7/1/2024 CMS update: Remove HCPCS J3490 and J3590 for Ryzneuta. Add HCPCS J9361 for Ryzneuta.
- 03/01/2024 – Step therapy table updates.
- 02/23/2024 – Select Review: Add new FDA approved Udenyca Onbody to the PA, ST, and QL. Add combination use of Mozobil (plerixafor) with Leukine (Sargramostim) for use in treatment for hematopoietic cell mobilization. Clarify existing language for use in combination with Mozobil in filgrastim, pegfilgrastim, and tbo-filgrastim criteria. Remove may not be approved criteria for “Individual is using for prophylaxis of FN during concomitant chemotherapy and radiation therapy”. Coding Reviewed: Added Udenyca Onbody to HCPCS J3490, J3590. Effective 4/1/2024 Added Udenyca Onbody to Q5111. Removed Udenyca Onbody from J3490 and J3590.
- 12/11/2023 – Select Review: Add a PA for FDA approved agent Ryzneuta. Update filgrastim agents--Neupogen and Granix-- criteria to include combination use with Reblozyl when used for MDS with ring sideroblasts. Coding Reviewed: Added HCPCS J3490, J3590 for Ryzneuta.
- 11/19/2023 – Select Review: Add combination use with Aphexda for hematopoietic cell mobilization with filgrastim and tbo-filgrastim criteria. Remove criteria for HSC use in Rolvedon. Coding Reviewed: No changes.
- 11/01/2023 – Step therapy table updates.
- 09/18/2023 – Step therapy table updates.
- 08/15/2023 – Step therapy table updates.
- 07/05/2023 – Step therapy table updates.
- 05/19/2023 – Annual Review: Add NCCN 2A use in Wilms Tumor for filgrastim and pegfilgrastim. Update Udencya for new autoinjector dosage formulation. Add criteria for use with Mozobil to Neulasta (and biosimilars), Neupogen (and biosimilars), and Granix. Format quantity limit table for all pegfilgrastim CSF agents (Neulasta and biosimilars). Update Appendix table for FN risk for selected chemotherapy regimens. Coding Reviewed: No changes.
- 05/01/2023 – Step therapy table updates.
- 03/27/2023 – Step therapy table updates.
- 01/25/2023 – Step therapy table updates.
- 12/21/2022 – Step therapy table updates.
- 10/24/2022 – Step therapy table updates.
- 09/12/2022 – Select Review: Add newly FDA approved Rolvedon criteria to document for PA, QL, and Non-Preferred LA CSF Step Therapy. Add new pegfilgrastim biosimilar Stimufend to Neupogen criteria, Non-Preferred LA Step therapy, and add a new QL for Stimufend prefilled syringe. Add criteria within G-CSF agents for use before Zynteglo gene therapy. Step therapy table updates. Coding reviewed: Added HCPCS J3490, C9399 for Rolvedon and Stimufend. Effective 10/1/2022 Added HCPCS Q5125 for Releuko. Removed HCPCS C9096 for Releuko. Effective 4/1/2023 Added HCPCS J1449, Q5127, Q5130 for Rolvedon, Stimufend, Fylnetra. Removed HCPCS J3590, J3490, C9399.
- 08/19/2022 – Select Review: Update Neulasta criteria with addition of new biosimilar Fylnetra. Add Fylnetra as a potential preferred agent in the Long-Acting CSF ST. Add QL for Fylnetra. Coding Reviewed: Added HCPCS J3590.
- 07/25/2022 – Step Therapy table updates.
- 05/20/2022 – Annual Review: Update Neupogen criteria with addition of new biosimilar Releuko. Update criteria for use in high-risk pediatric neuroblastoma (with or without IL-2). Coding Reviewed: Added HCPCS C9096.
- 12/20/2021 – Step Therapy table updates.

