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Subject: Granulocyte Colony Stimulating Factors

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Position Statement	Dosage and Administration	Billing/Coding	Reimbursement	Program Exceptions	Definitions
Related Guidelines	Other	References	Updates		

DESCRIPTION:

The risk of infection among patients receiving myelosuppressive chemotherapy who develop [neutropenia](#) is mitigated by two prophylactic strategies: antibiotics and myeloid growth factors. While antibiotics are generally recommended after febrile neutropenia has developed, guidelines from the American Society of Clinical Oncology and the National Comprehensive Cancer Network recommend the prophylactic use of myeloid growth factors to prevent neutropenia. Agents currently approved for the reduction of febrile neutropenia risk in patients receiving myelosuppressive chemotherapy include pegfilgrastim (Neulasta®), pegfilgrastim-jmdb (Fulphila®), pegfilgrastim-pbbk (Fylnetra), pegfilgrastim-apgf (Nyvepria™), pegfilgrastim-fpgk (Stimufend), pegfilgrastim-cbqv (Udenyca™), pegfilgrastim-bmez (Ziextenzo™), filgrastim (Neupogen®), filgrastim-sndz (Zarxio™), filgrastim-aafi (Nivestym™), tbo-filgrastim (Granix™), sargramostim (Leukine®), and eflapegrastim (Rolvedon). Filgrastim and pegfilgrastim products are recombinant granulocyte colony-stimulating factors (G-CSFs). Sargramostim is a granulocyte-macrophage colony-stimulating factor (GM-CSF). Eflapegrastim (Rolvedon) is a recombinant G-CSF produced by coupling of a human G-CSF analog to an Fc fragment of human immunoglobulin G4 (IgG4) via a polyethylene glycol linker. All agents are glycoproteins which act upon hematopoietic cells by binding to specific cell surface receptors to stimulate proliferation. In addition to being used for the prevention of febrile neutropenia, these agents are used in the treatment neutropenia in a number of clinical situations.

POSITION STATEMENT:

- I. The use of filgrastim-aafi (Nivestym), filgrastim-sndz (Zarxio), pegfilgrastim (Neulasta), pegfilgrastim-bmez (Ziextenzo), and sargramostim (Leukine) **meet the definition of medical necessity** for members meeting **ALL** of the following:

1. Indication for use (and any additional criteria) is listed in Table 1
2. Dose does not exceed the following and will be achieved using the fewest vials or syringes per day:
 - i. Filgrastim-aafi (Nivestym): 10 mcg/kg/day
 - i. Exception: 12 mcg/kg/day if indication for use is congenital neutropenia
 - ii. Filgrastim-sndz (Zarxio): 10 mcg/kg/day
 - i. Exception: 12 mcg/kg/day if indication for use is congenital neutropenia
 - iii. Pegfilgrastim (Neulasta): 6 mg
 - iv. Pegfilgrastim-bmez (Ziextenzo): 6 mg
 - v. Sargramostim (Leukine): 250 mcg/meter squared/day
 - i. Exception: Up to 7 mcg/kg/day for adults or 12 mcg/kg/day for pediatrics if used for Hematopoietic Syndrome of Acute Radiation Syndrome

Approval Duration: 1 year

- II. The use of filgrastim (Neupogen), filgrastim-ayow (Releuko), or tbo-filgrastim (Granix) **meet the definition of medical necessity** for members meeting **ALL** of the following:
 1. Member has a inadequate response, contraindication, or intolerance to filgrastim-aafi (Nivestym) **AND** filgrastim-sndz (Zarxio)
 2. Indication for use (and any additional criteria) is listed in Table 1
 3. Dose does not exceed the following and will be achieved using the fewest vials or syringes per day:
 - a. Filgrastim (Neupogen): 10 mcg/kg/day
 - i. Exception: 12 mcg/kg/day if indication for use is congenital neutropenia
 - b. Filgrastim-ayow (Releuko): 10 mcg/kg/day
 - i. Exception: 12 mcg/kg/day if indication for use is congenital neutropenia
 - c. Tbo-filgrastim (Granix): 5 mcg/kg/day

Approval Duration: 1 year

- III. The use of pegfilgrastim-jmdb (Fulphila), pegfilgrastim-pbbk(Fylnetra), pegfilgrastim-apgf (Nyvepria), (pegfilgrastim-fpgk) Stimufend, or pegfilgrastim-cbqv (Udenyca) **meets the definition of medical necessity** for members meeting **ALL** of the following:
 1. Member has a inadequate response, contraindication, or intolerance to pegfilgrastim (Neulasta) **AND** pegfilgrastim-bmez (Ziextenzo)†
 2. Indication for use (and any additional criteria) is listed in Table 1
 3. Dose does not exceed the following:
 - i. Pegfilgrastim-jmdb (Fulphila): 6 mg

- ii. Pegfilgrastim-pbbk (Fylmetra): 6 mg
- iii. Pegfilgrastim-apgf (Nyvepria): 6 mg
- iv. Pegfilgrastim-fpgk (Stimufend): 6 mg
- v. Pegfilgrastim-cbqv (Udenyca): 6 mg

Approval Duration: 1 year

IV. The use of eflapegrastim-xnst (Rolvedon) **meets the definition of medical necessity** for members meeting **ALL** of the following:

