

UTILIZATION REVIEW MEDICAL POLICY

- POLICY:** Colony Stimulating Factors – Pegfilgrastim Products Utilization Review (Medical) Policy
- Neulasta® (pegfilgrastim injection for subcutaneous use [includes single-dose prefilled syringes for manual use and single-dose prefilled syringe co-packaged with the On-body Injector] – Amgen)
 - Fulphila™ (pegfilgrastim-jmdb injection for subcutaneous use – Mylan)
 - Nyvepria™ (pegfilgrastim-apgf injection for subcutaneous use – Pfizer)
 - Udenyca™ (pegfilgrastim-cbqv injection for subcutaneous use – Coherus)
 - Ziextenzo™ (pegfilgrastim-bmez injection for subcutaneous use – Sandoz)

REVIEW DATE: 08/21/2019; selected revision 11/13/2019 and 06/17/2020

DESCRIPTION

Neulasta, a leukocyte growth factor, is sometimes also referred to as a granulocyte colony stimulating factor (G-CSF).¹ Fulphila, Nyvepria, Udenyca, and Ziextenzo are biosimilars to Neulasta.^{1-3,21} Pegfilgrastim products are indicated to 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. Neulasta is additionally indicated to increase survival in patients acutely exposed to myelosuppressive doses of radiation (Hematopoietic Subsyndrome of Acute Radiation Syndrome).¹ For patients with cancer receiving myelosuppressive chemotherapy, do not administer pegfilgrastim in the period between 14 days before and 24 hours after administration of cytotoxic chemotherapy. The dose is given subcutaneously once per chemotherapy cycle. For patients acutely exposed to myelosuppressive doses of radiation, administer the first dose as soon as possible after suspected or confirmed exposure to myelosuppressive doses of radiation; give the second dose 1 week after the first dose.

Guidelines

The National Comprehensive Cancer Network (NCCN) guidelines for hematopoietic growth factors (version 2.2019 – March 27, 2019) recommend pegfilgrastim, along with other granulocyte colony-stimulating factors (CSFs), for prophylactic use if the patient is receiving anti-cancer medications that are associated with a high (> 20%) incidence of severe neutropenia with fever (category 1).⁴ Consider CSF therapy for patients with an intermediate (10% to 20%) probability of developing febrile neutropenia based on risk factors. The NCCN guidelines also recommend therapy with a CSFs in other scenarios in those given myelosuppressive chemotherapy. The American Society of Clinical Oncology (ASCO) also has clinical practice guidelines for the use of white blood cell growth factors (2015) that also recommends CSFs to reduce the risk of febrile neutropenia in patients receiving cancer chemotherapy.⁵ The NCCN guidelines for hematopoietic growth factors (version 2.2019 – March 27, 2019) recommend pegfilgrastim products as supportive care after post-autologous hematopoietic cell transplantation.⁴ Data are also available.⁶⁻¹⁸

POLICY STATEMENT

Prior authorization is recommended for medical benefit coverage of pegfilgrastim products. Approval is recommended for those who meet the Criteria and Dosing for the listed indication(s). Extended approvals are allowed if the patient continues to meet the Criteria and Dosing. Requests for doses outside of the

established dosing documented in this policy will be considered on a case-by-case basis by a clinician (i.e., Medical Director or Pharmacist). All approvals are provided for the duration noted below. In cases where the approval is authorized in months, 1 month is equal to 30 days. Because of the specialized skills required for evaluation and diagnosis of patients treated with pegfilgrastim as well as the monitoring required for adverse events and long-term efficacy, approval for some conditions requires pegfilgrastim to be prescribed by or in consultation with a physician who specializes in the condition being treated.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of pegfilgrastim is recommended in those who meet one of the following criteria:

FDA-APPROVED INDICATIONS

1. Cancer in Patients Receiving Myelosuppressive Chemotherapy. Approve for 6 months if the patient meets the following criteria (A and B):

A) The agent is prescribed by or in consultation with an oncologist or hematologist; AND

B) The patient meets ONE of the following conditions (i, ii, or iii):

i. The patient is receiving myelosuppressive anti-cancer medications that are associated with a high risk of febrile neutropenia (i.e., the risk of febrile neutropenia is at least 20% based on the chemotherapy regimen); OR

ii. The patient is receiving myelosuppressive anti-cancer medications that are associated with a risk of febrile neutropenia, but the risk is less than 20% based on the chemotherapy regimen and the patient has at least one risk factor for febrile neutropenia according to the prescriber; OR

Note: Examples of risk factors include age \geq 65 years; prior chemotherapy or radiation therapy; persistent neutropenia; bone marrow involvement by tumor; recent surgery and/or open wounds; liver and/or renal function; poor performance status; or human immunodeficiency virus (HIV) infection.

iii. The patient has had a neutropenic complication from prior chemotherapy and did not receive prophylaxis with a colony stimulating factor and a reduced dose or frequency of chemotherapy may compromise treatment outcome. Note: Examples of colony-stimulating factors include filgrastim products, pegfilgrastim products, and sargramostim products (e.g., Leukine®).

