UM-CDG-013 White Cell Colony Stimulating Factors	Approved By: Director, Health Services	Effective Date: 11/10/2025

This Policy applies to all SECUR affiliates, associates, and subsidiaries.

Approved by Courtney Gonzales, Director of Health Services on behalf of the Utilization Management Committee.

PURPOSE

This coverage determination guideline serves to address white blood cell growth factors, also known as granulocyte colony stimulating factors (G-CSF), that are administered to enhance recovery of blood related functions in neutropenia including febrile neutropenia. CSFs are also used to decrease the incidence and severity of infection associated with select disease related and drug related myelosuppression. G-CSFs are glycoproteins which exert major control over the reproduction and maturation of certain white blood cells, which include the following US Food and Drug Administration (FDA) approved products:

- Filgrastim (Neupogen)
- Filgrastim-sndz biosimilar (Zarxio)
- Pegfilgrastim (Neulasta)
- Tbo-filgrastim (Granix)

Granulocyte-macrophage colony stimulating factor (GM-CSF) is a hematopoietic growth factor which stimulates proliferation and differentiation of hematopoietic progenitor cells.

- Sargramostim (Leukine)

For SECUR Health Plan members, National Coverage Determinations (NCD) and Local Coverage Determinations (LCD) will be applied to requests when applicable. SECUR Health Plan Coverage Determination Guidelines (CDG) will be utilized in the absence of an appropriate NCD and/or LCD.

DEFINITIONS

Severe Neutropenia: an absolute neutrophil count (ANC) of less than 500 cells/mL
Primary Prophylaxis: administration of CSF during the first cycle of chemotherapy
Secondary Prophylaxis: administration of CSF during subsequent cycles of chemotherapy

POLICY

Administration of G-CSF for primary prophylaxis should not be routinely used in all chemotherapy patients receiving usual outpatient regimens. It should be reserved for those at risk for febrile neutropenia (FN) with a risk of 20% or greater based upon the chemotherapy regimen. In patients whose risk of developing FN is greater than or equal to 10% and less than 20% based on chemotherapy, the use of primary prophylaxis should be reserved for those patients with one or more of the below risk factors for FN:

1. Age 65 or older
2. Poor performance status
3. Previous episodes of FN
4. History of previous chemotherapy or radiation therapy
5. Following completion of combined chemoradiotherapy
6. Bone marrow involvement by tumor producing cytopenias
7. Preexisting neutropenia
8. Poor nutritional status
9. Poor renal function
10. Liver dysfunction
11. Presence of open wounds and/or active infections
12. Recent surgery within the past twelve (12) weeks
13. Advanced cancer
14. Other serious comorbidities

Secondary prophylaxis is considered medically necessary by SECUR Health Plan after documented FN from a previous chemotherapy cycle, in which primary prophylaxis was not received, and in which a reduction in dosage of the chemotherapeutic agent(s) or a delay in treatment may compromise a disease-free or overall survival or treatment outcome.

G-CSF pegfilgrastim (Neulasta) and the biosimilar Fulphila are indicated for the following and considered medically necessary by SECUR Health Plan:

1. Members with cancer receiving myelosuppressive chemotherapy and/or immunotherapy to decrease the incidence of infection, as manifested by FN, in members with non-myeloid malignancies receiving myelosuppressive anticancer drugs associated with a clinically significant incidence of severe FN.
2. Members with hematopoietic subsyndrome of acute radiation syndrome to increase survival in members acutely exposed to myelosuppressive doses of radition.

Neulasta and biosimilars are not indicated for the mobilization of peripheral blood progenitor cells for hematopoietic stem cell transplantation and therefore are considered not medically necessary.

G-CSF tbo-filgrastim (Granix) is considered medically necessary for the following indications:

1. Members with cancer receiving myelosuppressive chemotherapy and/or immunotherapy to reduce the duration of severe neutropenia in members with nonmyeloid malignancies receiving myelosuppressive anticancer drugs associated with a clinically significant incidence of FN.