- 05/21/2021– Annual Review: Update pegfilgrastim criteria, Long-Acting Step therapy to clarify inclusion of Neulasta and Neulasta Onpro. Coding Review: No changes. 1/1/2022 Coding Review: Added HCPCS J2506, Removed HCPCS J2505.
- 02/26/2021 – Step Therapy table updates.
- 12/14/2020– Select Review: Add criteria for Leukine use in combination with Danyelza for relapsed or refractory neuroblastoma. Coding Reviewed Effective 1/1/2021 Added HCPCS Q5122 Removed HCPCS J3590 for Nyvepria. Effective 2/23/21 Added Neulasta Onpro to J2505.
- 11/20/2020– Select Review: Clarify pegfilgrastim products quantity limits. Add additional FN chemotherapy regimens in Appendix. Coding Reviewed: Removed HCPCS S9537.
- 08/21/2020– Select Review: Update Neulasta criteria to add new biosimilar Nyvepria (pegfilgrastim-apgf). Update NP Long-Acting Step therapy with new biosimilar Nyvepria. Add new quantity limit for Nyvepria. Add the term biosimilars to the "may not be approved" criteria. Updated Appendix for Febrile Neutropenia Risk of Selected Chemotherapy Regimens. Coding Reviewed: Added HCPCS J3590 for Nyvepria, All diagnosis pend
- 05/15/2020– Annual Review: Update Neupogen and Neulasta criteria to remove Acute Lymphocytic Leukemia criteria. Administrative update to Granix for risk factor criteria. Coding reviewed: Added HCPCS Q5120 (Effective 7/1/2020), Deleted 6/30/2020- HCPCS C9058, J3590 .
- 03/16/2020– Select Review: Update criteria for patient specific risk factors when using growth factors in the prophylaxis of febrile neutropenia. Administrative updates made for consistency.
- 02/21/2020– Select Review: Update Leukine criteria to include FDA use in combination for pediatric high-risk neuroblastoma. Update Neupogen criteria to include FDA biosimilar Ziextenzo. Add quantity limits for Ziextenzo. Update Long-acting CSF Step therapy with the addition of Ziextenzo as a potential preferred product. Coding Reviewed: Added HCPCS C9399, C9058, J3590 for Ziextenzo
- 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
- 08/16/2019 – Annual Review: Maintain low-, intermediate-, moderate-, high- risk ratings for febrile neutropenia with various chemotherapeutic regimens listed in NCCN Myeloid Growth Factors Guideline. Remove Leukine (sargramostim) prophylaxis criteria for use in primary prophylaxis of febrile neutropenia. Coding Reviewed: No changes.
- 03/18/2019 – Select Review: Update Neulasta and Fulphila criteria with the addition of new pegfilgrastim agent Udencya. Update NP Long-Acting CSF Step Therapy with the inclusion of Udencya as a potential preferred product. Remove off-label Clinical Pharmacology indications. Coding Reviewed: No changes.
- 12/20/2018 – HCPCS changes; added Q5111.
- 11/09/2018 – Coding review: J3590 for Fulphila deleted, Q5108 for Fulphila added, Q5110 Nivestym added. Kept ICD-10 at all diagnosis. Criteria to guide medical necessity.
- 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.

Appendix

Febrile Neutropenia Risk of Selected Chemotherapy Regimens

The following table represents selected chemotherapy regimens requiring further examination in their disease setting and the associated risk for development of febrile neutropenia. This is not a comprehensive list, as there are other regimens that are associated with risk for the development of FN. The FN risk of these other regimens will follow the guidance within the NCCN Guidelines Management of Neutropenia. A high-risk chemotherapy regimen is defined as a ≥ 20% probability of developing febrile neutropenia, an intermediate-risk chemotherapy regimen is associated with ≥10 to ≤ 20% incidence of developing FN, and a low-risk chemotherapy regimen is associated with <10% incidence of developing FN.