1. Member has a inadequate response, contraindication, or intolerance to pegfilgrastim (Neulasta) **AND** pegfilgrastim-bmez (Ziextenzo)[†]
2. **ONE** of the following:
 - i. When used to prevent febrile neutropenia with a myelosuppressive regimen at high-risk of febrile neutropenia with expected incidence greater than 20%
 - ii. When used for a FDA-label or NCCN diagnosis (not previously listed) and **ONE** of the following is met:
 - i. Member is diagnosed with a condition that is consistent with an indication listed in the product’s FDA-approved prescribing information (or package insert) **AND** member meets any additional requirements listed in the “Indications and Usage” section of the FDA-approved prescribing information (or package insert)
 - ii. Indication **AND** usage is recognized in NCCN Drugs and Biologics Compendium as a Category 1 or 2A recommendation
3. Dose does not exceed 13.2 mg once per chemotherapy cycle (not given more than 14 days prior to chemotherapy or within 24 hours of chemotherapy)

Approval Duration: 1 year

[†]Step therapy requirement does not apply if a prior health plan paid for the medication - documentation of a paid claim within the past 90 days must be submitted

TABLE 1:

Criteria for use of colony stimulating factors	
Indication for use	Additional Criteria
Congenital, cyclic, or idiopathic neutropenia (excludes requests for tbo-filgrastim)	Must be met: <ol style="list-style-type: none"> 1. Used to reduce the incidence and duration of sequelae of neutropenia (e.g., fever, infections, oropharyngeal ulcers) in symptomatic patients with severe chronic neutropenia (SCN)
Hematopoietic stem cell transplant	ONE must be met: <ol style="list-style-type: none"> 1. Use as an adjunct to Peripheral Blood Progenitor Cell (PBPC) transplantation to mobilize peripheral stem cells

	<ol style="list-style-type: none"> 2. Myeloid engraftment following hematopoietic stem cell transplant 3. Reduce severity of neutropenia in members with non-myeloid malignancies undergoing myeloablative chemotherapy followed by autologous or allogeneic bone marrow transplant 4. Delayed or failed engraftment in members who have undergone allogeneic or autologous hematopoietic stem cell transplant 5. Supportive care following hematopoietic stem cell transplant 6. Used as treatment for stem cell mobilization
<p>Hematopoietic Syndrome of Acute Radiation Syndrome</p>	<p>Must be met:</p> <ol style="list-style-type: none"> 1. Used to increase survival in members acutely exposed to myelosuppressive doses of radiation
<p>Myelodysplastic syndrome (excludes requests for pegfilgrastim, pegfilgrastim-jmdb, pegfilgrastim-cbqv, pegfilgrastim-bmez, pegfilgrastim-apgf, pegfilgrastim-pbbk, pegfilgrastim-fpgk, and sargramostim)</p>	<p>ONE of the following:</p> <ol style="list-style-type: none"> 1. Member is neutropenic and experiencing recurrent or resistant infections 2. Use is in combination with epoetin alfa or darbepoetin alpha when erythropoietin levels are 500 mUnits/mL or less
<p>Neuroblastoma (only applies to sargramostim)</p>	<p>Member is receiving dinutuximab (Unituxin) or naxitamab (Danyelza) for the treatment of high-risk neuroblastoma</p>
<p>Prevention of febrile neutropenia (excludes requests for sargramostim)</p>	<p>ONE must be met:</p> <ol style="list-style-type: none"> 1. Receiving myelosuppressive regimen at high-risk of febrile neutropenia with expected incidence greater than 20% 2. Febrile neutropenia or dose-limiting neutropenic event in earlier chemotherapy cycle 3. Receiving myelosuppressive chemotherapy with an intermediate-risk (10-20%) of febrile neutropenia, AND presence of at least one or more of the following: <ol style="list-style-type: none"> a. Age greater than 65 years b. Prior chemotherapy or radiation therapy c. Persistent neutropenia d. Bone marrow involvement by tumor

	<ul style="list-style-type: none"> e. Recent surgery and/or open wounds f. Liver dysfunction (bilirubin greater than 2 mg/dL) g. Renal dysfunction (creatinine clearance less than 50 ml/min) h. HIV infection i. Chronic immunosuppression in the transplant setting j. Poor performance status
<p>Treatment of chemotherapy-induced febrile neutropenia (excludes requests for pegfilgrastim, pegfilgrastim-jmdb, pegfilgrastim-cbqv, pegfilgrastim-apgf, pegfilgrastim-pbbk, pegfilgrastim-fpgk, and pegfilgrastim-bmez)</p>	<p>ONE of the following:</p> <ol style="list-style-type: none"> 1. Member was receiving prophylactic therapy with ONE of the following: filgrastim (Neupogen), filgrastim-aafi (Nivestym), filgrastim-ayow (Releuko), filgrastim-sndz (Zarxio), tbo-filgrastim (Granix) 2. Member did not receive prophylactic therapy and has ONE of the following risk factors: <ul style="list-style-type: none"> a. Sepsis syndrome b. Age greater than 65 years c. Absolute neutrophil count less than 100/microL d. Neutropenia expected more than 10 days duration e. Pneumonia or other infection f. Invasive fungal infection g. Hospitalization at time of fever h. Prior episode of febrile neutropenia
<p>Treatment (or adjunctive treatment) of neutropenia (excludes requests for tbo-filgrastim)</p>	<p>ONE must be met:</p> <ol style="list-style-type: none"> 1. HIV infection 2. Nonmalignant condition AND receiving myelosuppressive drug 3. Acute myelogenous leukemia (AML) in adults receiving chemotherapy (induction, consolidation, or relapsed/refractory disease) 4. Chronic myeloid leukemia (CML) for neutropenia associated with tyrosine kinase inhibitor therapy (e.g., bosutinib, dasatinib, imatinib, nilotinib, ponatinib)
<p>Treatment of Chimeric Antigen Receptor (CAR) T-cell induced</p>	<p>When used as supportive care for the treatment of neutropenia that developed following the use of CAR T-cell therapy (e.g.,</p>

