Medical Policy

Healthcare Services Department

Policy Name	Policy Number	Scope
Colony Stimulating Factors	MP-RX-FP-18-23	☒ MMM MA ☒ MMM Multihealth

Service Category

☐ Anesthesia
☐ Surgery
☐ Radiology Procedures
☐ Pathology and Laboratory Procedures
☐ Medicine Services and Procedures
☐ Evaluation and Management Services
☐ DME/Prosthetics or Supplies
☒ Part B Drugs

Service Description

This document addresses the use of white blood cell growth factors, also known as colony stimulating factors (CSF), **filgrastim (Neupogen and biosimilars), tbo-filgrastim (Granix), Pegfilgrastim (Neulasta Onpro/Neulasta and biosimilars), Eflapegrastim-xnst (Rolvedon), and Leukine,Prokine (sargramostim)** , drugs approved by the Food and Drug Administration (FDA) for the treatment of prophylaxis of Febrile Neutropenia (FN).

Background Information

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:
  - o Granix (tbo-filgrastim)
  - o Neulasta Onpro/Neulasta (pegfilgrastim) and Biosimilars
    - Fulphila (pegfilgrastim- jmdb)
    - Fylnetra (pegfilgrastim-pbbk)
    - Nyvepria (pegfilgrastim-apgf)
    - Stimufend (pegfilgrastim-fpgk)
    - Udenyca (pegfilgrastim-cbqv)
    - Ziextenzo (pegfilgrastim-bmez)
  - o Neupogen (filgrastim) and Biosimilars
    - Nivestym (filgrastim-aafi)
    - Releuko (filgrastim-ayow)
    - Zarxio (filgrastim-sndz)
    -
  - o Rolvedon (eflapegrastim-xnst)

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- GM-CSF:
  - o Leukine (sargramostim)

Rolvedon (eflapegrastim-xnst)

Rolvedon is a new 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 halflife, 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.

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 1500mm3) (Lyman 2014); **OR**
- Poor renal function (glomerular filtration rate [GFR] less than 60mL/min) (Lyman 2014; Aagaard 2018); **OR**
- Liver dysfunction (liver function tests 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)

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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.

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). At this time, there is a lack of published evidence regarding safety and efficacy for this use. A small retrospective analysis in diffuse large B-cell lymphoma members using GCSF 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): 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. NCCN currently does not provide any literature support for this use.

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.

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^{o}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.

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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.

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Applicable Codes

The following list(s) of procedure and/or diagnosis codes is provided for reference purposes only and may not be all inclusive. Inclusion or exclusion of a procedure, diagnosis or device code(s) does not constitute or imply member coverage or provider reimbursement policy. Benefit coverage for health services is determined by the member specific benefit plan document and applicable laws that may require coverage for a specific service. The inclusion of a code does not imply any right to reimbursement or guarantee claim payment. Other Policies and Guidelines may apply.

CPT	Description
96377	Application of on-body injector (includes cannula insertion) for timed subcutaneous injection [Neulasta OnPro injector]

HCPCS	Description
Q5122	Injection, pegfilgrastim-apgf, biosimilar, (Nyvepria), 0.5 mg
Q5120	Injection, pegfilgrastim-bmez, biosimilar, (Ziextenzo), 0.5 mg
J1442	Injection, filgrastim (G-CSF), excludes biosimilars, 1 microgram (Neupogen)
J1447	Injection, tbo-filgrastim, 1 microgram [Granix]
J2506	Injection, pegfilgrastim, excludes biosimilar, 0.5 mg
J2820	Injection, sargramostim (GM-CSF), 50 mcg [Leukine, Prokine]
Q5101	Injection, filgrastim-sndz, biosimilar, (Zarxio), 1 microgram
Q5108	Injection, pegfilgrastim-jmdb, biosimilar, (Fulphila), 0.5 mg
Q5110	Injection, filgrastim-aafi, biosimilar, (Nivestym), 1 microgram
Q5111	Injection, pegfilgrastim-cbqv, biosimilar, (Udenyca), 0.5 mg
Q5125	Injection, filgrastim-ayow, biosimilar, (Releuko), 1 microgram [Releuko]
J1449	Injection, eflapegrastim-xnst, 0.1 mg [Rolvedon]
Q5127	Injection, pegfilgrastim-fpgk (Fylnetra), biosimilar, 0.5 mg [Stimufend]
Q5130	Injection, pegfilgrastim-pbbk (Fylnetra), biosimilar, 0.5 mg [Fylnetra]

ICD-10	Description
All diagnoses.	