G-CSF filgrastim (Neupogen) is considered medically necessary for the following indications:

1. Members with cancer receiving myelosuppressive chemotherapy and/or immunotherapy to decrease the incidence of infection as manifested by FN, in members with nonmyeloid malignancies receiving myelosuppressive anticancer drugs associated with a clinically significant incidence of severe FN.
2. Members with acute myeloid leukemia (AML) receiving induction and/or consolidation chemotherapy to reduce the time to neutrophil recovery and the duration of fever following induction or consolidation chemotherapy treatment of members with AML.
3. Members with cancer undergoing bone marrow transplantation to reduce the duration of neutropenia and neutropenia related clinical sequelae, such as FN, in members with nonmyeloid malignancies undergoing myeloablative chemotherapy followed by bone marrow transplantation.

4. Members undergoing autologous peripheral blood progenitor cell collection and therapy for the mobilization of autologous hematopoietic progenitor cells into the peripheral blood for collection by leukapheresis.
5. Members with severe, chronic neutropenia for chronic administration to reduce the incidence and duration of sequelae of neutropenia in symptomatic members with congenital neutropenia, cyclic neutropenia, or idiopathic neutropenia.
6. Members with hematopoietic syndrome of acute radiation syndrome to increase survival in members acutely exposed to myelosuppressive doses of radiation.

G-CSF filgrastim-sndz biosimilar (Zarxio) is classified as biosimilar and is approved for all indications included in its reference product's label and for these indications are considered medically necessary.

GM-CSF sargramostim (Leukine) differs from the above listed products in that it is a recombinant human granulocyte macrophage colony stimulating factor and a hemopoietic growth factor which stimulates proliferation and differentiation of hematopoietic progenitor cells.
Sargramostim is indicated and considered medically necessary for the following:

1. Following induction of chemotherapy in acute myelogenous leukemia in members 55 years of age and older with AML to shorten time to neutrophil recovery and to reduce the incidence of severe and life-threatening infections and infections resulting in death. Safety and effectiveness have not been assessed in patients under 55 years of age with AML and will therefore be considered not medically necessary.
2. Use in mobilization and following transplantation of autologous peripheral blood progenitor cells into peripheral blood for collection by leukapheresis.
3. Use in myeloid reconstitution after allogenic bone marrow transplantation for acceleration of myeloid recovery in members undergoing allogenic bone marrow transplantation from HLA-matched related donors.
4. Use in bone marrow transplantation failure or engraftment delay in members who have undergone allogenic or autologous bone marrow transplantation that has failed. Sargramostim has not been found to be safe and effective in prolonging survival of patients experiencing graft failure or engraftment delay, in the presence or absence of infection, following autologous or allogenic bone marrow transplantation. Hematologic response can be detected with a complete blood count with differential performed twice per week.

In addition to the FDA-approved uses, medical necessity will be considered met when any of the drugs- Filgrastim (Neupogen) or Filgrastim-sndz biosimilar (Zarxio), Pegfilgrastim (Neulasta), Sargramostim (GM-CSF, Leukine), or Tbo-Filgrastim (Granix) and biosimilars are used as adjunctive treatment when any of the conditions listed below are present:

- Expected prolonged (greater than 10 days) and profound (less than 0.1 x 10^9/L) neutropenia
- Age greater than 65 years
- Uncontrolled primary disease
- Pneumonia
- Hypotension and multi organ dysfunction (sepsis syndrome)
- Invasive fungal infection
- Hospitalized at the time of the development of fever.

