

Department:	Pharmacy Management	Original Approval:	07/11/2019
Policy #:	PM155	Last Approval:	07/11/2019
Title:	Granulocyte Colony Stimulating Factors (gCSFs)		
Approved By:	UM Pharmacy Subcommittee		

REQUIRED CLINICAL DOCUMENTATION FOR REVIEW.

Documentation required to determine medical necessity for Filgrastim products p): History and/or physical examination notes and relevant specialty consultation notes that address the problem and need for the service: -Diagnosis -Prescribed by or in consultation with an oncologist or hematologist or a physician that specializes in transplantation -Medication list (current and past) to include start and end dates of all chemotherapy agents -Age -Labs/diagnostics -Weight -Dosing and duration requested - Initial/extended approval.

BACKGROUND

Granulocyte colony stimulating factor (G-CSF), or colony-stimulating factor 3, is a glycoprotein cytokine that stimulates formation of granulocyte colonies from the proliferation of a single hematopoietic stem cell. G-CSFs can be used to treat or prevent infections for patients with a low white cell count.

Filgrastim, a recombinant human G-CSF, increases the production of neutrophilic granulocytes in patients with chemotherapy-induced neutropenia and febrile neutropenia. Pegfilgrastim is a modified version of filgrastim that has an extended half-life and can work for a longer duration in the body and requires fewer administrations. However, pegfilgrastim has fewer approved uses than filgrastim.

DEFINITIONS

None.

INDICATIONS/CRITERIA

Medicaid Members	<p>Neupogen is the preferred Filgrastim on the WA HCA Single Preferred Drug list. Zarxio and Nivestym are not considered for approval unless member has tried and failed the preferred product (Neupogen).</p> <p>Note:</p> <p>☒ For non-preferred agents in this class/category, patients must have had an inadequate response or have had a documented intolerance due to severe adverse reaction or contraindication to at least TWO* preferred agents.</p>
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	<p><i>*If there is only one preferred agent in the class/category documentation of inadequate response to ONE preferred agent is needed</i></p> <p><i>☒ If a new-to-market drug falls into an existing class/category, the drug will be considered non-preferred and subject to this class/category prior authorization (PA) criteria</i></p> <p><i>Continue to criteria for approval below.</i></p>
Medicare Members	<i>Step-utilization of Part D drugs not required.</i>

Filgrastim may be considered medically necessary when used to:

1. Decrease the incidence of infection, as manifested by febrile neutropenia, in patients with nonmyeloid malignancies receiving myelosuppressive anti-cancer drugs associated with a significant incidence of severe neutropenia with fever
2. Reduce the time to neutrophil recovery and the duration of fever, following induction or consolidation chemotherapy treatment of patients with acute myeloid leukemia (AML)
3. Reduce the duration of neutropenia and neutropenia-related clinical sequelae, e.g., febrile neutropenia, in patients with nonmyeloid malignancies undergoing myeloablative chemotherapy followed by bone marrow transplantation (BMT)
4. Mobilize autologous hematopoietic progenitor cells into the peripheral blood for collection by leukapheresis
5. Reduce the incidence and duration of sequelae of severe neutropenia (e.g., fever, infections, oropharyngeal ulcers) in symptomatic patients with congenital neutropenia, cyclic neutropenia, or idiopathic neutropenia
6. Increase survival in patients acutely exposed to myelosuppressive doses of radiation (hematopoietic syndrome of acute radiation syndrome)

Filgrastim is NOT considered medically necessary for:

1. Splenic rupture
2. Acute respiratory distress syndrome
3. Serious allergic reactions to pegfilgrastim
4. Sickle cell crisis
5. WBC count greater than $100 \times 10^9/L$ (100,000 K/mL) or ANC greater than $10 \times 10^9/L$ (10,000 K/mL)
6. Capillary leak syndrome
7. Aortitis
8. Cutaneous vasculitis
9. Within 24 hours before/after chemotherapy
10. Routine use as prophylaxis with chemotherapy regimens associated with low risk for febrile neutropenia
11. Routine use as prophylaxis with chemoradiation

Pegfilgrastim may be considered medically necessary when used to:

1. Decrease the incidence of infection, as manifested by febrile neutropenia, in patients with non-myeloid malignancies receiving myelosuppressive anti-cancer drugs associated with a clinically significant incidence of febrile neutropenia.

2. Increase survival in patients acutely exposed to myelosuppressive doses of radiation (hematopoietic subsyndrome of acute radiation syndrome).

