Short-acting Granulocyte-colony stimulating factor (CSF) and Granulocyte macrophage-CSF

EOCCO POLICY

Policy Type: PA/SP Pharmacy Coverage Policy: EOCCO031

Description

Granulocyte-colony stimulating factors (G-CSF) and granulocyte macrophage-CSF (GM-CSF) act on the hematopoietic cells by binding to specific cell surface receptors thereby stimulating the production, maturation, and activation of neutrophils.

Length of Authorization

- Initial: Four months
- Renewal: Four months

Quantity Limits

Product Name	Dosage Form	Indication	Quantity Limit
filgrastim (Neupogen)	300 mcg/mL vial	• Bone marrow transplant • Peripheral progenitor cell (PBPC) mobilization and transplant • Prophylactic use in patients with non-myeloid malignancy • Treatment of chemotherapy-induced febrile neutropenia • Neutropenic complications from prior chemotherapy cycle • Acute myeloid leukemia (AML) patient following induction or consolidation chemotherapy • Bone marrow transplantation failure or engraftment delay • Severe chronic neutropenia • Myelodysplastic syndrome • Exposure to myelosuppressive doses of radiation • Warts, hypogammaglobulinemia, infections, and myelokathexis (WHIM) syndrome†	15 prefilled syringes or vials per 30-day supply
	300 mcg/0.5mL syringe		
	480 mcg/1.6mL vial		
	480 mcg/0.8mL syringe		
filgrastim-sndz (Zarxio)*	300 mcg/0.5mL syringe		
	480 mcg/0.8mL syringe		
filgrastim-aafi (Nivestym)	300 mcg/mL vial		
	300 mcg/0.5mL syringe		
	480 mcg/1.6mL vial		
	480 mcg/0.8mL syringe		
tbo-filgrastim (Granix)	300 mcg/mL vial		
	300 mcg/0.5mL syringe		
	480 mcg/1.6mL vial		
	480 mcg/0.8mL syringe		
filgrastim-ayow (Releuko)	300 mcg/mL vial		
	300 mcg/0.5mL syringe		
	480 mcg/1.6mL vial		
	480 mcg/0.8mL syringe		
sargramostim (Leukine)	250 mcg/mL vial		
filgrastim-txid (Nypozi)	300mg/0.5mL PF syringe		
	480mg/0.8mL PF syringe		

** There is no prior authorization required for Zarxio (filgrastim-sndz) unless requesting above the quantity limit noted above*

† Higher doses may be needed for the treatment of WHIM syndrome. Quantity limit exceptions will be reviewed on a case by case basis.

Initial Evaluation

I. **Neupogen (filgrastim), Nivestym (filgrastim-aafi), Granix (tbo-filgrastim), and Releuko (filgrastim-ayow), Nypozi (filgrastim-txid)** may be considered medically necessary when the following criteria below are met:

Zarxio is the preferred short-acting G-CSF • **Patients must have failed, or have a contraindication, or intolerance to Zarxio prior to consideration of any other short-acting G-CSF** o There is no prior authorization* required for Zarxio unless requesting above the quantity limit noted above.

A. A diagnosis of:
   1. **Peripheral Blood Progenitor Cell (PBPC) mobilization and transplant; OR**
   2. **Patient who experienced a neutropenic complication from a prior cycle of the same chemotherapy; OR**
   3. **Bone Marrow Transplant (BMT); OR**
   4. **Bone Marrow Transplantation (BMT) failure or Engraftment Delay; OR**
   5. **Patients acutely exposed to myelosuppressive doses of radiation (Hematopoietic Subsyndrome of Acute Radiation Syndrome); OR**
   6. **Acute Myeloid Leukemia (AML) patient following induction or consolidation chemotherapy; OR**
   7. **Prophylactic use in patients with non-myeloid malignancy; AND**
      i. Member is undergoing myelosuppressive chemotherapy with an expected incidence of febrile neutropenia of 20% or greater; **OR**
      ii. Member is undergoing myelosuppressive chemotherapy with an expected incidence of febrile neutropenia of 10% or greater **AND** has one or more of the following co-morbidities:
         a. Age 65 years or older AND receiving full dose intensity chemotherapy
         b. History of recurrent febrile neutropenia from chemotherapy
         c. Extensive prior exposure to chemotherapy
         d. Previous exposure of pelvis, or other areas of large amounts of bone marrow, to radiation
         e. Pre-existing neutropenia (ANC ≤ 1000/mm3) or bone marrow involvement with tumor
         f. Member has a condition that can potentially increase the risk of serious infection (i.e. HIV/AIDS)
         g. Infection/open wounds
         h. Recent surgery
         i. Poor performance status
         j. Poor renal function (creatinine clearance <50)
         k. Liver dysfunction (elevated bilirubin >2.0)
         l. Chronic immunosuppression in the post-transplant setting including organ transplant; **OR**
   8. **Myelodysplastic Syndrome**; **AND**
      i. Endogenous serum erythropoietin level of ≤500 mUnits/mL; **AND**

