Long-acting Granulocyte Colony Stimulating Factor
EOCCO POLICY

Policy Type: PA/SP Pharmacy Coverage Policy: EOCCO052

Description
Granulocyte-colony stimulating factors (G-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
pegfilgrastim (Neulasta)	6 mg/0.6 mL prefilled syringe	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 Warts, hypogammaglobulinemia, infections, and myelokathexis (WHIM) syndrome†	Two prefilled syringes per 28-day supply
pegfilgrastim (Neulasta Onpro)	6 mg/0.6 mL prefilled syringe with on-body injector kit		Two kits per 28-day supply
pegfilgrastim-cbqv (Udenyca)	6 mg/0.6 mL prefilled syringe		Two prefilled syringes per 28-day supply
	6 mg/0.6 mL autoinjector		Two autoinjectors per 28-day supply
pegfilgrastim-cbqv (Udenyca ON-BODY)	6 mg/0.6 mL prefilled syringe co-packaged with the on-body injector		2 prefilled syringe co-packaged with the on-body injector/28 days
pegfilgrastim-jmdb (Fulphila)*	6 mg/0.6 mL prefilled syringe		Two prefilled syringes per 28-day supply
pegfilgrastim-bmez (Ziextenzo)			
pegfilgrastim-apgf (Nyvepria)*			
pegfilgrastim-pbbk (Fylnetra)			
pegfilgrastim-fpgk (Stimufend)			

** There is no prior authorization required for pegfilgrastim-apgf (Nyvepria) and pegfilgrastim-jmdb (Fulphila) 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. **Pegfilgrastim (Neulasta, Neulasta Onpro), pegfilgrastim-cbqv (Udenyca, Udenyca On-body), pegfilgrastim-pbbk (Fylnetra), pegfilgrastim-bmez (Ziextenzo), and pegfilgrastim-fpgk (Stimufend)** may be considered medically necessary when the following criteria below are met:

pegfilgrastim-apgf (Nyvepria) and pegfilgrastim-jmdb (Fulphila) are the preferred long-acting G-CSF

- **Patients must have failed, or have a contraindication, or intolerance to pegfilgrastim-apgf (Nyvepria) AND pegfilgrastim-jmdb (Fulphila) prior to consideration of any other long-acting G-CSF**

There is no prior authorization required for pegfilgrastim-apgf (Nyvepria) or pegfilgrastim-jmdb (Fulphila) unless requesting above the quantity limit noted above.

A. Treatment with pegfilgrastim-jmdb (Fulphila) AND pegfilgrastim-apgf (Nyvepria) have been ineffective, contraindicated, or not tolerated; **AND**
B. A diagnosis of the following:
    1. **Peripheral Blood Progenitor Cell (PBPC) mobilization and transplant; OR**
    2. **A neutropenic complication from a prior cycle of the same chemotherapy; OR**
    3. **Bone Marrow Transplantation (BMT) failure or Engraftment Delay; OR**
    4. **Member acutely exposed to myelosuppressive doses of radiation (Hematopoietic Subsyndrome of Acute Radiation Syndrome); OR**
    5. **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:
            a. Age 65 years or older AND receiving full dose intensity chemotherapy; **OR**
            b. History of recurrent febrile neutropenia from chemotherapy; **OR**
            c. Extensive prior exposure to chemotherapy; **OR**
            d. Previous exposure of pelvis, or other areas of large amounts of bone marrow, to radiation; **OR**
            e. Pre-existing neutropenia (ANC ≤ 1000/mm3) or bone marrow involvement with tumor; **OR**
            f. Member has a condition that can potentially increase the risk of serious infection (e.g. HIV/AIDS) ; **OR**

g. Infection/open wounds; **OR**
h. Recent surgery; **OR**
i. Poor performance status; **OR**
j. Poor renal function (creatinine clearance <50mL/min) ; **OR**
k. Liver dysfunction (elevated bilirubin >2.0mg/dL) ; **OR**
l. Chronic immunosuppression in the post-transplant setting including organ transplant.

6. **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

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 pegfilgrastim as once per chemotherapy cycle, but no sooner than 14 days before and 24 hours after chemotherapy administration. Generally, chemotherapy is administered every 2-3 weeks, whereby frequency of pegfilgrastim is not expected to be more often than every two weeks. There are insufficient data to support use of weekly pegfilgrastim. For other indications, such as transplant and WHIM syndrome, therapy is continued until adequate neutrophil recovery is achieved. Accordingly, quantity exceptions may be considered when frequent administration of pegfilgrastim is deemed medically necessary.
III. Duration of approval is based on usual duration of chemotherapy or radiation therapy cycles. 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. 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.

VI. 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.

VII. 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.

VIII. 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.

IX. 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 biosimilars pegfilgrastim-apgf (Nyvepria) and pegfilgrastim-jmdb (Fulphila) is required prior to approval of non-preferred pegfilgrastim products.