Filgrastim (Neupogen) or Filgrastim-sndz biosimilar (Zarxio):

1. In an individual with acute lymphocytic leukemia (ALL) after completion of the first few days of initial induction chemotherapy or first post-remission course of chemotherapy; or
2. Use in adult individuals with AML shortly after the completion of induction or repeat induction chemotherapy, or after the completion of consolidation chemotherapy for AML; or
3. Treatment of severe neutropenia in individuals with hairy cell leukemia; or
4. In an individual with myelodysplastic syndromes (MDS) with severe neutropenia (ANC less than or equal to 500 mm3) or experiencing recurrent infection; or
5. In an individual receiving dose dense therapy (treatment given more frequently, such as every 2 weeks instead of every 3 weeks) for adjuvant treatment of breast cancer, or other malignancies for which dose dense chemotherapy is an accepted treatment option; or
6. Chronic administration to reduce the incidence and duration of sequelae of neutropenia (e.g., fever, infections, oropharyngeal ulcers) in symptomatic individuals with congenital neutropenia, cyclic neutropenia, or idiopathic neutropenia; or
7. Treatment of (non-chemotherapy) drug-induced neutropenia; or
8. Treatment of low neutrophil counts in individuals with glycogen storage disease type 1b; or
9. Treatment for neutropenia associated with human immunodeficiency virus (HIV) infection and antiretroviral therapy; or
10. In individuals receiving radiation therapy in the absence of chemotherapy if prolonged delays secondary to neutropenia are expected; or
11. After a hematopoietic progenitor stem cell transplant (HPCT/HSCT) for the following indications:

    - To promote myeloid reconstitution; or
    - When engraftment is delayed or has failed; or
    - To mobilize progenitor cells into peripheral blood for collection by leukapheresis, as an adjunct to peripheral blood/hematopoietic stem cell transplantation (PBSCT/PHSCT); or
    - Use as an alternate or adjunct to donor leukocyte infusions (DLI) in individuals with leukemic relapse after an allogeneic hematopoietic stem cell transplant.

Pegfilgrastim (Neulasta) and Biosimilars:

1. In an individual with ALL after completion of the first few days of initial induction chemotherapy or first post-remission course of chemotherapy; or
2. In an individual with MDS with severe neutropenia (ANC less than or equal to 500 mm3 or experiencing recurrent infection; or
3. In an individual receiving dose dense therapy (treatment given more frequently, such as every 2 weeks instead of every 3 weeks) for adjuvant treatment of breast cancer, or other malignancies for which dose dense chemotherapy is an accepted treatment option. If a patient is on a dose dense 14-day chemotherapy cycle, it would be acceptable to administer Neulasta® outside of the 14-day before and 24-hour after rule for chemotherapy. Neulasta® would typically be administered on the second day of a 14–day dose dense chemotherapy cycle. The medical record should clearly indicate that the patient is on a 14-day dose dense chemotherapy cycle regimen; or
   D. After HPCT/HSCT for the following indications:

    - To promote myeloid reconstitution; or
    - When engraftment is delayed or has failed.

Sargramostim (GM-CSF, Leukine):

1. In an individual receiving dose dense therapy (treatment given more frequently, such as every 2 weeks instead of every 3 weeks) for adjuvant treatment of breast cancer; or
2. In an individual with ALL after completion of the first few days of initial induction chemotherapy or first post-remission course of chemotherapy; or
3. For administration shortly after the completion of induction or repeat induction chemotherapy of AML for individuals over 55 years of age; or
4. In an individual with MDS with severe neutropenia (ANC less than or equal to 500 mm3) or experiencing recurrent infection; or
5. In individuals receiving radiation therapy in the absence of chemotherapy if prolonged delays secondary to neutropenia are expected; or
6. After accidental or intentional total body radiation of myelosuppressive doses (greater than 2 Grays [Gy]) (such as Hematopoietic Syndrome of Acute Radiation Syndrome); or
7. After HPCT/HSCT for the following indications:

    - To promote myeloid reconstitution; or
    - When engraftment is delayed or has failed; or
    - To mobilize progenitor cells into peripheral blood for collection by leukapheresis, as an adjunct to PBSCT/PHSCT; or

The following uses do not have safety and/or efficacy established and are considered not medically necessary.

