



<b>Department:</b>	Pharmacy Management	<b>Original Approval:</b>	01/20/2016
<b>Policy #:</b>	PM128	<b>Last Approval:</b>	03/26/2019
<b>Title:</b>	Pegfilgrastim Products (Neulasta, Fulphila, Udenyca)		
<b>Approved By:</b>	UM Pharmacy Subcommittee		

## REQUIRED CLINICAL DOCUMENTATION FOR REVIEW.

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

Neulasta is a leukocyte growth factor, sometimes referred to as a granulocyte colony stimulating factor (G-CSF).<sup>1</sup> Neulasta is 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.<sup>1</sup> For this indication, Neulasta is to be administered as a single subcutaneous (SC) injection (6 mg) once per chemotherapy cycle. The Neulasta prescribing information also gives dosing recommendations in pediatric patients weighing < 45 kg. Neulasta should not be administered in the period between 14 days before and 24 hours after administration of cytotoxic chemotherapy. Neulasta is also indicated to increase survival in patients acutely exposed to myelosuppressive doses of radiation (patients with hematopoietic subsyndrome of acute radiation syndrome). For this indication, the recommended dose of Neulasta is two doses, 6 mg each, given SC once week apart. Refer to the Neulasta prescribing information for pediatric patients < 45 kg. Administer the first dose as soon as possible after suspected or confirmed exposure to radiation levels greater than 2 gray. Give the second dose 1 week after the first dose. Fulphila and Udenyca are biosimilars to Neulasta.<sup>23,24</sup> Both 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. The dosing for this use is similar to the common indication for Neulasta.

## DEFINITIONS

None.

## INDICATIONS/CRITERIA

<b>Medicaid Members</b>	There is no preferred Pegfilgrastim on the WA HCA Single Preferred Drug list. Neulasta, Neulasta Onpro and Fulphila are not considered for approval unless member has tried and failed the preferred product (Neupogen). <b><i>Continue to criteria for approval below.</i></b>
<b>Medicare Members</b>	<b><i>Step-utilization of Part D drugs not required.</i></b>

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

### FDA-Approved Indications

#### 1. Patients with Cancer Receiving Myelosuppressive Chemotherapy.

**Criteria.** *The patient must meet 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 one or more risk factors for febrile neutropenia according to the prescribing physician (e.g., aged ≥ 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); OR
  - iii.** The patient has had a neutropenic complication from prior chemotherapy and did not receive prophylaxis with a colony stimulating factor (Leukine® [sargramostim injection], filgrastim products [Neupogen, Zarxio, Granix, Nivestym], pegfilgrastim products [Neulasta, Fulphila, Udencya]) and a reduced dose or frequency of chemotherapy may compromise treatment outcome.

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.<sup>1-3</sup> The National Comprehensive Cancer Network (NCCN) guidelines for myeloid growth factors (version 1.2018), recommends use of G-CSF in various scenarios in patients with cancer receiving myelosuppressive chemotherapy.<sup>2</sup> Data are also available in children.<sup>1,4-7</sup> In the professional opinion of specialist physicians reviewing the data, we have adopted these criteria.

**Dosing in Patients with Cancer Receiving Myelosuppressive Chemotherapy:** *Dosing must meet ONE of the following (A, B OR C):*

- A)** In adults, the dose is a single SC injection of 6 mg administered once per chemotherapy cycle<sup>1</sup>;  
OR

- B) In children, a single 100 mcg per kg dose is given SC once per chemotherapy cycle; maximum dose is 6 mg.<sup>1-2,4-7</sup>
- C) For pediatric patients < 45 kg give a single SC dose once per chemotherapy cycle as follows: 4 mg (0.4 mL) is recommended in patients 31 to 44 kg; 2.5 mg (0.25 mL) is recommended for patients 21 to 30 kg; 1.5 mg (0.15 mL) is recommended for patients 10 to 20 kg; and 0.1 mg/kg (0.01 mL/kg) is recommended for patients < 10 kg. 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.