Dosing. Approve 6 mg or less given by subcutaneous injection no more frequently than once every 2 weeks.

2. Radiation Syndrome (Hematopoietic Syndrome of Acute Radiation Syndrome). Approve for 1 month if prescribed by or in consultation with a physician with expertise in treating acute radiation syndrome.

Dosing. Approve two doses of 6 mg or less by subcutaneous injection given no more frequently than 1 week apart.

Other Uses with Supportive Evidence

- 3. Peripheral Blood Progenitor Cell (PBPC) Transplantation in Patients with Cancer.** Approve one dose if prescribed by or in consultation with an oncologist, a hematologist, or a physician who specializes in transplantation.

Dosing. Approve one dose as follows (A or B):

- A)** In adults 6 mg by subcutaneous injection one time; OR
B) In children up to 200 mcg per kg by subcutaneous injection.

Conditions Not Recommended For Approval.

Pegfilgrastim has not been shown to be effective, or there are limited or preliminary data or potential safety concerns that are not supportive of general approval for the following conditions. Rationale for non-coverage for these specific conditions is provided below. (Note: This is not an exhaustive list of Conditions Not Recommended for Approval.).

- 1. Myelodysplastic syndrome (MDS).** Only limited data report use of pegfilgrastim for patients with MDS.¹⁹ Guidelines from the NCCN for MDS (version 2.2019 – October 18, 2018) do not mention use of pegfilgrastim in this patient population.²⁰
- 2.** Coverage is not recommended for circumstances *not* listed in the *Recommended Authorization Criteria*. Criteria will be updated as new published data are available.

REFERENCES

1. Neulasta® injection for subcutaneous use [prescribing information]. Thousand Oaks, CA: Amgen, Inc.; April 2019.
2. Fulphila® injection for subcutaneous use [prescribing information]. Rockford, IL: Mylan; May 2019.
3. Udenyca™ injection for subcutaneous use [prescribing information]. Redwood City, CA: Coherus BioSciences; February 2019.
4. The NCCN Hematopoietic Growth Factors Clinical Practice Guidelines in Oncology (version 2.2019 – March 27, 2019). ©2019 National Comprehensive Cancer Network, Inc. Available at: <http://www.nccn.org>. Accessed on August 12, 2019.
5. Smith TJ, Bohlke K, Lyman GH, Carson KR, et al. Recommendations for the use of WBC growth factors: American Society of Clinical Oncology Clinical Practice Guideline Update. *J Clin Oncol.* 2015;33(28):3199-3212. Available at: <http://jco.ascopubs.org/content/early/2015/07/08/JCO.2015.62.3488.full.pdf+html> Accessed on August 12, 2019.
6. Kim MG, Han N, Lee EK, Kim T. Pegfilgrastim vs. filgrastim in PBSC mobilization for autologous hematopoietic SCT: a systematic review and meta-analysis. *Bone Marrow Transplant.* 2015;50(4):523-530.
7. Vanstraelen G, Frere P, Ngirabacu MC, et al. Pegfilgrastim compared with filgrastim after autologous hematopoietic peripheral blood stem cell transplantation. *Exp Hematol.* 2006;34:382-388.
8. Martino M, Pratico G, Messina G, et al. Pegfilgrastim compared with filgrastim after high-dose melphalan and autologous hematopoietic peripheral blood stem cell transplantation in multiple myeloma patients. *Eur J Haematol.* 2006;77:410-415.
9. Ballestrero A, Boy D, Gonella R, et al. Pegfilgrastim compared with filgrastim after autologous peripheral stem cell transplantation in patients with solid tumors and lymphomas. *Ann Hematol.* 2008;87:49-55.
10. Gerds A, Fox-Geiman M, Dawravoo K, et al. Randomized phase III trial of pegfilgrastim versus filgrastim after autologous peripheral blood stem cell transplantation. *Biol Blood Marrow Transplant.* 2010;16:678-685.
11. Castagna L, Bramanti S, Levis A, et al. Pegfilgrastim versus filgrastim after high-dose chemotherapy and autologous peripheral blood stem cell support. *Ann Oncol.* 2010;21:1482-1485.
12. Sebban C, Lefranc A, Perrier L, et al. A randomized, phase II study of the efficacy, safety and cost-effectiveness of pegfilgrastim and filgrastim after autologous stem cell transplant for lymphoma and myeloma (PALM study). *Eur J Cancer.* 2012;48:713-720.
13. Rifkin R, Spitzer G, Orloff G, et al. Pegfilgrastim appears equivalent to daily dosing of filgrastim to treat neutropenia after autologous peripheral blood stem cell transplantation in patients with non-Hodgkin lymphoma. *Clin Lymphoma Myeloma Leuk.* 2010;10(3):186-191.
14. Kahl C, Sayer HG, Hinke A, et al. Early versus late administration of pegfilgrastim after high-dose chemotherapy and autologous hematopoietic stem cell transplantation. *J Cancer Res Clin Oncol.* 2012;138:513-517.