- Administration of G-CSF in cancer patients in order to increase chemotherapy dose-intensity except as noted above.
- Routine, continuous use of G-CSF in patients with MDS or Felty's syndrome without infections.
- Given the concerns for adverse events, avoidance of G-CSFs in patients receiving concomitant chemoradiotherapy for either head and neck cancer or lung cancer may be warranted.
- Chemo sensitization of myeloid leukemias.
- Continued use if no response is seen within 28-42 days (individuals who have failed to respond within this time frame are considered non-responders).
- Administration of G-CSF in patients with chronic aplastic anemia. Growth factors, as single agents, have not been shown to be effective in severe aplastic anemia. Their use in combination with other agents such as a cyclosporine and/or antilymphocyte globulin (ALG) is still investigational.

For members, coverage requirements for chemotherapy and/or immunotherapy related uses are reserved only for those members receiving a drug known to be associated with the development of severe neutropenia and the drug must be covered by SECUR Health Plan.

The G-CSFs and GM-CSFs will only be covered when administered under the direct supervision of the physician in office or in a hospital setting. If the medication is administered by the member or caregiver, the drug will be considered self-administered and will not be covered.

References:

1. Aapro M, Crawford J, Kamioner D. Prophylaxis of chemotherapy-induced febrile neutropenia with granulocyte colony-stimulating factors: where are we now? *Support Care Cancer.* 2010;18(5):529-541.

2. Marion S, Tzivelekis S, Darden C, et al. "Same-Day" administration of pegfilgrastim following myelosuppressive chemotherapy: clinical practice and provider rationale. *Support Care Cancer.* 2016;24(9):3889-3896.
3. Burris HA, Belani CP, Kaufman PA, et al. Pegfilgrastim on the same day versus next day of chemotherapy in patients with breast cancer, non-small-cell lung cancer, ovarian cancer, and non-hodgkin's lymphoma: Results of four multicenter, double-blind, randomized phase II studies. *J Oncol Pract.* 2010;6(3):133-140.
4. Kitchen K, Mosier MC. Real-world febrile neutropenia rates with same-day versus next-day pegfilgrastim after myelosuppressive chemotherapy. *Future Oncol.* 2022.
5. McBride A, Alrawashdh N, Bartels T, Moore L, Persky D, Abraham I. Same-day versus next-day pegfilgrastim or pegfilgrastim-cbqv in patients with lymphoma receiving CHOP-like chemotherapy. *Future Oncol.* 2021;17(26):3485-3497.
6. Lyman GH, Allcott K, Garcia J, et al. The effectiveness and safety of same-day versus next-day administration of long-acting granulocyte colony-stimulating factors for the prophylaxis of chemotherapy-induced neutropenia: a systematic review. *Support Care Cancer.* 2017;25(8):2619-2629.
7. Schuman SI, Lambrou N, Robson K, et al. Pegfilgrastim dosing on same day as myelosuppressive chemotherapy for ovarian or primary peritoneal cancer. *The Journal of Supportive Oncology.* 2009;7(6):225-228.
8. Whitworth JM, Matthews KS, Shipman KA, et al. The safety and efficacy of day 1 versus day 2 administration of pegfilgrastim in patients receiving myelosuppressive chemotherapy for gynecologic malignancies. *Gynecologic Oncology.* 2009;112(3):601-604.
9. Griffiths EA, Roy V, Alwan L, et al. NCCN Guidelines® Insights: Hematopoietic growth factors, Version 1.2022. *Journal of the National Comprehensive Cancer Network: JNCCN.* 2022;20(5):436-442.
10. Local Coverage Determination (LCD) L37176, White Cell Colony Stimulating Factors, 2/4/2023 https://www.cms.gov/medicare-coverage-database/view/lcd.aspx?lcdid=37176&ver=54&