ii. Member has lower risk disease (i.e., defined as IPSS-R [Very Low, Low, Intermediate], IPSS [Low/Intermediate-1], WPSS [Very Low, Low, Intermediate]); **AND**
iii. Used for treatment of symptomatic anemia in patients without del(5q); **AND**
iv. Member is receiving concurrent therapy with Erythropoiesis Stimulating Agents (ESA); **AND**
    a. Member has ring sideroblasts < 15% and will use in combination with lenalidomide following no response (despite adequate iron stores) or loss or response to an ESA alone; **OR**
    b. Member has ring sideroblasts ≥ 15%; **OR**

9. **Treatment of chemotherapy-induced febrile neutropenia; AND**
    i. Member has been on prophylactic therapy with filgrastim; **OR**
    ii. Member has not received prophylactic therapy with a granulocyte colony stimulating factor; **AND**
        a. Member has one or more of the following risk factors for developing infection-related complications:
            i. Sepsis Syndrome
            ii. Age >65
            iii. Absolute neutrophil count [ANC] <100/mcL
            iv. Duration of neutropenia expected to be greater than 10 days
            v. Pneumonia or other clinically documented infections
            vi. Invasive fungal infection
            vii. Hospitalization at the time of fever
            viii. Prior episode of febrile neutropenia; **OR**
10. **Severe chronic neutropenia; AND**
    i. Member has an absolute neutrophil count (ANC) < 500/mm3; **AND**
    ii. Member has a diagnosis of one of the following:
        a. Congenital neutropenia
        b. Cyclic neutropenia
        c. Idiopathic neutropenia; **OR**
11. **Management of CAR-T related Toxicity; AND**
    i. Member has been receiving therapy with CAR T-cell therapy (e.g. tisangenleclecleucel (Kymriah), axicabtagene ciloleucel (Yescarta), etc.); **AND**
    ii. Member is experiencing neutropenia related to their therapy; **OR**
12. **Warts, hypogammaglobulinemia, infections, and myelokathexis (WHIM) syndrome; AND**
    i. Documented genotype-confirmed mutation of *CXCR4* consistent with WHIM phenotype; **AND**
    ii. Documentation of severe symptoms and complications associated with WHIM syndrome (e.g., history of recurrent infections, chronic neutropenia, history of lymphopenia, history of hypogammaglobulinemia, detected myelokathexis, refractory or recalcitrant warts, etc.); **AND**

iii. Documentation of absolute neutrophil count (ANC) < 1500 cells/µL that is not related to medication, chemotherapy, or secondary to viral infection

II. **Leukine (sargramostim)** may be considered medically necessary when the following criteria below are met:
   A. **High-Risk Neuroblastoma; AND**
      1. Used in combination with GD2-binding monoclonal antibodies (i.e., naxitamab, dinutuximab, etc.) for the treatment of high-risk neuroblastoma; **OR**
   B. Both of the following (1 and 2):
      1. A diagnosis of one of the following:
         i. **Peripheral Blood Progenitor Cell (PBPC) mobilization and transplant; OR**
         ii. **Patient who experienced a neutropenic complication from a prior cycle of the same chemotherapy; OR**
         iii. **Bone Marrow Transplant (BMT); OR**
         iv. **Bone Marrow Transplantation (BMT) failure or Engraftment Delay; OR**
         v. **Patients acutely exposed to myelosuppressive doses of radiation (Hematopoietic Subsyndrome of Acute Radiation Syndrome); OR**
         vi. **Acute Myeloid Leukemia (AML) patient following induction or consolidation chemotherapy; OR**
         vii. **Treatment of chemotherapy-induced febrile neutropenia; AND**
            a. Member has been on prophylactic therapy with filgrastim; **OR**
            b. Member has not received prophylactic therapy with a granulocyte colony stimulating factor; **AND**
               i. Member has one or more of the following risk factors for developing infection-related complications:
                  1. Sepsis Syndrome
                  2. Age >65
                  3. Absolute neutrophil count [ANC] <100/mcL
                  4. Duration of neutropenia expected to be greater than 10 days
                  5. Pneumonia or other clinically documented infections
                  6. Invasive fungal infection
                  7. Hospitalization at the time of fever
                  8. Prior episode of febrile neutropenia; **AND**
      2. Treatment with Zarxio (filgrastim-sndz) has been ineffective, contraindicated, or not tolerated

