



# Policies & Guidelines

## Colony Stimulating Factors – Pegfilgrastim: Neulasta®; Fulphila™; Udenyca™; Ziextenzo™; Nyvepria™ (Subcutaneous)

Policy Number: VP-0234

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### I. Length of Authorization

- Bone marrow transplantation (BMT) failure or engraftment delay: Coverage will be provided for 1 dose only and may not be renewed.
- Peripheral blood progenitor cell (PBPC) mobilization and transplant: Coverage will be provided for 1 dose only and may not be renewed.
- All other indications: Coverage will be provided for six months and may be renewed unless otherwise specified.

### II. Dosing Limits

#### A. Quantity Limit (max daily dose) [NDC Unit]:

- Neulasta 6 mg prefilled syringe: 1 syringe per 14 days
- Fulphila 6 mg prefilled syringe: 1 syringe per 14 days
- Udenyca 6 mg prefilled syringe: 1 syringe per 14 days
- Ziextenzo 6 mg prefilled syringe: 1 syringe per 14 days
- Nyvepria 6 mg prefilled syringe: 1 syringe per 14 days

#### B. Max Units (per dose and over time) [HCPCS Unit]:

	Neulasta (J2505)	Fulphila (Q5108)	Udenyca (Q5111)	Ziextenzo (Q5120)	Nyvepria (J3590)
Acute Radiation Exposure	1 billable unit weekly x 2 doses	12 billable units weekly x 2 doses	12 billable units weekly x 2 doses	12 billable units weekly x 2 doses	6 mg weekly x 2 doses
BMT failure or engraftment delay/ PBPC mobilization and transplant	1 billable unit x 1 dose	12 billable units x 1 dose	12 billable units x 1 dose	12 billable units x 1 dose	6 mg x 1 dose
All other indications	1 billable unit per 14 days	12 billable units per 14 days	12 billable units per 14 days	12 billable units per 14 days	6 mg per 14 days

### III. Initial Approval Criteria

The patient has another FDA labeled or guideline supported (at highest level of evidence) indication.

Coverage is provided in the following conditions:

Prophylactic use in patients with non-myeloid malignancy †

- Patient is undergoing myelosuppressive chemotherapy with an expected incidence of febrile neutropenia\* of 20% or greater §; **OR**
- Patient is undergoing myelosuppressive chemotherapy with an expected incidence of febrile neutropenia\* of 10% or greater § **AND** one or more of the following co-morbidities:
  - Age >65 years receiving full dose intensity
  - History of recurrent febrile neutropenia from chemotherapy
  - Extensive prior exposure to chemotherapy
  - Previous exposure of pelvis, or other areas of large amounts of bone marrow, to radiation
  - Persistent neutropenia (ANC  $\leq$  1000/mm<sup>3</sup>)
  - Bone marrow involvement by tumor
  - Patient has a condition that can potentially increase the risk of serious infection (i.e., HIV/AIDS with low CD4 counts)
  - Recent surgery and/or open wounds
  - Poor performance status
  - Renal dysfunction (creatinine clearance <50 mL/min)

- Liver dysfunction (elevated bilirubin >2.0 mg/dL)
- Chronic immunosuppression in the post-transplant setting, including organ transplant

*Note:* Dose-dense therapy, in general, requires growth factor support to maintain dose intensity and schedule. In the palliative setting, consideration should be given to dose reduction or change in regimen.

Patient who experienced a neutropenic complication from a prior cycle of the same chemotherapy § ‡

*Note:* Dose-dense therapy, in general, requires growth factor support to maintain dose intensity and schedule. In the palliative setting, consideration should be given to dose reduction or change in regimen.

Patients acutely exposed to myelosuppressive doses of radiation (Hematopoietic Acute Radiation Syndrome [H-ARS]) † Φ

Bone marrow transplantation (BMT) failure or engraftment delay ‡

Peripheral blood progenitor cell (PBPC) mobilization and transplant ‡

† FDA-labeled indication(s); ‡ Compendia recommended indication(s); Φ Orphan Drug

\*Febrile neutropenia is defined as:

- a single temperature  $\geq 38.3$  °C orally or  $\geq 38.0$  °C over 1 hour; AND
- neutropenia: <500 neutrophils/mcL or <1,000 neutrophils/mcL and a predicted decline to  $\leq 500$  neutrophils/mcL over the next 48 hours

§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

**IV. Renewal Criteria**

*Note:* Coverage for use in BMT failure or engraftment delay and PBPC mobilization and transplant may NOT be renewed.