neutropenia (excludes requests for pegfilgrastim, pegfilgrastim-jmdb, pegfilgrastim-cbqv, pegfilgrastim-bmez, pegfilgrastim-apgf, pegfilgrastim-pbbk, pegfilgrastim-fpgk, sargramostim, and tbo-filgrastim)	axicabtagene ciloleucel, brexucabtagene autoleucel, ciltacabtagene autoleucel, idecabtagene vicleucel, lisocabtagene maraleucel, tisagenlecleucel)
Wilm’s tumor (nephroblastoma) (excludes requests for sargramostim and tbo-filgrastim)	When used with ONE of the following: <ol style="list-style-type: none"> 1. cyclophosphamide and etoposide 2. cyclophosphamide, doxorubicin, and vincristine
Other FDA-approved or NCCN supported diagnosis (not previously listed above)	ONE of the following is met: <ol style="list-style-type: none"> 1. Member is diagnosed with a condition that is consistent with an indication listed in the product’s FDA-approved prescribing information (or package insert) AND member meets any additional requirements listed in the “Indications and Usage” section of the FDA-approved prescribing information (or package insert) 2. Indication AND usage is recognized in NCCN Drugs and Biologics Compendium as a Category 1 or 2A recommendation

Filgrastim, filgrastim-aafi, filgrastim-ayow, filgrastim-sndz, pegfilgrastim, pegfilgrastim-jmdb, pegfilgrastim-pbbk, pegfilgrastim-cbqv, pegfilgrastim-bmez, pegfilgrastim-apgf, pegfilgrastim-fpgk, tbo-filgrastim, eflapegrastim-xnst, and sargramostim are considered **experimental or investigational** when administered for all other indications, as there is insufficient clinical evidence to support their use.

NOTE: Dose-dense regimens (treatment given more frequently), specifically in the treatment of node positive breast cancer, small cell lung cancer, and diffuse aggressive non-Hodgkin’s lymphoma will be considered.

DOSAGE/ADMINISTRATION:

THIS INFORMATION IS PROVIDED FOR INFORMATIONAL PURPOSES ONLY AND SHOULD NOT BE USED AS A SOURCE FOR MAKING PRESCRIBING OR OTHER MEDICAL DETERMINATIONS. PROVIDERS SHOULD REFER TO THE MANUFACTURER’S FULL PRESCRIBING INFORMATION FOR DOSAGE GUIDELINES AND OTHER INFORMATION RELATED TO THIS MEDICATION BEFORE MAKING ANY CLINICAL DECISIONS REGARDING ITS USAGE.

Dosage is based on body weight and varies dependent upon response, product selected, and indication. Refer to product-specific labeling for complete dosing and administration instructions.

Filgrastim, filgrastim-aafi, filgrastim-ayow, filgrastim-sndz, tbo-filgrastim

Should not be administered in the period 24 hours before through 24 hours after the administration of cytotoxic chemotherapy.

Pegfilgrastim, pegfilgrastim-jmdb, pegfilgrastim-pbbk, pegfilgrastim-cbqv, pegfilgrastim-bmez, pegfilgrastim-apgf, pegfilgrastim-fpgk

Should not be administered in the period between 14 days before and 24 hours after administration of cytotoxic chemotherapy. An on-body injector delivers pegfilgrastim 27 hours after the injector is applied; therefore, a healthcare provider may apply an on-body injector on the same day as the administration of cytotoxic chemotherapy.

Sargramostim

Should not be administered in the period 24 hours before through 24 hours after the administration of cytotoxic chemotherapy or radiation therapy.

Eflagegrastim-xnst

Should not be administered in the period 14 days before through 24 hours after the administration of cytotoxic chemotherapy or radiation therapy.

PRECAUTIONS:

Contraindications

Filgrastim, filgrastim-aafi, filgrastim-ayow, filgrastim-sndz, pegfilgrastim, pegfilgrastim-jmdb, pegfilgrastim-pbbk, pegfilgrastim-cbqv, pegfilgrastim-bmez, pegfilgrastim-apgf, pegfilgrastim-fpgk, eflapegrastim-xnst, tbo-filgrastim

Contraindicated in patients with a history of serious allergic reactions to other granulocyte colony-stimulating factors

Sargramostim

Contraindicated in patients with excessive leukemic myeloid blasts in the bone marrow or peripheral blood ($\geq 10\%$), in patients with known hypersensitivity to GM-CSF, yeast-derived products or any component of the product, and in concomitant use with chemotherapy and radiotherapy.

Precautions/Warnings

Filgrastim, filgrastim-aafi, filgrastim-ayow, filgrastim-sndz, pegfilgrastim, pegfilgrastim-jmdb, pegfilgrastim-pbbk, pegfilgrastim-cbqv, pegfilgrastim-bmez, pegfilgrastim-apgf, pegfilgrastim-fpgk, eflapegrastim-xnst, tbo-filgrastim

Splenic Rupture - Splenic rupture, including fatal cases, has been reported. Evaluate patients who report left upper abdominal or shoulder pain for an enlarged spleen or splenic rupture.

Acute Respiratory Distress Syndrome - Acute respiratory distress syndrome (ARDS) has been reported. Evaluate patients who develop fever and lung infiltrates or respiratory distress for ARDS. Discontinue in patients with ARDS.

Serious Allergic Reactions - Serious allergic reactions, including anaphylaxis, have been reported. The majority of reported events occurred upon initial exposure. Provide symptomatic treatment for allergic reactions. Allergic reactions, including anaphylaxis, can recur within days after the discontinuation of initial anti-allergic treatment. Permanently discontinue in patients with serious allergic reactions.

Sickle Cell Disorders - Sickle cell crisis, in some cases fatal, has been reported in patients with sickle cell trait or sickle cell disease.