Pegfilgrastim is NOT considered medically necessary for:

1. Mobilization of peripheral blood progenitor cells for hematopoietic stem cell transplantation
2. Splenic rupture
3. Acute respiratory distress syndrome
4. Serious allergic reactions to filgrastim
5. Sickle cell crisis
6. WBC count greater than $100 \times 10^9/L$ (100,000 K/mL) or ANC greater than $10 \times 10^9/L$ (10,000 K/mL)
7. Capillary leak syndrome
8. Aortitis
9. Cutaneous vasculitis
10. Within 24 hours after chemotherapy or with cytotoxic chemotherapy given more often than every 14 days
11. Routine use as prophylaxis with chemotherapy regimens associated with low risk for febrile neutropenia
12. Routine use as prophylaxis with chemoradiation

Coverage is recommended in those who meet the following criteria:

1. Patients receiving induction and/or consolidation chemotherapy for AML

Filgrastim may be approved for patients set to receive induction or consolidation chemotherapy for acute myeloid leukemia (AML)

If ALL the criteria are met, the request will be approved for 3 months.

2. Primary Prevention of febrile neutropenia in patients receiving myelosuppressive chemotherapy

Filgrastim may be approved for the primary prevention of febrile neutropenia if ONE (1, 2, or 3) of the following criteria is met or **pegfilgrastim** may be approved for the primary prevention of febrile neutropenia if ONE (1, 2 or 3) and 4 are met:

1. The chemotherapy regimen has a greater than 20% risk for febrile neutropenia; **OR**
2. The chemotherapy regimen has a 10 - 20% risk for febrile neutropenia and the member meets ONE of the following:
 - a. Extensive prior chemotherapy or radiation therapy to pelvis or other areas important for bone marrow reserve
 - b. Persistent neutropenia (ANC 1000/mm³ or less)
 - c. Bone marrow involvement by tumor
 - d. Recent surgery and/or open wounds
 - e. Liver dysfunction (bilirubin > 2.0 mg/dL)
 - f. Renal dysfunction (eGFR < 50 mL/min/1.73m²)
 - g. Age > 65 years and receiving full chemotherapy dose intensity
 - h. Poor performance status

3. The member has experienced treatment delay of curative chemotherapy due to a dose-limiting neutropenic event, with the same dose and schedule planned for future cycles; OR

For pegfilgrastim only:

4. Documented treatment failure or a clearly stated rational of an inability to complete course of treatment (e.g. patient is unable to administer daily injections, patient is a young child, etc.) with a preferred short-acting G-CSF

If ALL the criteria are met, the request will be approved for 3 months.

3. Secondary Prevention of febrile neutropenia in patients receiving myelosuppressive chemotherapy

Filgrastim may be approved for the secondary prevention of febrile neutropenia if ONE (1, 2, or 3) of the following criteria is met or **pegfilgrastim** may be approved for the secondary prevention of febrile neutropenia if ONE (1, 2, or 3) and 4 are met:

1. The member has experienced febrile neutropenia with a previous cycle of similar chemotherapy, with the same dose and schedule planned for future cycles; OR
2. The member has experienced treatment delay of curative chemotherapy due to a dose-limiting neutropenic event, with the same dose and schedule planned for future cycles; OR
3. The member has experienced treatment delay of palliative chemotherapy due to a dose-limiting neutropenic event, and dose reduction or a delay in frequency of subsequent chemotherapy cycles is not recommended

For pegfilgrastim only:

4. Documented treatment failure or a clearly stated rational of an inability to complete course of treatment (e.g. patient is unable to administer daily injections, patient is a young child, etc.) with a preferred short-acting G-CSF

If ALL the criteria are met, the request will be approved for 3 months.

4. Treatment of febrile neutropenia

Filgrastim may be approved for the treatment of febrile neutropenia if BOTH (1 and 2) of the following criteria are met:

1. The patient has been diagnosed with febrile neutropenia; **AND**
2. The patient has ONE or more of the following high-risk factors:
 - a. age greater than 65 years;
 - b. hospitalized for febrile neutropenia;
 - c. sepsis syndrome;
 - d. invasive fungal infection;
 - e. clinically documented infection such as pneumonia;
 - f. prolonged or profound neutropenia;
 - g. history of prior episodes of febrile neutropenia

If ALL the criteria are met, the request will be approved for 1 month.

5. Patients with cancer undergoing bone marrow transplantation
Filgrastim may be approved if BOTH (1 and 2) are met:

1. Filgrastim is administered at least 24 hours after:
 - a. cytotoxic chemotherapy; OR
 - b. bone marrow infusion;
2. CBC & platelet counts are monitored daily during neutrophil recovery.

If ALL the criteria are met, the request will be approved for 3 months.