Coverage for all other indications can be renewed based upon the following criteria:

- Patient continues to meet indication-specific relevant criteria such as concomitant therapy requirements (not including prerequisite therapy), performance status, etc. identified in section III; AND
- Absence of unacceptable toxicity from the drug. Examples of unacceptable toxicity include: splenic rupture, acute respiratory distress syndrome (ARDS), serious allergic reactions/anaphylaxis, sickle cell crisis, glomerulonephritis, leukocytosis, capillary leak syndrome, potential for tumor growth stimulation of malignant cells, aortitis, etc.

**V. Dosage/Administration**

Indication	Dose
Prophylactic use in patients with non-myeloid malignancy  Patient who experienced a neutropenic complication from a prior cycle of the same chemotherapy	<ul style="list-style-type: none"> <li>• 6 mg subcutaneously once per chemotherapy cycle and dosed no more frequently than every 14 days</li> <li>• For pediatric patients weighing &lt;45 kg:                             <ul style="list-style-type: none"> <li>• &lt;10 kg = 0.1 mg/kg</li> <li>• 10-20 kg = 1.5 mg</li> <li>• 21-30 kg = 2.5 mg</li> <li>• 31-44 kg = 4 mg</li> </ul> </li> </ul>
Acute Radiation Exposure (Hematopoietic Acute Radiation Syndrome)	<ul style="list-style-type: none"> <li>• 6 mg subcutaneously weekly x 2 doses</li> <li>• For pediatric patients weighing &lt;45 kg:                             <ul style="list-style-type: none"> <li>• &lt;10 kg = 0.1 mg/kg</li> <li>• 10-20 kg = 1.5 mg</li> <li>• 21-30 kg = 2.5 mg</li> <li>• 31-44 kg = 4 mg</li> </ul> </li> </ul>
BMT failure or engraftment delay  PBPC mobilization and transplant	6 mg subcutaneously for 1 dose only

\*Do not administer within 14 days before and 24 hours after administration of cytotoxic chemotherapy.

\*Onpro On-body Injector may be applied on the same day as chemotherapy as long as the Neulasta is administered no less than 24 hours after administration of chemotherapy. Not recommended for use in patients with acute radiation exposure or in pediatric patients.

## VI. Billing Code/Availability Information

### HCPCS Code:

- J2505 – Injection, pegfilgrastim, 6 mg; 1 billable unit = 6 mg
- Q5108 – Injection, pegfilgrastim-jmdb, biosimilar, (Fulphila), 0.5 mg: 1 billable unit = 0.5 mg
- Q5111 – Injection, Pegfilgrastim-cbqv, biosimilar, (Udenyca), 0.5 mg; 1 billable unit = 0.5 mg
- J3590 – Unclassified biologic (*applicable to Nyvepria [pegfilgrastim-apgf] ONLY*)
- Q5120 – Injection, pegfilgrastim-bmez, biosimilar, (Ziextenzo), 0.5 mg: 1 billable unit = 0.5 mg

### NDC:

- Neulasta 6 mg prefilled syringe: 55513-0190-xx
- Neulasta 6 mg prefilled syringe Onpro Kit: 55513-0192-xx
- Fulphila 6 mg prefilled single-dose syringe: 67457-0833-xx
- Udenyca 6 mg prefilled single-dose syringe: 70114-0101-xx
- Ziextenzo 6 mg single-dose prefilled syringe: 61314-0866-xx
- Nyvepria 6 mg single-dose prefilled syringe: 00069-0324-xx