Glomerulonephritis - Glomerulonephritis has occurred. The diagnoses were based upon azotemia, hematuria (microscopic and macroscopic), proteinuria, and renal biopsy. Generally, events of glomerulonephritis resolved after dose reduction or discontinuation. If glomerulonephritis is suspected, evaluate for cause. If causality is likely, consider dose-reduction or interruption.

Alveolar Hemorrhage and Hemoptysis - Alveolar hemorrhage manifesting as pulmonary infiltrates and hemoptysis requiring hospitalization have been reported in healthy donors undergoing peripheral blood progenitor cell (PBPC) collection mobilization. Hemoptysis resolved with discontinuation.

Capillary Leak Syndrome - Capillary leak syndrome (CLS) has been reported after G-CSF administration, and is characterized by hypotension, hypoalbuminemia, edema and hemoconcentration. Episodes vary in frequency, severity and may be life-threatening if treatment is delayed. Patients who develop symptoms of capillary leak syndrome should be closely monitored and receive standard symptomatic treatment, which may include a need for intensive care.

Leukocytosis - In patients with cancer receiving therapy as an adjunct to myelosuppressive chemotherapy, to avoid the potential risks of excessive leukocytosis, it is recommended that therapy be discontinued if the ANC surpasses 10,000/mm after the chemotherapy-induced ANC nadir has occurred. Monitor CBCs at least twice weekly during therapy. Dosages that increase the ANC beyond 10,000/mm may not result in any additional clinical benefit. During the period of administration for PBPC mobilization in patients with cancer, discontinue if the leukocyte count rises to > 100,000/mm.

Cutaneous Vasculitis - Cutaneous vasculitis has been reported. In most cases, the severity of cutaneous vasculitis was moderate or severe. Hold therapy in patients with cutaneous vasculitis.

Potential Effect on Malignant Cells - The possibility that GCS-F acts as a growth factor for any tumor type cannot be excluded

Nuclear Imaging - Increased hematopoietic activity of the bone marrow in response to growth factor therapy has been associated with transient positive bone-imaging changes. This should be considered when interpreting bone-imaging results.

Aortitis – Manifestations may include generalized signs and symptoms such as fever, abdominal pain, malaise, back pain, and increased inflammatory markers. Discontinue if aortitis is suspected.

Myelodysplastic Syndrome (MDS) and Acute Myeloid Leukemia (AML) – MDS and AML have been reported to occur in the natural history of congenital neutropenia without cytokine therapy. It has also occurred in patients with breast cancer and lung cancer. Consider the risk and benefit of continuing therapy in this setting.

Thrombocytopenia - Thrombocytopenia has been reported in patients receiving pegfilgrastim. Monitor platelet counts.

On body-injector only - Acrylic adhesive may result in a significant reaction. If device failure is suspected, a healthcare provider should be contacted.

Sargramostim

Cardiovascular Symptoms - Occasional transient supraventricular arrhythmia has been reported.

Fluid Retention - Edema, capillary leak syndrome, pleural and/or pericardial effusion have been reported. Use with caution in patients with preexisting fluid retention, pulmonary infiltrates or congestive heart failure.

Growth Factor Potential - Because of the possibility of tumor growth potentiation, precaution should be exercised when using this drug in any malignancy with myeloid characteristics.

Hypersensitivity reactions including serious allergic or anaphylactic reactions- If any serious allergic or anaphylactic reaction occurs, discontinue and initiate appropriate therapy.

Immunogenicity – Neutralizing anti-drug antibodies may develop and be related to duration of drug exposure.

Infants and benzyl alcohol - Benzyl alcohol is a constituent of sargramostim has been reported to be associated with a fatal "Gasping Syndrome" in premature infants. Do not administer to neonates.

Infusion related reactions - A syndrome characterized by respiratory distress, hypoxia, flushing, hypotension, syncope, and/or tachycardia has been reported following the first administration.

Severe Myelosuppression – Do not administer within 24 hours preceding chemotherapy or radiotherapy or 24 hours following chemotherapy due to increased risk of adverse reactions including infections and thrombocytopenia.

Leukocytosis - Stimulation of marrow precursors may result in a rapid rise in white blood cell (WBC) count. If the ANC exceeds 20,000 cells/mm or if the platelet count exceeds 500,000/mm, administration should be interrupted or the dose reduced by half.

BILLING/CODING INFORMATION:

The following codes may be used to report these services:

HCPCS Coding:

J1442	Injection, filgrastim (G-CSF), excludes biosimilars,1 microgram
J1447	Injection, tbo-filgrastim, 1 microgram
J2506	Injection, pegfilgrastim, excludes biosimilar, 0.5 mg
J2820	Injection, sargramostim (GM-CSF), 50 mcg (Leukine®)
J3590	Unclassified biologics [for pegfilgrastim-pbbk, pegfilgrastim-fpgk, eflapegrastim-xnst only]

Q5101	Injection, filgrastim-sndz, biosimilar, (Zarxio), 1 microgram
Q5108	Injection, pegfilgrastim-jmdb, biosimilar (Fulphila), 0.5 mg
Q5110	Injection, filgrastim-aafi, biosimilar (Nivestym), 1 mcg
Q5111	Injection, pegfilgrastim-cbqv, biosimilar, (Udenyca), 0.5 mg
Q5120	Injection, pegfilgrastim-bmez, biosimilar, (Ziextenzo), 0.5 mg
Q5122	Injection, pegfilgrastim-apgf, biosimilar, (Nyvepria), 0.5 mg
Q5125	Injection, filgrastim-ayow, biosimilar, (Releuko), 1 microgram