According to the NCCN guidelines for myeloid growth factors (version 2.2018), Pegfilgrastim should be administered the day after chemotherapy but Pegfilgrastim can also be administered up to 3 to 4 days after chemotherapy.<sup>2</sup> For patients who cannot return to the clinic for next-day administration, alternative options exist. Evidence is available to support use for chemotherapy regimens given once every 3 weeks. Phase II data demonstrate efficacy for chemotherapy regimens given every 2 weeks. In sufficient data support use for cytotoxic chemotherapy regimens given once every week; therefore, Pegfilgrastim should not be used.

#### **Initial Approval/Extended Approval.**

- A) *Initial Approval.* Approval is for up to 6 months at one dose per each chemotherapy cycle. Multiple doses in the same cycle are not recommended.
- B) *Extended Approval.* Approval is for up to 6-month intervals if the patient continues to receive myelosuppressive chemotherapy.

**Duration of Therapy in Patients with Cancer Receiving Myelosuppressive Chemotherapy.** Therapy may continue as long as the patient is receiving myelosuppressive chemotherapy with one dose per cycle.

**Labs/Diagnostics.** None required.

## **2. Radiation Syndrome (Hematopoietic Syndrome of Acute Radiation Syndrome).**

**Criteria.** *The patient must meet the following criteria:* The agent is prescribed by, or in consultation with, a physician with expertise in treating acute radiation syndrome.

Neulasta is indicated to increase survival in patients acutely exposed to myelosuppressive doses or radiation (hematopoietic subsyndrome of acute radiation syndrome).<sup>1</sup> The recommended dose of Neulasta is two doses, 6 mg each, given SC 1 week apart. Dosing in pediatric patients < 45 kg is cited in the Neulasta prescribing information. Give the first Neulasta dose as soon as possible after suspected or confirmed exposure to radiation levels > 2 gray. Administer the second dose 1 week after the first dose. Fulphila and Udenyca are not specifically indicated for this use but it is the same chemical and, therefore, should act similarly.<sup>23</sup>



**Dosing in Radiation Syndrome (Hematopoietic Syndrome of Acute Radiation Syndrome):** Dosing must meet ONE of the following (A OR B):

- A) Two doses, 6 mg each, given SC 1 week apart;<sup>1</sup> OR
- B) For pediatric patients < 45 kg give two doses SC 1 week apart as follows: 4 mg (0.4 mL) for patients 31 to 44 kg; 2.5 mg (0.25 mL) for patients 21 to 30 kg; 1.5 mg (0.15 mL) for patients 10 to 20 kg; and 0.1 mg/kg (0.01 mL/kg) is recommended for pediatric patients < 10 kg. 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.

**Initial Approval/Extended Approval.**

- A) Initial Approval. Initial approval is for 1 month.
- B) Extended Approval. Not applicable.

**Duration of Therapy in Radiation Syndrome (Hematopoietic Syndrome of Acute Radiation Syndrome).**

Two doses of pegfilgrastim are given 1 week apart until the ANC is adequate.

**Labs/Diagnostics.** None required.

**Other Uses with Supportive Evidence**

### **3. Patients with Cancer Following Peripheral Blood Progenitor Cell (PBPC) Transplantation.**

**Criteria.** The patient must meet the following criteria: The agent is prescribed by, or in consultation with, an oncologist, a hematologist, or a physician that specializes in transplantation.

Pegfilgrastim has been studied in patients with cancer undergoing high dose chemotherapy, followed by infusion of stem cell transplantation, which was usually autologous.<sup>8-20</sup> Results have been similar to that noted with use of daily Neupogen. Pegfilgrastim was usually administered on Day 1 and sometimes up to Day 5 after stem cell transplantation. The NCCN guidelines for myeloid growth factors (version 1.2018) note that pegfilgrastim has been utilized for post autologous hematopoietic cell transplantation.

**Dosing in Patients with Cancer Following PBPC Transplantation.** Dosing must meet ONE of the following (A OR B):<sup>8-20</sup>

- A) The dose in adults is 6 mg SC on Day +1 or up to Day +5 after PBPC transplantation; OR
- B) The dose in children is 100 mcg per kg or 200 mcg per kg SC one time.

**Initial Approval/Extended Approval.**

- A) Initial Approval. Initial approval is for one dose.
- B) Extended Approval. Not applicable.