6. Patients undergoing autologous peripheral blood progenitor cell collection and therapy
Filgrastim may be approved if BOTH (1 and 2) are met:
 1. Filgrastim is administered for at least 4 days before the first leukapheresis procedure; **AND**
 2. Filgrastim is continued until the last leukapheresis.

If ALL the criteria are met, the request will be approved for 3 months.

7. Patients with severe chronic neutropenia (SCN)
Filgrastim may be approved after confirmation of diagnosis of SCN by evaluating serial CBCs with differential and platelet counts, and evaluating bone marrow morphology and karyotype.
Filgrastim can only be approved after confirmation of a correct diagnosis of SCN.

If ALL the criteria are met, the request will be approved for 12 months.

8. Patients acutely exposed to myelosuppressive doses of radiation
Filgrastim or **pegfilgrastim** may be approved for hematopoietic subsyndrome of acute radiation syndrome when patients are exposed to lethal doses of total-body radiation, but not doses high enough to lead to certain death as a result of injury to other organs. This includes accidental or intentional total-body radiation of doses of 3 to 10 Gy.

If ALL the criteria are met, the request will be approved for 1 month.

Dosage and quantity limits:

- A. Patients with cancer receiving myelosuppressive chemotherapy or induction and/or consolidation chemotherapy for AML
 1. Filgrastim:
 - a. Starting dose is 5 µg/kg/d, administered by subcutaneous injection or by intravenous infusion, rounded to nearest dosage size, up to 14 doses per month.
 2. Pegfilgrastim:
 - a. Limited to 1 dose per chemotherapy cycle
 - b. 6 mg for patients >45 kg
 - c. 4 mg for pediatric patients 31-44 kg
 - d. 2.5 mg for pediatric patients 21-30 kg
 - e. 1.5 mg for pediatric patients 10-20 kg
 - f. 0.1 mg/kg for pediatric patients <10 kg
- B. Patients with cancer undergoing bone marrow transplantation
 1. 10 µg/kg/day given as an intravenous infusion.



2. Filgrastim is reduced to 5 µg/kg/d when ANC is greater than $1 \times 10^9/L$ (1000 K/mL) for 3 consecutive days, then discontinued if ANC remains greater than $1 \times 10^9/L$ (1000 K/mL) for 3 more consecutive days, then resumed at 5 µg/kg/d if ANC decreases to less than $1 \times 10^9/L$ (1000 K/mL).
 3. If ANC decreases to less than $1 \times 10^9/L$ (1000 K/mL) during 5 µg/kg/d periods, filgrastim is increased to 10 µg/kg/d, then steps in #2 repeated.
- C. Patients undergoing autologous peripheral blood progenitor cell collection and therapy
1. 10 µg/kg/day given as a subcutaneous injection.
- D. Patients with severe chronic neutropenia (SCN)
1. Recommended starting dose is 6 µg/kg subcutaneous injection twice daily for congenital neutropenia.
 2. Recommended starting dose is 5 µg/kg subcutaneous injection once daily for cyclic or idiopathic neutropenia.
- E. Patients acutely exposed to myelosuppressive doses of radiation
1. Filgrastim:
 - a. 10 µg/kg/day subcutaneous injection
 2. Pegfilgrastim:
 - a. Limited to 2 doses per radiation exposure
 - b. 6 mg/dose for patients >45 kg
 - c. 4 mg/dose for pediatric patients 31-44 kg
 - d. 2.5 mg/dose for pediatric patients 21-30 kg
 - e. 1.5 mg/dose for pediatric patients 10-20 kg
 - f. 0.1 mg/kg/dose for pediatric patients <10 kg

SPECIAL CONSIDERATIONS

None.

LIMITATIONS/EXCLUSIONS

Please refer to a product line's certificate of coverage for benefit limitations and exclusions for these services:

PRODUCT LINE	LINK TO CERTIFICATE OF COVERAGE
MEDICARE ADVANTAGE	http://healthfirst.chpw.org/for-members/resource-library/handbooks-and-guides
WASHINGTON APPLE HEALTH	http://chpw.org/our-plans/apple-health/
INTEGRATED MANAGED CARE	http://chpw.org/our-plans/apple-health/