ICD-10 Diagnosis Codes That Support Medical Necessity for Filgrastim (Neupogen®), Filgrastim-aafi (Nivestym™), filgrastim-ayow (Releuko®), Filgrastim-sndz (Zarxio™), Pegfilgrastim (Neulasta®), Pegfilgrastim-jmdb (Fulphila™), Pegfilgrastim-pbbk (Fylnetra), Pegfilgrastim-apgf (Nyvepria™), Pegfilgrastim-bmez (Ziextenzo®), Pegfilgrastim-cbqv (Udenyca™), (pegfilgrastim-fpgk) Stimufend, and Sargramostim (Leukine®):

B20	Human immunodeficiency virus [HIV] disease
C00.0 – C02.9	Malignant neoplasm of lip, base of tongue and other and unspecified parts of the tongue
C03.0 – C06.9	Malignant neoplasm of gum, floor of mouth, palate and other and unspecified parts of mouth
C07 – C08.9	Malignant neoplasm of other and unspecified major salivary glands
C09.0 – C11.9	Malignant neoplasm of tonsil, oropharynx and nasopharynx
C12 – C26.9	Malignant neoplasm of pyriform sinus, hypopharynx and other and ill-defined sites in the lip, oral cavity and pharynx, esophagus, stomach, small intestine, colon, rectosigmoid junction, rectum, anus and anal canal, liver and intrahepatic bile ducts, gallbladder, other and unspecified parts of biliary tract, pancreas and other and ill-defined digestive organs
C30.0 – C34.9	Malignant neoplasm of nasal cavity and middle ear, accessory sinuses, larynx, trachea and bronchus and lung
C37 – C39.9	Malignant neoplasm of thymus, heart, mediastinum and pleura, and other and ill-defined sites in the respiratory system
C40.00 – C41.9	Malignant neoplasm of bone and articular cartilage of limbs and other and unspecified sites
C43.0 – C44.9	Malignant melanoma of skin and other malignant neoplasm of skin
C46.0 – C46.9	Kaposi's sarcoma
C48 – C48.9	Malignant neoplasm of retroperitoneum and peritoneum
C49.0 – C49.9	Malignant neoplasm of other connective and soft tissue
C49.A0 – C49.A9	Gastrointestinal stromal tumor
C50.0 – C50.929	Malignant neoplasm of breast
C51.0 – C68.0	Malignant neoplasm of vulva, vagina, cervix uteri, corpus uteri, uterus, part unspecified, ovary, other and unspecified female genital organs, placenta, penis, prostate, testis, other and unspecified male genital organs, kidney, except renal pelvis, renal pelvis, ureter, bladder and other and unspecified urinary organs
C69.00 – C69.92	Malignant neoplasm of eye and adnexa

C71.0 – C75.09	Malignant neoplasm of brain, spinal cord, cranial nerves and other parts of central nervous system, thyroid gland, adrenal gland and other endocrine glands and related structures
C76.0 – C80.2	Malignant neoplasm of other and ill-defined sites and secondary and unspecified malignant neoplasm of lymph, respiratory and digestive organs, other and unspecified sites and without specification of site
C7A.00 – C7.A8 C7B.00 – C7.B8	Malignant neuroendocrine tumors
C81.00 – C83.99	Hodgkin, follicular and non-follicular lymphoma
C88.0	Waldenstrom macroglobulinemia
C88.8	Other malignant immunoproliferative diseases
C90.00 – C92.92	Multiple myeloma and malignant plasma cell neoplasms, lymphoid and myeloid leukemia
C93.00 – C93.10	Acute monoblastic/monocytic leukemia, Chronic myelomonocytic leukemia
C94.0 – C94.22	Acute erythroid leukemia, Acute megakaryoblastic leukemia
C94.40 – C94.42	Acute panmyelosis with myelofibrosis
D03.0 – D03.9	Melanoma in situ
D45 – D48.9	Polycythemia Vera, myelodysplastic syndromes, other neoplasms of uncertain behavior of lymphoid, hematopoietic and related tissue and uncertain behavior of other and unspecified sites
D49.0 – D49.9	Neoplasms of unspecified behavior
D61.1	Drug-induced aplastic anemia
D61.2	Aplastic anemia due to other external agents
D61.810 – D61.811	Antineoplastic chemotherapy induced pancytopenia or other drug-induced pancytopenia
D61.89	Other specified aplastic anemias and other bone marrow failure syndromes
D70.0 – D70.9	Neutropenia
E40 – E60	Kwashiorkor, nutritional marasmus, marasmic kwashiorkor, unspecified severe protein-calorie malnutrition, protein-calorie malnutrition of moderate and mild degree, retarded development following protein-calorie malnutrition, unspecified protein-calorie malnutrition, vitamin A deficiency, thiamine deficiency, niacin deficiency (pellagra) deficiency of other B group vitamins, vitamin D deficiency, other vitamin deficiencies, dietary calcium deficiency, dietary selenium deficiency and dietary zinc deficiency
E61.4 – E61.5	Chromium and molybdenum deficiency
T36.0 – T50.996	Poisoning by, adverse effect of and underdosing of antineoplastic and immunosuppressive drugs, systemic antibiotics, underdosing of other systemic anti-infectives and antiparasitics, hormones and their synthetic substitutes and antagonists, not elsewhere classified, nonopioid analgesics, antipyretics and antirheumatics, narcotics and psychodysleptics (hallucinogens), anesthetics and therapeutic gases, antiepileptic, sedative-hypotonic and antiparkinsonism drugs, primarily affecting the autonomic nervous system, primarily systemic and hematological agents, not elsewhere