**Duration of Therapy in Patients with Cancer Following PBPC Transplantation.** Usually only one dose of pegfilgrastim is needed until the absolute neutrophil count (ANC) is adequate.<sup>8-20</sup>

**Labs/Diagnostics.** None required.

**Waste Management for All Indications.**

Pegfilgrastim is available as a 6 mg syringe. This dose should be sufficient in most situations.

**Conditions Not Recommended For Approval.**

Neulasta 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.<sup>21</sup> Guidelines from the NCCN for MDS (version 1.2019) do not mention use of pegfilgrastim in this patient population.<sup>22</sup>
- 2.** Coverage is not recommended for circumstances *not* listed in the *Recommended Authorization Criteria*. Criteria will be updated as new published data are available.

**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	<a href="http://healthfirst.chpw.org/for-members/resource-library/handbooks-and-guides">http://healthfirst.chpw.org/for-members/resource-library/handbooks-and-guides</a>
WASHINGTON APPLE HEALTH	<a href="http://chpw.org/our-plans/apple-health/">http://chpw.org/our-plans/apple-health/</a>
INTEGRATED MANAGED CARE	<a href="http://chpw.org/our-plans/apple-health/">http://chpw.org/our-plans/apple-health/</a>

## Citations & References

References	
	<ol style="list-style-type: none"> <li>1. Neulasta® injection for subcutaneous use [prescribing information]. Thousand Oaks, CA: Amgen, Inc.; June 2018.</li> <li>2. The NCCN Myeloid Growth Factors Clinical Practice Guidelines in Oncology (Version 1.2018 – March 2, 2018). © 2018 National Comprehensive Cancer Network, Inc. Available at: <a href="http://www.nccn.org">http://www.nccn.org</a>. Accessed on July 30, 2018.</li> <li>3. 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. <i>J Clin Oncol</i>. 2015;33(28):3199-3212. Available at: <a href="http://jco.ascopubs.org/content/early/2015/07/08/JCO.2015.62.3488.full.pdf+html">http://jco.ascopubs.org/content/early/2015/07/08/JCO.2015.62.3488.full.pdf+html</a> Accessed on July 30, 2018.</li> <li>4. Wendelin G, Lackner H, Schwinger W, et al. Once-per-cycle pegfilgrastim versus daily filgrastim in pediatric patients with Ewing sarcoma. <i>J Pediatr Hematol Oncol</i>. 2005;27(8):449-451.</li> <li>5. te Poele EM, Kamps WA, Tamminga RYJ, et al. Pegfilgrastim in pediatric cancer patients. <i>J Pediatr Hematol Oncol</i>. 2005;27:627-629.</li> <li>6. Borinstein SC, Pollard J, Winter L, Hawkins DS. Pegfilgrastim for prevention of chemotherapy-associated neutropenia in pediatric patients with solid tumors. <i>Pediatr Blood Cancer</i>. 2009;53:375-378.</li> <li>7. Dallorso S, Berger M, Caviglia I, et al. Prospective single-arm study of pegfilgrastim activity and safety in children with poor-risk malignant tumors receiving chemotherapy. <i>Bone Marrow Transplant</i>. 2008;42:507-513.</li> <li>8. Kim MG, Han N, Lee EK, Kim T. Pegfilgrastim vs. filgrastim in PBSC mobilization for autologous hematopoietic SCT: a systematic review and meta-analysis. <i>Bone Marrow Transplant</i>. 2015;50(4):523-530.</li> <li>9. Vanstraelen G, Frere P, Ngirabacu MC, et al. Pegfilgrastim compared with filgrastim after autologous hematopoietic peripheral blood stem cell transplantation. <i>Exp Hematol</i>. 2006;34:382-388.</li> <li>10. 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. <i>Eur J Haematol</i>. 2006;77:410-415.</li> <li>11. 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. <i>Ann Hematol</i>. 2008;87:49-55.</li> <li>12. Gerds A, Fox-Geiman M, Dawravoo K, et al. Randomized phase III trial of pegfilgrastim versus filgrastim after autologous peripheral blood stem cell transplantation. <i>Biol Blood Marrow Transplant</i>. 2010;16:678-685.</li> </ol>