## VII. References

1. Neulasta [package insert]. Thousand Oaks, CA; Amgen Inc; January 2020. Accessed August 2020.
2. Fulphila [package insert]. Morgantown, WV; Mylan Pharmaceuticals; June 2020. Accessed August 2020.
3. Udenyca [package insert]. Redwood City, California; Coherus Biosciences; September 2019. Accessed August 2020.
4. Ziextenzo [package insert]. Princeton, NJ; Sandoz, Inc; November 2019. Accessed August 2020.
5. Nyvepria [package insert]. Lake Forest, IL; Pfizer Oncology; June 2020. Accessed August 2020.
6. Vogel CL, Wojtukiewicz MZ, Carroll RR, et al. First and subsequent cycle use of pegfilgrastim prevents febrile neutropenia in patients with breast cancer: a multicenter, double-blind, placebo-controlled phase III study. *J Clin Oncol.* 2005 Feb 20;23(6):1178-84.
7. Referenced with permission from the NCCN Drugs & Biologics Compendium (NCCN Compendium®) pegfilgrastim. National Comprehensive Cancer Network, 2020. The NCCN Compendium® is a derivative work of the NCCN Guidelines®. NATIONAL COMPREHENSIVE CANCER NETWORK®, NCCN®, and NCCN GUIDELINES® are trademarks owned by the National Comprehensive Cancer Network, Inc. To view the most recent and complete version of the Compendium, go online to NCCN.org. Accessed August 2020.
8. Referenced with permission from the NCCN Drugs & Biologics Compendium (NCCN Compendium®) Hematopoietic Growth Factors. Version 2.2020. National Comprehensive Cancer Network, 2020. The NCCN Compendium® is a derivative work of the NCCN Guidelines®. NATIONAL COMPREHENSIVE CANCER NETWORK®, NCCN®, and NCCN GUIDELINES® are trademarks owned by the National Comprehensive Cancer Network, Inc. To view the most recent and complete version of the Compendium, go online to NCCN.org. Accessed August 2020.
9. Holmes FA, O'Shaughnessy JA, Vukelja S, et al. Blinded, randomized, multicenter study to evaluate single administration pegfilgrastim once per cycle versus daily filgrastim as an adjunct to chemotherapy in patients with high-risk stage II or stage III/IV breast cancer. *J Clin Oncol.* 2002;20:727–31.
10. Green MD, Koelbl H, Baselga J, et al.; International Pegfilgrastim 749 Study Group. A randomized double-blind multicenter phase III study of fixed-dose single-administration pegfilgrastim versus daily filgrastim in patients receiving myelosuppressive chemotherapy. *Ann Oncol.* 2003;14(1):29-35.
11. 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.
12. Russel N, Mesters R, Schubert J, et al. A phase 2 pilot study of pegfilgrastim and filgrastim for mobilizing peripheral blood progenitor cells in patients with non-Hodgkin's lymphoma receiving chemotherapy. *Haematologica* March 200893:405-412;doi:10.3324/haematol.11287
13. Isidori A, Tani M, Bonifazi F, et al. Phase II study of a single pegfilgrastim injection as an adjunct to chemotherapy to mobilize stem cells into the peripheral blood of pretreated lymphoma patients. *Haematologica* January 200590:225-231
14. Jagasia MH, Greer JP, Morgan DS, et al. Pegfilgrastim after high-dose chemotherapy and autologous peripheral blood stem cell transplant: phase II study. *Bone Marrow Transplant.* 2005 Jun;35(12):1165-9.
15. Bruns I, Steidl U, Kronenwett R, et al. A single dose of 6 or 12 mg of pegfilgrastim for peripheral blood progenitor cell mobilization results in similar yields of CD34+ progenitors in patients with multiple myeloma. *Transfusion.* 2006 Feb;46(2):180-5.
16. Staber PB, Holub R, Linkesch W, et al. Fixed-dose single administration of Pegfilgrastim vs daily Filgrastim in patients with haematological malignancies undergoing autologous peripheral blood stem cell transplantation. *Bone Marrow Transplant.* 2005 May;35(9):889-93.
17. Vanstraelen G, Frere P, Ngirabacu MC, et al. Pegfilgrastim compared with Filgrastim after autologous hematopoietic peripheral blood stem cell transplantation. *Exp Hematol.* 2006 Mar;34(3):382-8.
18. Spunt S, Irving H, Frost J, et al. Phase II, Randomized, Open-Label Study of Pegfilgrastim-Supported VDC/IE Chemotherapy in Pediatric Sarcoma Patients. *J Clin Oncol.* 2010 Mar 10; 28(8): 1329–1336.
19. Hankey KG, Farese AM, Blaauw EC, et al. Pegfilgrastim Improves Survival of Lethally Irradiated Nonhuman Primates. *Radiat Res.* 2015 Jun;183(6):643-55. Epub 2015 Jun 2.