Table 1

Disease State	Chemotherapy regimen	Risk of developing FN	References
Breast Cancer	Adjuvant TC in those ≥ 65 years old	Intermediate	Do 2015; Jones 2009; Jones 2006; Kosaka 2015; Younis 2012
Breast Cancer (Metastatic)	Fam-trastuzuamab deruxtecan-nxki	Low	Modi S et al. 2020; Modi S et al. 2022; Cortes J et al 2022;
Breast cancer (Neoadjuvant)	Pembrolizumab, paclitaxel, and carboplatin	Intermediate	Schmid P, et al. 2022
Breast Cancer (Metastatic)	Pembrolizumab, and chemotherapy	Low	Cortes J, et al 2022; Tolaney SM et al 2021; Tolaney SM et al 2020; Perez-Garcia JM et al

			2021; Shah AN et al 2020; de la Cruz-Merino L et al 2022
Breast Cancer	Metastatic Sacituzumab govitecan-hziy	Low	Bardia A et al 2021; Bardia A et al 2019; Rugo HS et al 2022; Kathpalia M et al. 2023
Breast Cancer	Neoadjuvant TCHP (docetaxel, carboplatin, trastuzumab, and pertuzumab)	High	Gilbar 2014; Hurvitz 2018
Breast Cancer (Advanced)	Docetaxel (dosing of less than 75 mg/m^2)	Low	Harvey V 2006; Mauri D 2010; Rivera E 2008; Sparano JA 2008; Tabernero J 2004
Breast Cancer (Advanced)	Docetaxel (dosing of 75 mg/m^2)	Intermediate	Andersson M 2011; Baselga J 2012; Burris HA 1999; Harvey V 2006; Jones SE 2005; Marty M 2005;
Castrate-Resistant Prostate Cancer (CRPC) (Advanced)	Cabazitaxel	Intermediate	De Bono JS. 2010; Eisenberger M 2017; Oudard S 2017
Cervical Cancer (Advanced)	Cisplatin and paclitaxel ± bevacizumab	Intermediate	Angioli R 2015; Lissoni AA 2009; Lorusso D 2014; Monk BJ 2009; Moore DH 2004; Tewari KS 2014, 2017; Yang Z 2016
	Topotecan	Intermediate	Bookman MA 2000; Coronel J 2009; Lorusso D 2011; Muderspach LI 2001;
	Pembrolizumab and platinum-based chemotherapy ± bevacizumab	Low	Colombo N et al. 2021
Gastroesophageal Cancer	Cisplatin and irinotecan	Intermediate	Ajani JA 2002; Enzinger PC 2016; Ilson DH 2004, 2012; Knox JJ 2010; Newman E 2005
	Nivolumab and FOLFOX or XELOX	Low	Janjigian YY et al. 2021
Germ Cell Tumors (Advanced)	Bleomycin, etoposide, and cisplatin	Intermediate	de Wit R 2012; Fizazi K 2014; Garcia del Muro X 2008; Nichols CR 1991
	Etoposide and cisplatin	Intermediate	Arranz A 2001; Horwich A 2000; Motzer RJ 1995
Head and Neck Cancer (Recurrent/Metastatic)	EGFR-inhibitor (cetuximab or panitumumab) and platinum-based chemotherapy	Low	Burtness B 2005; Vermorken JB 2008; Vermorken JB 2013;
	Pembrolizumab plus platinum-based chemotherapy	Low	Burtness B 2019;
Non-Hodgkin Lymphoma	Gemcitabine, dexamethasone, and cisplatin ± rituximab	Intermediate	Baetz T 2003; Crump M 2004, 2014
Non-Small Cell Lung Cancer	Cisplatin and vinorelbine	Intermediate	Douillard JY 2006; Fossella F 2003; Gebbia V 2008; Georgoulias V 2005; Kenmotsu H 2020; Pujol JL 2005; Winton T 2005
Non-Small Cell Lung Cancer (Advanced)	Docetaxel	Intermediate	Abe T 2015; Barlesi F 2018; Camps C 2006; Georgoulias V 2004; Gridelli C 2004; Hanna N 2004; Herbst RS 2010; Karampeazis A 2011; Kudoh S 2006; Okamoto I 2020; Paz-Ares L 2008
Non-Small Cell Lung Cancer (Advanced)	Docetaxel and cisplatin	Low	Abe T 2015; Fossella F 2003; Kubota K 2015; Schiller JH 2002