Citations & References

References
<p>1. Neupogen [prescribing information]. Thousand Oaks CA: Amgen Inc; 2018. https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/103353s5194lbl.pdf</p> <p>2. Granix [prescribing information]. North Wales PA: Teva Pharmaceuticals USA Inc; 2018. https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/125294s045lbl.pdf</p> <p>3. Zarxio [prescribing information]. Princeton NJ: Sandoz Inc; 2017. https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/125553s007lbl.pdf</p> <p>4. Nivestym [prescribing information]. Lake Forest IL: Pfizer Inc; 2018. https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/761080s000lbl.pdf</p> <p>5. Neulasta [prescribing information]. Thousand Oaks CA: Amgen Inc; 2018. https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/125031s193lbl.pdf</p> <p>6. Fulphila [prescribing information]. Zurich Switzerland: Mylan GmbH; 2018. https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/761075s000lbl.pdf</p> <p>7. Micromedex (electronic version). Greenwood Village CO: IBM Watson Health; 2018. https://www.micromedexsolutions.com/ (accessed 10/2018)</p> <p>8. General cancer information. Granulocyte colony stimulating factor (G-CSF). London England: Cancer Research UK; 2018. https://www.cancerresearchuk.org/about-cancer/cancer-in-general/treatment/cancer-drugs/drugs/g-csf (accessed 10/2018)</p> <p>9. Roberts AW. G-CSF: a key regulator of neutrophil production, but that's not all! Growth Factors. 2005 Mar; 23(1): 33–41. doi: 10.1080/08977190500055836 https://www.ncbi.nlm.nih.gov/pubmed/16019425 (accessed 10/2018)</p>

	<p>10. AHFS Patient Medication Information. Filgrastim, Filgrastim-sndz, Tbo-filgrastim Injection. Bethesda MD: American Society of Health-System Pharmacists Inc; 2017. https://medlineplus.gov/druginfo/meds/a692033.html (accessed 10/2018)</p> <p>11. Wishart DS, Knox C, Guo AC, Shrivastava S, Hassanali M, Stothard P, Chang Z, Woolsey J. Drugbank: a comprehensive resource for in silico drug discovery and exploration. Nucleic Acids Res. 2006 Jan 1;34 (Database issue):D668-72. 16381955. https://www.drugbank.ca/drugs/DB00099 (accessed 10/2018)</p> <p>12. DrugBank. Lipegfilgrastim. Edmonton AB: The Governors of the University of Alberta; 2018. https://www.drugbank.ca/drugs/DB13200 (accessed 10/2018)</p> <p>13. Mahler F, Schmidt K, Allgaier H, Liu P, Müller U, Shen W. Rational Development Of Lipegfilgrastim, a Novel Long-Acting Granulocyte Colony-Stimulating Factor, Using Glycopegylation Technology. Blood 2013; 122(21): 4853. http://www.bloodjournal.org/content/122/21/4853 (accessed 10/2018)</p> <p>14. Schrader, J. Colony-Stimulating Factors. Vancouver BC: The Biomedical Research Centre; 1998. doi: 10.1006/rwei.1999.0158 https://www.sciencedirect.com/topics/neuroscience/colony-stimulating-factor</p> <p>15. Metcalf D. The colony-stimulating factors and cancer. Cancer Immunol Res. 2013;1(6):351-6. doi: 10.1158/2326-6066.CIR-13-0151 https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3918448/</p> <p>16. National Comprehensive Cancer Network Guidelines Version 2.2018, “Myeloid Growth Factors”</p> <p>17. 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. J Clin Oncol 2015; 33:3199-3212.</p> <p>18. Smith TJ, Khatcheressian J, Lyman GH et al. Recommendations for the Use of White Blood Cell Growth Factors: An Evidence-Based Clinical Practice Guideline. J Clin Oncol 2006; 24:3187-3205.</p> <p>19. Lyman GH, Reiner M, Morrow PK, and Crawford J. The effect of filgrastim or pegfilgrastim on survival outcomes of patients with cancer receiving myelosuppressive chemotherapy. Ann Oncol 2015; 26:1452-1458.</p> <p>20. Lyman GH, Dale DC, Culakova E et al. The impact of the granulocyte colony-stimulating factor on chemotherapy dose intensity and cancer survival: a systematic review and meta-analysis of randomized controlled trials. Ann Oncol 2013; 24: 2475-2484.</p>	
CFR	42 CFR § 438.210	
WAC	284-43-2050	
RCW		
Contract Citation	<input type="checkbox"/> WAH	AH section 17.3.2.1 General Description of Contracted Services - Pharmacy Benefit and Services - Apple Health Preferred Drug List and Plan Formularies
	<input type="checkbox"/> IMC	IMC section 16.12.2 General Description of Contracted Services - Pharmacy Benefit and Services - Apple Health Preferred Drug List and Plan Formularies

	<input type="checkbox"/> MA	
Other Requirements		
NCQA Elements		

Revision History

Revision Date	Revision Description	Revision Made By
07/08/2019	New policy based on WA HCA Medical Policy no. 82.40.15-1	Jennifer Farley, PharmD
07/11/2019	Approval	UM Pharmacy Subcommittee