15. Ziakas PD, Kourbeti IS. Pegfilgrastim vs. filgrastim for supportive care after autologous stem cell transplantation: can we decide. *Clin Transplant*. 2012;26:16-22.
16. Samaras P, Blockenstorfer M, Siciliano RD, et al. Pegfilgrastim reduces the length of hospitalization and the time to engraftment in multiple myeloma patients treated with melphalan 200 and auto-SCT compared with filgrastim. *Ann Hematol*. 2011;90:98-94.
17. Cesaro S, Zanazzo AG, Frenos S, et al. A phase II study on the safety and efficacy of a single dose of pegfilgrastim for mobilization and transplantation of autologous hematopoietic stem cells in pediatric oncohematology patients. *Transfusion*. 2011;51(11):2480-2487.
18. Fritsch P, Schwinger W, Schwantzer G, et al. Peripheral blood stem cell mobilization with pegfilgrastim compared to filgrastim in children and young adults with malignancies. *Pediatric Blood Cancer*. 2010;54:134-137.
19. Jakob A, Hirsch FW, Engelhardt M. Successful treatment of a patient with myelodysplastic syndrome (RAEB) with darbepoetin alfa in combination with pegfilgrastim. *Ann Hematol*. 2005;84(10):694-695.
20. The NCCN Myelodysplastic Syndromes Clinical Practice Guidelines in Oncology (Version 2.2019 – October 18, 2018). © 2018 National Comprehensive Cancer Network, Inc. Available at: <http://www.nccn.org>. Accessed on August 8, 2019.
21. Ziextenzo™ injection for subcutaneous use [prescribing information]. Princeton, NJ: Sandoz; August 2019.
22. Nyvepria™ injection for subcutaneous use [prescribing information]. New York, NY: Pfizer, June 2020.

HISTORY

Type of Revision	Summary of Changes	Review Date
Annual revision	--	07/12/2017
Selected revision	Selected revision to add Fulphila to the policy. The title of the policy was altered to denote “Pegfilgrastim Products” after “Colony Stimulating Factors.”	06/13/2018
Annual revision	For the criteria regarding patients with cancer receiving myelosuppressive therapy in the criteria that reference a colony stimulating factor, the terminology of filgrastim and pegfilgrastim products were added, along with the listing of the individual products, which included adding Nivestym.	08/01/2018
Selected revision	For the indication regarding patients with cancer (adults and children) receiving myelosuppressive chemotherapy, removed “adults and children”.	08/08/2018
Selected revision	Selected revision to add Udenyca to the policy	01/03/2019
Selected revision	For the dosing in patients with cancer receiving myelosuppressive chemotherapy, the following wording was removed: “Of note, the Neulasta/Fulphila/Udenyca prefilled syringes are not designed to allow for direct administration of doses < 0.6 mL (6 mg). The syringe does not bear graduation marks, which are needed to accurately measure doses of Neulasta/Fulphila/Udenyca < 0.6 mL (6 mg) for direct administration to patients. Thus, the direct administration to patients requiring dosing of < 0.6 mL (6 mg) is not recommended due to the potential for errors”.	02/05/2019
Annual revision	For all conditions, the Dosing sections were revised to provide for the maximum range of dosing (see Policy). Additionally, the following sections were removed: initial/extended approval, duration of therapy, and labs/diagnostics. The waste management section was deleted. Additional changes per the specific indication were as follows: 1. Cancer in Patients Receiving Myelosuppressive Chemotherapy: CSFs are now provided as examples in a Note rather than as part of the criterion. Also, risk factors are now listed as Notes rather than as part of the criterion. The wording in reference to “according to the prescribing physician” was changed to “according to the prescriber”.	08/21/2019
Selected revision	Ziextenzo added to the policy. The dosing for the indication of cancer in patients receiving myelosuppressive chemotherapy was changed from once monthly to no more frequently than once every 2 weeks.	11/13/2019
Selected revision	Nyvepria added to the policy.	06/17/2020

CSFs – Colony stimulating factors.