	<p>13. Castagna L, Bramanti S, Levis A, et al. Pegfilgrastim versus filgrastim after high-dose chemotherapy and autologous peripheral blood stem cell support. <i>Ann Oncol.</i> 2010;21:1482-1485.</p> <p>14. 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). <i>Eur J Cancer.</i> 2012;48:713-720.</p> <p>15. 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. <i>Clin Lymphoma Myeloma Leuk.</i> 2010;10(3):186-191.</p> <p>16. Kahl C, Sayer HG, Hinke A, et al. Early versus late administration of pegfilgrastim after high-dose chemotherapy and autologous hematopoietic stem cell transplantation. <i>J Cancer Res Clin Oncol.</i> 2012;138:513-517.</p> <p>17. Ziakas PD, Kourbeti IS. Pegfilgrastim vs. filgrastim for supportive care after autologous stem cell transplantation: can we decide. <i>Clin Transplant.</i> 2012;26:16-22.</p> <p>18. 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. <i>Ann Hematol.</i> 2011;90:98-94.</p> <p>19. 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. <i>Transfusion.</i> 2011;51(11):2480-2487.</p> <p>20. 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. <i>Pediatric Blood Cancer.</i> 2010;54:134-137.</p> <p>21. Jakob A, Hirsch FW, Engelhardt M. Successful treatment of a patient with myelodysplastic syndrome (RAEB) with darbepoetin alfa in combination with pegfilgrastim. <i>Ann Hematol.</i> 2005;84(10):694-695.</p> <p>22. The NCCN Myelodysplastic Syndromes Clinical Practice Guidelines in Oncology (Version 1.2019 – July 16, 2018). © 2018 National Comprehensive Cancer Network, Inc. Available at: <a href="http://www.nccn.org">http://www.nccn.org</a>. Accessed on July 30, 2018.</p> <p>23. Fulphila™ injection for subcutaneous use [prescribing information]. Zurich, Switzerland: Mylan; June 2018.</p> <p>24. Udenyca™ injection for subcutaneous use [prescribing information]. Redwood City, CA: Coherus BioSciences; November 2018.</p> <p><b>OTHER REFERENCES UTILIZED</b></p> <ul style="list-style-type: none"> <li>• Bennett CL, Djulbegovic B, Morris LB, Armitage JO. Colony-stimulating factors for febrile neutropenia during cancer therapy. <i>N Engl J Med.</i> 2013;368:1131-1139.</li> <li>• DiCarlo AL, Maher C, Hick JL, et al. Radiation injury after a nuclear detonation: medical consequences and need for scarce resources allocation. <i>Disaster Med Public Health Preparedness.</i> 2011;5:S32-S44.</li> <li>• Renwick W, Pettengell R, Green M. Use of filgrastim and pegfilgrastim to support delivery of chemotherapy. Twenty years of clinical experience. <i>Biodrugs.</i> 2009;23(3):175-186.</li> <li>• Radiation Injury Treatment Network (RITN). Acute Radiation Syndrome Treatment Guidelines. March 2016. Available at: <a href="https://ritn.net/treatment/">https://ritn.net/treatment/</a>. Accessed on July 18, 2018.</li> </ul>
<b>CFR</b>	
<b>WAC</b>	<a href="#">WAC 284-43-2050</a>
<b>RCW</b>	
<b>Contract Citation</b>	<input type="checkbox"/> WAH

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

### Revision History

Revision Date	Revision Description	Revision Made By
01/13/2016	New	Kelly Force; Yusuf Rashid, RPh
01/20/2016	Approval	MMLT
01/12/2017	No revisions	Fran McGaugh
01/13/2017	Approval	MMLT
07/24/2017	Criteria completely updated and revised	Michael Sporck, Pharmacy Intern Sophia Yun, PharmD
07/25/2017	Approved	MMLT
03/09/2018	Reassigned from UM139 to PM128	Cindy Bush
04/27/2018	Transferred to new template	Cindy Bush
05/25/2018	No revisions	Jennifer Farley, PharmD
06/14/2018	Approval	UM Committee
11/28/2018	Revisions from ESI annual update	Jennifer Farley, PharmD
12/12/2018	Approval	UM Committee
02/27/2019	Revisions- addition of new med	Jennifer Farley, PharmD
03/26/2019	Approval	UM Pharmacy Subcommittee