	classified, primarily affecting the cardiovascular system, primarily affecting the gastrointestinal system, primarily acting on smooth and skeletal muscles and the respiratory system, topical agents primarily affecting skin and mucous membrane and by ophthalmological, otorhinolaryngological and dental drugs and diuretics and other and unspecified drugs, medicaments and biological substances
T66.XXXA, T66.XXXD, T66.XXXS	Radiation sickness, unspecified
T80.82XA – T80.89XS	Complication of immune effector cellular therapy (CAR-T)
T86.00 – T86.02	Unspecified complication of bone marrow transplant, rejection or failure
T86.09	Other complications of bone marrow transplant
W88.1XXA - W88.8XXS	Exposure to radioactive isotopes or other ionizing radiation
Z41.8	Encounter for other procedures for purposes other than remedying health state
Z48.290 – Z48.298	Encounter for aftercare following bone marrow or other organ transplant
Z51.11 – Z51.12	Encounter for antineoplastic chemotherapy or immunotherapy
Z51.89	Encounter for other specified aftercare
Z52.001	Unspecified donor, stem cells
Z52.011	Autologous blood donor, stem cells
Z52.091	Other blood donor, stem cells
Z52.3	Bone marrow donor
Z52.89	Donor of other specified organs or tissues
Z52.091	Other blood donor stem cells
Z94.6	Bone transplant status
Z94.81	Bone marrow transplant status
Z94.84	Stem cells transplant status
Z94.9	Transplanted organ and tissue status, unspecified

ICD-10 Diagnosis Codes That Support Medical Necessity for Tbo-Filgrastim (Granix™):

D46.0 – D46.9	Myelodysplastic syndromes
D46.A	Refractory cytopenia with multilineage dysplasia
D46.B	Refractory cytopenia with multilineage dysplasia and ring sideroblasts
D46.Z	Other myelodysplastic syndromes
D61.810 – D61.811	Antineoplastic chemotherapy induced pancytopenia or other drug-induced pancytopenia
D70.0 – D70.9	Neutropenia
T45.1X5A – T45.1X5S	Adverse effect of antineoplastic and immunosuppressive drugs
T66.XXXA, T66.XXXD, T66.XXXS	Radiation sickness, unspecified

W88.1XXA – W88.8XXS	Exposure to radioactive isotopes or other ionizing radiation
Z41.8	Encounter for other procedures for purposes other than remedying health state
Z48.290 - Z48.298	Encounter for aftercare following bone marrow or other organ transplant
Z51.11 – Z51.12	Encounter for antineoplastic chemotherapy or immunotherapy
Z51.89	Encounter for other specified aftercare
Z52.001	Unspecified donor, stem cells
Z52.011	Autologous blood donor, stem cells
Z52.091	Other blood donor, stem cells
Z94.81	Bone marrow transplant status
Z94.84	Stem cells transplant status

ICD-10 Diagnosis Codes That Support Medical Necessity for eflapegrastim-xnst (Rolvedon):

D61.810 – D61.811	Antineoplastic chemotherapy induced pancytopenia or other drug-induced pancytopenia
D70.1 - D70.9	Neutropenia
T45.1X5A – T45.1X5S	Adverse effect of antineoplastic and immunosuppressive drugs
Z51.11 – Z51.12	Encounter for antineoplastic chemotherapy or immunotherapy

REIMBURSEMENT INFORMATION:

Refer to section entitled [POSITION STATEMENT](#).

PROGRAM EXCEPTIONS:

Federal Employee Program (FEP): Follow FEP guidelines.

State Account Organization (SAO): Follow SAO guidelines.

Medicare Part D: Florida Blue has delegated to Prime Therapeutics authority to make coverage determinations for the Medicare Part D services referenced in this guideline.

Medicare Advantage products: Medical necessity is determined using any applicable NCD or LCD and then Step therapy Requirements for Medicare Outpatient (Part B) Medications outlined in Policy (09-J3000-39). The following Local Coverage Determination (LCD) was reviewed on the last guideline revised date: G-CSF (Neupogen, Granix, Zarxio) (L34002) and Pegfilgrastim (Neulasta) (L33747)) located at fcso.com.

DEFINITIONS:

Chemotherapy dose maintenance: is defined as attempts to maintain administration of chemotherapy at full doses on a specific, planned schedule.

Chemotherapy dose modification or reduction: is defined as attenuation in dose or delay in delivery of chemotherapy because of the occurrence of excessive toxicity in a prior cycle of treatment.

Curative chemotherapy: is defined as that with a high probability of cure, such as combination therapy for testicular cancer, Hodgkin's disease (HD), non-Hodgkin's lymphoma (NHL), or acute leukemia.

Dose-intense chemotherapy: is treatment given at higher doses or on a more frequent schedule than is conventional in an attempt to induce either more complete remissions or a greater cure rate.

Febrile neutropenia: is generally designated as a temperature of approximately 38.5°C (greater than approx. & lt: 101°F) or greater, sustained for more than 1 hour, and developing concurrently with absolute neutropenia of less than 500 cells/ μ L. These combined criteria are generally the impetus for initiation of antibiotic therapy, often with hospitalization.

Neutropenia: A hematological disorder characterized by an abnormally low number of neutrophil granulocytes (a type of white blood cell).

Non-myeloid malignancy: All cancers other than myeloid leukemias. Non-myeloid cancers include all types of carcinoma, all types of sarcoma, melanoma, lymphomas, lymphocytic leukemias (ALL and CLL), and multiple myeloma.

Palliative chemotherapy: is that given in an attempt to prolong survival or relieve symptoms but without chance of cure.