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Medical Necessity Guidelines

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.

Provider must submit documentation (such as office chart notes, lab results or other clinical information) supporting that member has met all approval criteria.

A. Criteria:

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 1500mm3) (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 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 109/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 for autologous hematopoietic stem cell (HSC) mobilization as part of the development of an FDA-approved ex vivo gene therapy (e.g. Zynteglo (betibeglogene autotemcel)).

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

Requests for Neulasta (pegfilgrastim), Fulphila (pegfilgrastim-jmdb), Fylnetra (pegfilgrastim-pbbk), Nyvepria (pegfilgrastim-apgf), Udencya (pegfilgrastim-cbqv), or Ziextenzo (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 1500mm3) (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 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 109/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);
OR

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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 for hematopoietic cell mobilization for autologous donors 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. 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), Releuko (filgrastim-ayow), or Zarxio (filgrastim-sndz)

Requests for Neupogen (filgrastim), Nivestym (filgrastim-aafi), 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 1500mm3) (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 2X upper limit of normal or bilirubin > 2.0 mg/dL) (Lyman 2014; Aagaard 2018); **OR**

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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;

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 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

XVII. 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
XVIII. Individual is using for the treatment of (non-chemotherapy) drug-induced neutropenia (AHFS);
OR
XIX. Individual is less than 21 years of age and is diagnosed with glycogen storage disease type 1b;
AND
XX. Individual is using for the treatment of low neutrophil counts (AHFS);
OR
XXI. Individual is using for the treatment of neutropenia associated with human immunodeficiency virus infection and antiretroviral therapy (AHFS);
OR
XXII. 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
XXIII. 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
XXIV. 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
XXV. 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
XXVI. 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); OR XXVII. Individual is using for treatment for hematopoietic cell mobilization for autologous donors in combination with plerixafor (NCCN 2A);
OR
XXVIII. Individual is using for Wilms Tumor (Nephroblastoma) (NCCN 2A); AND
XXIX. Using with Regimen M and Regimen I for one of the following courses:
A. Cyclophosphamide and etoposide; **OR**
B. Cyclophosphamide, doxorubicin, and vincristine;
OR
XXX. 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).

Leukine (Sargramostim)

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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 109/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 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

XVII. Individual is 18 years of age or younger; **AND**
XVIII. Individual is diagnosed with relapsed/refractory high-risk neuroblastoma; **AND**
XIX. Individual is using in combination with dinutuximab (Unituxin), 13-cis-retinoic acid (i.e. isotretinoin) and with or without interleukin-2 (IL-2) (i.e. aldesleukin); **AND**
XX. 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

XXI. Individual is diagnosed with relapsed/refractory high-risk neuroblastoma; **AND**
XXII. 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 1500mm3) (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 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

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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 109/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 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

XV. XV. Individual is using for treatment for hematopoietic cell mobilization for autologous donors in combination with plerixafor (NCCN 2A);
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)).

B. Criteria For Continuation of Therapy: N/A

C. Authorization Duration: N/A

D. Conditions Not Covered
Any other use is considered experimental, investigational, or unproven, including the following (this list may not be all inclusive).

Medical Policy

Healthcare Services Department

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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 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.

Limits or Restrictions

Step Therapy

This medical policy may be subject to Step Therapy. Please refer to the document published on the MMM Website: https://www.mmm-pr.com/planes-medicos/formulario-medicamentos

Quantity Limitations: N/A

Policy Name	Policy Number	Scope
Colony Stimulating Factors	MP-RX-FP-18-23	☒ MMM MA ☒ MMM Multihealth

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Medical Policy

Healthcare Services Department

Policy Name	Policy Number	Scope
Colony Stimulating Factors	MP-RX-FP-18-23	☒ MMM MA ☒ MMM Multihealth

Policy History

Revision Type	Summary of Changes	P&T Approval Date	MPCC Approval Date
Policy Inception	Elevance Health's Medical Policy adoption.	N/A	11/30/2023