Non-Small Cell Lung Cancer (Advanced)	Docetaxel and ramucirumab	Intermediate	Garon 2014; Yoh 2016
Non-Small Cell Lung Cancer (Metastatic)	Carboplatin/cisplatin, pemetrexed, and pembrolizumab	Low	Gandhi 2018; Langer 2016; Rodrigues-Pereira 2011; Scagliotti 2008
Non-Small Cell Lung Cancer (Metastatic, non-squamous)	Carboplatin, paclitaxel, and atezolizumab ± bevacizumab	Low	Lilenbaurm 2005; Ohe 2007; Socinski 2018; Williamson 2005
Non-Small Cell Lung Cancer (Metastatic, squamous)	Carboplatin, paclitaxel/nab-paclitaxel, and pembrolizumab	Low	Gadgeel 2018; Lilenbaum 2005; Ohe 2007; Paz-Ares 2018; Williamson 2005
Ovarian Cancer	Carboplatin and paclitaxel	Low	Clamp 2019; Coleman 2017; Katsumata 2009, 2013; Lhomme 2008; Pignata 2014; Sugiyama 2016; Vasey 2004
Ovarian Cancer (Advanced)	Topotecan	Intermediate	Aoki 2011; Gordon 2001, 2004; Gore 2002; McGonigle 2011; Meier 2009; Sehouli J 2008; Spannuth WA 2007; Swisher 1997
Ovarian Cancer (Advanced)	Carboplatin and docetaxel	Intermediate	Vasey 2004; Vorobiof 2003; Wang 2014
Pancreatic Cancer	FOLFIRINOX	Intermediate	Chlorean 2019; Conroy 2011; Conroy 2005; Hosein 2012; Okusaka 2014; Peddi 2012; Suker 2016; Thibodeau 2018; Tong 2018
Small Cell Lung Cancer (Extensive Stage)	Carboplatin, etoposide, and atezolizumab	Low	Horn 2018; Kosmidis 1994; Socinski 2009
Soft Tissue Sarcoma (Advanced)	Doxorubicin	High	Judson I 2014; Lorigan P 2007; Nielsen OS 1998; Seddon B 2017; Tap WD 2017; Tap WD 2020

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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.

CC-0002 Colony Stimulating Factor Agents

Short Acting Colony Stimulating Factor Agents

Commercial Medical Benefit

Effective Date	Preferred Agents	Non-Preferred Agents
11/01/2022	Zarxio	Granix Neupogen Nivestym Releuko
02/01/2025	Zarxio	Granix Neupogen Nivestym Nypozi Releuko

Medicaid Medical Benefit

Effective Date	Preferred Agents	Non-Preferred Agents
04/01/2023: DC 05/08/2023: GA, KY, MD, NJ, NV, NY, WNY	Zarxio	Granix Neupogen Nivestym Releuko

Medicare Medical Benefit

Effective Date	Preferred Agents	Non-Preferred Agents
12/01/2022	Zarxio	Granix Neupogen Nivestym Releuko
04/01/2025	Zarxio	Granix Neupogen Nivestym Nypozi Releuko

Long Acting Colony Stimulating Factor Agents

Commercial Medical Benefit

Effective Date	Preferred Agents	Non-Preferred Agents

06/01/2024	Neulasta Neulasta OnPro Udenyca Udenyca Onbody	Fulphila Fylnetra Nyvepria Rolvedon Ryzneuta Stimufend Ziextenzo

Medicaid Medical Benefit

Effective Date	Preferred Agents	Non-Preferred Agents
03/01/2021: WNY	Neulasta Neulasta OnPro Udenyca Udenyca Onbody	Fulphila Nyvepria Ziextenzo
03/01/2024: CA, GA, KY, MD, NJ, NV, NY, TN, VA, WI	Neulasta Neulasta OnPro Udenyca Udenyca Onbody	Fulphila Fylnetra Nyvepria Rolvedon Stimufend Ziextenzo

Medicare Medical Benefit

Effective Date	Preferred Agents	Non-Preferred Agents
06/01/2024	Neulasta Neulasta OnPro Udenyca Udenyca Onbody	Fulphila Fylnetra Nyvepria Rolvedon Ryzneuta Stimufend Ziextenzo