Renewal Evaluation

I. Same as initial prior authorization policy criteria.

Supporting Evidence

I. Indications listed under section I are supported by FDA-labeled indication(s) or are recommended per Compendia.

II. Quantity limits are based on usual FDA dosing of once daily until complete blood count (CBC) or absolute neutrophil count (ANC) has returned to an appropriate range. Generally, chemotherapy is administered every 2-3 weeks, whereby frequency of filgrastim is not expected to be needed for greater than two weeks. For other indications, such as transplant, WHIM syndrome, myelodysplastic syndrome, or chronic neutropenia, therapy is continued until adequate neutrophil recovery is achieved. Accordingly, quantity exceptions may be considered when frequent administration of filgrastim is deemed medically necessary.

III. Duration of approval is based on usual duration of chemotherapy or radiation therapy cycle. There is no guideline consensus on optimal duration of G-CSF or GM-CSF treatment or prophylaxis, therefore continued use is driven by clinical scenario and lab monitoring.

IV. Risk of developing febrile neutropenia is related to intensity and toxicity of chemotherapy regimen, as well as patient-specific factors. Expected incidence of febrile neutropenia percentages for myelosuppressive chemotherapy regimens can be found in the NCCN Hematopoietic Growth Factors Clinical Practice Guideline at NCCN.org. NCCN and ASCO guidelines recommend use of a G-CSF for prophylaxis when risk is 20% or greater. When risk is between 10-20%, prophylactic G-CSF is recommended when patients have one or more of the risk factors listed above. Routine prophylaxis with G-CSF for febrile neutropenia when risk is less than 10% is not recommended.

V. In myelodysplastic syndromes (MDS), G-CSF may be used in combination with an erythropoiesis-stimulating agent (ESA) when patients have symptomatic anemia, as G-CSF can boost erythroid response. Likelihood of erythroid response is influenced by serum erythropoietin, MDS prognostic category, presence of ring sideroblasts, and other factors, therefore criteria outlined above follow NCCN guidelines to target the patient population expected to achieve a response.

VI. In the setting of high risk neuroblastoma (HRNB), GD2-binding monoclonal antibodies are labeled for used in combination with GM-CSF products specifically.

VII. Warts, hypogammaglobulinemia, infections, and myelokathexis (WHIM) syndrome is a rare immunodeficiency and a congenital neutropenic disorder that results from impaired leukocyte trafficking. Warts, hypogammaglobulinemia, infections, and myelokathexis (WHIM) syndrome presents with chronic neutropenia, lymphopenia, monocytopenia, recurrent infections, and warts. Individuals with WHIM syndrome are susceptible to bacterial infections and human papillomavirus (HPV) infections and cancer risk. Warts, hypogammaglobulinemia, infections, and myelokathexis (WHIM) syndrome as an autosomal dominant condition is predominately caused by gain-of-function variants in CXCR4, which is a key regulator of the mobilization of white blood cells (neutrophils and lymphocytes) with a prevalence of less than 1 in 1,000,000. Treatment is intended to target symptoms of WHIM and includes the use of granulocyte-colony stimulating factor (G-CSF) to correct neutropenia, immunoglobulin (Ig) for hypogammaglobulinemia, and antibiotics for infections.

VIII. As of August 2024, WHIM syndrome does not have a specific ICD-10 code; however, ICD-10 codes of D81.8 “Other combined immunodeficiencies” or D89.9 “Disorder involving the immune mechanism, unspecified” may apply to mavorixafor (Xolremdi). The confirmation of documented genotype-confirmed mutation of *CXCR4* consistent with WHIM phenotype should be done in those presenting with common symptoms of WHIM, such as history of recurrent infections, chronic neutropenia, lymphopenia, monocytopenia, hypogammaglobulinemia, recalcitrant or recurrent warts, and presence of neutropenia based on absolute neutrophil ANC count <1500 cells/µL.

IX. Long-term efficacy and safety of G-CSF therapy has been demonstrated in treating neutropenia and preventing infection in various conditions, including in patients who have chronic neutropenia that are not caused by cancer treatment. Several case reports have been published on the off-label use of G-CSFs in WHIM syndrome, which resulted in a correction in neutropenia; however, limited evidence to suggest efficacy in treating lymphopenia. While their use is off-label, the correction for neutropenia with G-CSF therapy has been the standard in treating patients with severe neutropenia. In absence of clinical guidelines or guidance on therapy sequencing, the use of G-CSF therapy is considered an appropriate first step in the treatment of severe neutropenia as it provides an efficacious and cost-effective treatment option for patients with WHIM syndrome.