References

1. Neulasta [Prescribing Information]. Amgen Inc. Thousand Oaks, CA. February 2021.
2. Fulphila [Prescribing Information]. Mylan GmbH. Zurich, Switzerland. June 2018.
3. Udenyca [Prescribing Information]. Coherus Biosciences, Inc. Redwood City, CA. April 2019.
4. Ziextenzo [Prescribing Information]. Sandoz Inc. Princeton, NJ. November 2019.
5. Nyvepria [Prescribing Information]. Hospira, Inc., a Pfizer Company. Lake Forest, IL. October 2021.
6. Fylnetra [Prescribing Information]. Kashiv BioSciences, LLC. Piscataway, NJ. May 2022.
7. Stimufend [Prescribing Information]. Fresenius Kabi USA, LLC. Lake Zurich, IL. September 2022.
8. Smith TJ, Bohlke K, Lyman GH, et al. Recommendations for the use of wbc growth factors: American Society of Clinical Oncology clinical practice guideline update. JCO. 2015;33(28):3199-3212.
9. Wisconsin Physicians Service Insurance Corporation. Local Coverage Determination (LCD): Human Granulocyte/Macrophage Colony Stimulating Factors (L34699). Centers for Medicare & Medicaid Services, Inc. Updated on 1/23/2018 with effective date 02/1/2018. Accessed March 2018.
10. First Coast Service Options, Inc. Local Coverage Determination (LCD): G-CSF (Neupogen®, Granix™, Zarxio™) (L34002). Centers for Medicare & Medicaid Services, Inc. Updated on 6/10/2016 with effective date 7/5/2016. Accessed March 2018.

11. National Government Services, Inc. Local Coverage Article: Filgrastim, Pegfilgrastim, Tbofilgrastim, Filgrastim-sndz (e.g., Neupogen®, Neulasta™, Granix™, Zarxio™) - Related to LCD L33394 (A52408). Centers for Medicare & Medicaid Services, Inc. Updated on 9/23/2016 with effective date 10/1/2016. Accessed March 2018.
12. Palmetto GBA. Local Coverage Determination: White Cell Colony Stimulating Factors (L37176). Centers for Medicare & Medicaid Services, Inc. Updated on 12/7/2017 with effective date 2/26/2018. Accessed March 2018.
13. National Comprehensive Cancer Network. NCCN Clinical Practice Guidelines in Oncology for Hematopoietic Growth Factors, Version 1.2022. Updated December 22, 2021.
14. U.S. Food and Drug Administration. Biosimilars – Healthcare provider materials. Updated July 28, 2021. https://www.fda.gov/drugs/biosimilars/health-care-provider-materials?utm_campaign=cder-factsheets&utm_content=&utm_medium=social&utm_source=linkedin
15. Biologics and Biosimilars Collective Intelligence Consortium. Biosimilar facts. https://www.bbcic.org/resources/biosimilars-facts
16. Dale DC, Bonilla MA, Davis MW, et al. A randomized controlled phase III trial of recombinant human granulocyte colony-stimulating factor (filgrastim) for treatment of severe chronic neutropenia. *Blood*. 1993;81(10):2496-2502.
17. 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
Short-acting Granulocyte-colony stimulating factor (CSF) and Granulocyte macrophage-CSF (GM-CSF)	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 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
Mavorixafor (Xolremdi)	WHIM syndrome

Policy Implementation/Update:

Action and Summary of Changes	Date
Added pathway to coverage in the setting of WHIM syndrome. Updated supporting evidence, quantity limits table, references, and related policies sections.	08/2024
Added Udenyca On-Body to the policy	04/2024
Updated policy to reflect new preferred product strategy (pegfilgrastim-apgf (Nyvepria) and pegfilgrastim-jmdb (Fulphila) [Effective 01/01/2024]	12/2023
Added Udenyca autoinjector to QL table	03/2023
Added new product pegfilgrastim-fpgk (Stimufend) after trial of pegfilgrastim-jmdb (Fulphila) AND pegfilgrastim-bmez (Ziextenzo)	09/2022
Updated policy supporting evidence and references. Added related policies table. Added new product Fylnetra (pegfilgrastim-pbbk) after trial of pegfilgrastim-jmdb (Fulphila) AND pegfilgrastim-bmez (Ziextenzo)	08/2022

Updated policy name from "pegfilgrastim (Neulasta®; Neulasta Onpro®; Fulphila®; Udenyca®; Ziextenzo®, Nyvepria™)" to "Long-acting Granulocyte colony stimulating factor"	04/2022
Updated pegfilgrastim-jmdb (Fulphila) as preferred product; removed pegfilgrastim-cbqv (Udenyca) from preferred products. (Effective 7/1/2021)	05/2021
Updated preferred products to add Ziextenzo (effective 1/1/2021) and move Neulasta/Neulasta Onpro to non-preferred (effective 1/1/2021). Added Nyvepria, biosimilar to Neulasta.	11/2020
Updated policy to allow for 28 days supply	02/2020
Added Ziextenzo, biosimilar to Neulasta; update quantity limits to allow for 30 days supply	12/2019
Added Udenyca, biosimilar to Neulasta	01/2019
Neulasta, Neulasta Onpro preferred GCSF	12/2018
Added Fulphila, biosimilar to Neulasta	07/2018
Policy created	02/2018