Progenitor cell: A progenitor cell, often confused with stem cell, is an early descendant of a stem cell that can only differentiate, but it cannot renew itself anymore. In contrast, a stem cell can renew itself (make more stem cells by cell division) or it can differentiate (divide and with each cell division evolve more and more into different types of cells). A progenitor cell is often more limited in the kinds of cells it can become than a stem cell. In scientific terms, it is said that progenitor cells are more differentiated than stem cells.

Progenitor-cell support: refers to transplantation of hematopoietic cells derived from either the bone marrow or the peripheral blood as a means to increase patient safety and tolerance of treatment when very high doses of chemotherapy are administered to increase remission rates and increase disease-free survival (DFS).

Standard-dose chemotherapy: is treatment with a regimen of chemotherapy given at doses and intervals that have become generally accepted by practicing oncologists.

Stem Cell: a type of undifferentiated cell with the ability to divide and proliferate to form precursor cells that can differentiate into more specialized cells.

RELATED GUIDELINES:

None.

OTHER:

Laboratory Monitoring

To assess a patient's hematologic status and ability to tolerate myelosuppressive chemotherapy, a complete blood count and platelet count should be obtained before chemotherapy is administered. Regular monitoring of hematocrit value and platelet count is recommended.

Chemotherapy Regimens and Risk for Febrile Neutropenia

Examples of Chemotherapy Regimens with a High Risk of Febrile Neutropenia (>20%)

1. Acute Lymphoblastic Leukemia (ALL)
 - a. ALL induction regimens
2. Bladder Cancer
 - a. Dose-dense MVAC (methotrexate, vinblastine, doxorubicin, cisplatin)
3. Bone cancer
 - a. VAI (vincristine, doxorubicin or dactinomycin, ifosfamide)
 - b. VDC-IE (vincristine, doxorubicin, or dactinomycin, etoposide)
 - c. Cisplatin/doxorubicin
 - d. VDC (cyclophosphamide, vincristine, doxorubicin or dactinomycin)
 - e. VIDE (vincristine, ifosfamide, doxorubicin or dactinomycin, etoposide)
4. Breast Cancer
 - a. Dose-dense AC followed by T (doxorubicin, cyclophosphamide, paclitaxel)
 - b. TAC (docetaxel, doxorubicin, cyclophosphamide)
 - c. TC (docetaxel, cyclophosphamide)
 - d. TCH (docetaxel, carboplatin, trastuzumab)
5. Colorectal Cancer
 - a. FOLFOXIRI (flurouracil, leucovorin, oxaliplatin, irinotecan)
6. Head and Neck Squamous Cell carcinoma
 - a. TPF (docetaxel, cisplatin, 5-fluorouracil)
7. Hodgkin Lymphoma
 - a. Brentuximab vedotin +AVD (doxorubicin, vinblastine, dacarbazine)
 - b. BEACOPP (bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, prednisone)
8. Kidney Cancer
 - a. Doxorubicin/gemcitabine
9. Non-Hodgkin's Lymphoma
 - a. CHP (cyclophosphamide, doxorubicin, prednisone) + brentuximab vedotin
 - b. EPOCH (etoposide, prednisone, vincristine, cyclophosphamide, doxorubicin)
 - c. ICE (ifosfamide, carboplatin, etoposide)
 - d. CHOP-14 (cyclophosphamide, doxorubicin, vincristine, prednisone) ± rituximab
 - e. MINE (mesna, ifosfamide, novatrone, etoposide)

- f. DHAP (dexamethasone, cisplatin, cytarabine)
 - g. ESHAP (etoposide, methylprednisolone, cisplatin, cytarabine)
 - h. HyperCVAD (cyclophosphamide, vincristine, doxorubicin, dexamethasone) + rituximab
10. Melanoma
- a. Dacarbazine-based combination with IL-2, interferon alfa (dacarbazine, cisplatin, vinblastine, IL-2, interferon alfa)
11. Multiple Myeloma
- a. DT-PACE
(dexamethasone/thalidomide/cisplatin/doxorubicin/cyclophosphamide/etoposide)
 - b. VTD-PACE (DT-PACE (dexamethasone, thalidomide, cisplatin, doxorubicin, cyclophosphamide, etoposide) + bortezomib)
12. Ovarian Cancer
- a. Topotecan
 - b. Docetaxel
13. Pancreatic Cancer
- a. FOLFIRINOX (flurouracil, leucovorin, irinotecan, oxaliplatin)
14. Soft Tissue Sarcoma
- a. MAID (mesna, doxorubicin, ifosfamide, dacarbazine)
 - b. Doxorubicin
 - c. Ifosfamide/doxorubicin
15. Small Cell Lung Cancer
- a. Topotecan
16. Testicular Cancer
- a. VeIP (vinblastine, ifosfamide, cisplatin)
 - b. VIP (etoposide, ifosfamide, cisplatin)
 - c. TIP (paclitaxel, ifosfamide, cisplatin)

Examples of Chemotherapy Regimens with an Intermediate Risk of Febrile Neutropenia (10-20%)

- 1. Occult Primary – Adenocarcinoma
 - a. Gemcitabine/docetaxel
- 2. Breast Cancer
 - a. Docetaxel
 - b. AC (doxorubicin, cyclophosphamide) + sequential docetaxel
 - c. Paclitaxel every 21 days