X. While G-CSF have not been directly compared to mavorixafor (Xolremdi), they have been studied against a CXCR4 inhibitor in WHIM syndrome (NCT02231879) in patients with ANC <1500cells/µL and a history of severe infection. In a Phase 3 crossover trial of plerixafor versus G-CSF for the treatment of WHIM syndrome (N = 19), twice daily plerixafor was non-superior to twice daily G-CSF for total infection severity score (*P* = 0.54). The study was not designed to answer whether plerixafor is non-inferior to G-CSF for infection severity; however, no differences between the G-CSF and plerixafor arms were found for any infection outcome measures. In exploratory endpoints, plerixafor was non-inferior to G-CSF for maintaining neutrophil counts of >500 cells/µL (*P* = 0.023) and was superior to G-CSF for maintaining lymphocyte counts >1000cells/µL (p <0.0001). Complete regression of a subset of large wart areas occurred on plerixafor in 5 of 7 patients with major wart burdens at baseline. There were no significant differences in drug preference or quality of life or the incidence of drug failure or serious adverse events. The exploratory endpoints suggested that plerixafor may be non-inferior to G-CSF for durably increasing the ANC and may have an advantage over G-CSF for elevating the ALC, for wart regression, and for limiting bone pain. Given the above, the risks of mavorixafor (Xolremdi) are generally comparable to those of approved G-CSF and CXCR4 antagonists.

XI. Quantity limits for G-CSF in WHIM syndrome may be needed for up to two doses per day supply, based on prior studies in WHIM syndrome and chronic neutropenia; therefore, quantity limit exceptions may be granted in these cases as treatment efficacy is based on ANC.

XII. All FDA-approved biosimilars undergo a rigorous testing process to compare safety, purity, and potency between the proposed biosimilar and the parent or originator product, otherwise known as the reference product, to ensure there are no clinically meaningful differences. Only minor differences between products are allowed, such as in clinically inactive components. Biosimilars may be approved for all, or a subset, of the indications for the reference product. It is not uncommon for biosimilars to have fewer labeled indications if the reference product has remaining patent or exclusivity rights. It can be expected that biosimilar products will have the same clinical efficacy and safety profile as the reference product due to thorough FDA testing. With a goal to increase access to high-quality, cost-effective care, biosimilars may fill an unmet need as a more affordable alternative to brand biologic therapies. Notably, NCCN Guidelines similarly recommend that FDA-approved biosimilars be used as substitutes for originator filgrastim and pegfilgrastim. In addition, ASCO recommends that pegfilgrastim, filgrastim and biosimilars be considered therapeutically equivalent, with product selection being based on convenience, cost and clinical situation (i.e., chemotherapy frequency). As such, trial of preferred short-acting G-CSF biosimilar Zarxio (filgrastim-sndz) is required prior to approval of non-preferred filgrastim products.

References

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19. National Organization for Rare Diseases (NORD). WHIM Syndrome. January 16, 2024. Accessed May 23, 2024. https://rarediseases.org/rare-diseases/whim-syndrome

Related Policies

Policies listed below may be related to the current policy. Related policies are identified based on similar indications, similar mechanisms of action, and/or if a drug in this policy is also referenced in the related policy.

Policy Name	Disease state
Long-acting Granulocyte Colony Stimulating Factor (G-CSF)	Prophylactic use in patients with non-myeloid malignancy
	Neutropenic complications from prior chemotherapy cycle
	Exposure to myelosuppressive doses of radiation
	Bone marrow transplantation failure or engraftment delay
	Peripheral progenitor cell (PBPC) mobilization and transplant
Mavorixafor (Xolremdi)	WHIM syndrome

Policy Implementation/Update:

Action and Summary of Changes	Date
Added Nypozi (filgrastim-txid) to the policy	12/2024
Added pathway to coverage in the setting of WHIM syndrome. Updated supporting evidence, quantity limits table, references, and related policies sections.	08/2024

Updating policy formatting to align to medical policy and references. Added criteria to allow use of Leukine for the treatment of high-risk neuroblastoma prior to Zarxio when used in combination with anti-GD2 therapy.	05/2024
Updated policy supporting evidence and references. Added related policies table.	08/2022
Added Releuko (filgrastim-ayow) to policy in the non-preferred position	04/2022
Updated quantity level limit to allow 15 doses per 30-day supply	12/2019
Policy title change, designate Zarxio as a preferred product, add “No PA Required” to Initial Evaluation Section 1 boxed information	10/2019
Previous Reviews	12/2018
Added Nivestym, biosimilar to Neupogen	10/2018
Previous Reviews	02/2018; 07/2018
Criteria update. Zarxio is the preferred short-acting G-CSF	2/2017