3. Cervical cancer
 - a. Cisplatin/topotecan
 - b. Paclitaxel/cisplatin
 - c. Topotecan
 - d. Irinotecan
4. Colorectal Cancer
 - a. FOLFOX (fluorouracil, leucovorin, oxaliplatin)
5. Esophageal and Gastric Cancers
 - a. Irinotecan/cisplatin
6. Non-Hodgkin's Lymphomas
 - a. GDP (gemcitabine, dexamethasone, cisplatin/carboplatin)
 - b. CHOP (cyclophosphamide, doxorubicin, vincristine, prednisone) + rituximab, including regimens with pegylated liposomal doxorubicin or mitoxantrone substituted for doxorubicin
 - c. Bendamustine
7. Non-Small Cell Lung Cancer
 - a. Cisplatin/paclitaxel
 - b. Cisplatin/vinorelbine
 - c. Cisplatin/docetaxel
 - d. Cisplatin/etoposide
 - e. Carboplatin/paclitaxel
 - f. Docetaxel
8. Ovarian Cancer
 - a. Carboplatin/docetaxel
9. Prostate Cancer
 - a. Cabazitaxel
10. Small Cell Lung Cancer
 - a. Etoposide/carboplatin
11. Testicular Cancer
 - a. BEP (bleomycin, etoposide, cisplatin)
 - b. Etoposide/cisplatin

12. Uterine Sarcoma

a. Docetaxel

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COMMITTEE APPROVAL:

This Medical Coverage Guideline (MCG) was approved by the Florida Blue Pharmacy Policy Committee on 10/12/22.

GUIDELINE UPDATE INFORMATION:

11/15/00	New Medical Coverage Guideline.
12/15/02	Reviewed with no revisions.
08/15/05	Updated when services are covered, dosage and administration, when services are not covered, ICD-9 codes, definitions and references.
01/15/06	ICD-9 code update: deleted expired code V58.1, added new code V58.11.
07/01/06	Updated MCG number from 09-A9140-13 to 09-J0000-62.
09/15/06	Biennial review; excluded Medicare Advantage and updated references.
01/01/07	MCG revised to include Medicare Part D as a program exception.

09/15/07	Review and revision to guideline; consisting of renaming guideline, reformatted guideline, added indications, updated ICD-9 coding, removed Medicare Advantage from exceptions, updated internet links and updated references.
09/15/08	Review and revision to guideline; consisting of renaming guideline, updating description section, incorporating pegfilgrastim, reformatting position statement, changing dosage and administration section, adding precautions section, updating coding, definitions and references.
10/15/08	Revision to guideline; consisting of combining diagnoses for all three GCSFs.
04/15/09	Revision to guideline; consisting of adding ICD-9 codes and maximum dosages.
09/15/09	Review and revision to guideline; consisting of updating references.
10/15/09	Revision to guideline; consisting of clarifying dosage.
06/15/10	Review and revision to guideline; consisting of updating references and an adding a note to the position statement.
10/01/10	Revision to guideline; consisting of updating codes.
11/15/10	Revision to guideline consisting of formatting changes.
06/15/11	Review and revision to guideline; consisting of updating precautions, coding and references.
06/15/12	Review and revision to guideline; consisting of updating references.
05/15/13	Review and revision to guideline; consisting of updating references and formatting changes.
01/01/14	Revision to guideline; consisting of coding update.
03/15/14	Revision to guideline; consisting of description, position statement, dosage/administration, and references.
05/15/14	Review and revision to guideline; consisting of updating the description, position statement, billing/coding information, program exceptions and references.
05/15/15	Review and revision to guidelines; consisting of updating references, revision position statement.
07/01/15	Revision to guidelines; consisting of HCPCS code update.
07/15/15	Revision to guideline; removed adalimumab from CMN text in position statement.
10/01/15	Revision consisting of update to Program Exceptions section.
11/01/15	Revision: ICD-9 Codes deleted.
11/15/15	Revision consisting of update to position statement.
12/15/15	Revision consisting of update to position statement.
01/01/16	Annual HCPCS coding update: added code J1447, deleted code J1446, and revised descriptor for code J1442.
05/15/16	Review and revision to guideline; consisting of updating position statement, precautions, coding and references.
10/01/16	Update to ICD-10 codes.
07/01/17	Review and revision to guideline; consisting of updating position statement, coding and references.
11/15/17	Review and revision to guideline; consisting of updating position statement.
04/01/18	Revision to Q5101 code description.

06/15/18	Review and revision to guideline; consisting of updating position statement, warnings, coding and references.
07/15/18	Revision to guideline; consisting of updating position statement, coding and references.
12/15/18	Revision to guideline; consisting of updating position statement, description, dosing, warnings, coding and references.
01/01/19	Revision: HCPCS code updates. Added Q5101.
04/01/19	Review and revision to guideline; consisting of updating position statement.
07/01/19	Review and revision to guideline; consisting of updating position statement.
07/15/19	Update to Program Exceptions.
12/15/19	Revision to guideline consisting of updating the position statement and references.
01/01/20	Revision to guideline consisting of updating the position statement and references.
04/01/20	HCPCS Update: Added code C9058.
06/15/20	Revision to guideline consisting of updating Table 1 and references.
07/01/20	Revision: Added HCPCS code Q5120 and deleted codes C9058 and J3590.
10/01/20	Revision to guideline consisting of updating the position statement and references.
01/01/21	Revision: Added HCPCS code Q5122 and deleted code J3590.
07/01/21	Revision to guideline consisting of updating the position statement and references.
01/01/22	Revision: Added HCPCS code J2506 and deleted code J2505.
05/15/22	Review and revision to guideline; consisting of updating position statement, dosing, coding and references.
07/01/22	Revision: Added HCPCS code C9096.
09/15/22	Review and revision to guideline; consisting of updating the position statement to include pegfilgrastim-pbbk (Flynetra). Updated description, dosing, coding, and references.
10/01/22	Revision: Added HCPCS code Q5125 and deleted code C9096.
01/01/23	Review and revision to guideline; consisting of adding (pegfilgrastim-fpgk) Stimufend and eflapegrastim-xnst (Rolvedon) to the position statement, description, dosing, coding, and references.