20. Waller CF, Ranganna GM, Pennella EJ, et al. Randomized phase 3 efficacy and safety trial of proposed pegfilgrastim biosimilar MYL-1401H in the prophylactic treatment of chemotherapy-induced neutropenia. *Ann Hematol.* 2019 May;98(5):1217-1224. doi: 10.1007/s00277-019-03639-5. Epub 2019 Mar 1.
21. Hoy SM. Pegfilgrastim-jmdb/MYL-1401H: A Pegfilgrastim Biosimilar. *BioDrugs.* 2019 Feb;33(1):117-120. doi: 10.1007/s40259-019-00334-9.
22. Blackwell K, Donskih R, Jones CM, et al. A Comparison of Proposed Biosimilar LA-EP2006 and Reference Pegfilgrastim for the Prevention of Neutropenia in Patients With Early-Stage Breast Cancer Receiving Myelosuppressive Adjuvant or Neoadjuvant Chemotherapy: Pegfilgrastim Randomized Oncology (Supportive Care) Trial to Evaluate Comparative Treatment (PROTECT-2), a Phase III, Randomized, Double-Blind Trial. *Oncologist.* 2016 Jul; 21(7): 789–794. Published online 2016 Apr 18. doi: 10.1634/theoncologist.2016-0011
23. Nakov R, Gattu S, Wang J, et al. Abstract P3-14-10: Proposed biosimilar pegfilgrastim LA-EP2006 shows similarity in pharmacokinetics and pharmacodynamics to reference pegfilgrastim in healthy subjects. Abstracts: 2017 San Antonio Breast Cancer Symposium; December 5-9, 2017; San Antonio, Texas. DOI: 10.1158/1538-7445.SABCS17-P3-14-10 Published February 2018
24. Glaspy JA, O'Connor PG, Tang H, et al. Randomized, single-blind, crossover study to assess the pharmacokinetic and pharmacodynamic bioequivalence of CHS-1701 to pegfilgrastim in healthy subjects *Journal of Clinical Oncology*35, no. 15\_suppl. DOI: 10.1200/JCO.2017.35.15\_suppl.e21693. Published online May 30, 2017.
25. National Government Services, Inc. Local Coverage Article: Billing and Coding: Filgrastim, Pegfilgrastim, Tbo-filgrastim and biosimilars (A52408). Centers for Medicare & Medicaid Services, Inc. Updated on 07/24/2020 with effective date 08/01/2020. Accessed August 2020.
26. Palmetto GBA. Local Coverage Article: Billing and Coding: Neulasta® (pegfilgrastim) Onpro® Kit (On-body Injector) (A54682). Centers for Medicare & Medicaid Services, Inc. Updated on 10/03/2019 with effective date 10/10/2019. Accessed August 2020.
27. First Coast Service Options, Inc. Local Coverage Article: Billing and Coding: Pegfilgrastim (A57725). Centers for Medicare & Medicaid Services, Inc. Updated on 07/22/2020 with effective date 07/01/2020. Accessed August 2020.
28. Palmetto GBA. Local Coverage Article: Billing and Coding: White Cell Colony Stimulating Factors (A56748). Centers for Medicare & Medicaid Services, Inc. Updated on 12/10/2019 with effective date 01/01/2020. Accessed August 2020.

#### Appendix 1 – Covered Diagnosis Codes

ICD-10	ICD-10 Description
D61.81	Pancytopenia
D70.1	Agranulocytosis secondary to cancer chemotherapy
D70.9	Neutropenia, unspecified
T45.1X5A	Adverse effect of antineoplastic and immunosuppressive drugs initial encounter
T45.1X5D	Adverse effect of antineoplastic and immunosuppressive drugs subsequent encounter
T45.1X5S	Adverse effect of antineoplastic and immunosuppressive drugs sequela
T66.XXXA	Radiation sickness, unspecified, initial encounter
T66.XXXD	Radiation sickness, unspecified, subsequent encounter
T66.XXXS	Radiation sickness, unspecified, sequela
W88.1	Exposure to radioactive isotopes
W88.8	Exposure to other ionizing radiation
Z41.8	Encounter for other procedures for purposes other than remedying health state
Z48.290	Encounter for aftercare following bone marrow transplant
Z51.11	Encounter for antineoplastic chemotherapy
Z51.12	Encounter for antineoplastic immunotherapy
Z51.89	Encounter for other specified aftercare
Z52.011	Autologous donor, stem cells
Z76.89	Persons encountering health services in other specified circumstances
Z94.81	Bone marrow transplant status
Z94.84	Stem cells transplant status

## Appendix 2 – Centers for Medicare and Medicaid Services (CMS)

Medicare coverage for outpatient (Part B) drugs is outlined in the Medicare Benefit Policy Manual (Pub. 100-2), Chapter 15, §50 Drugs and Biologicals. In addition, National Coverage Determination (NCD), Local Coverage Determinations (LCDs), and Local Coverage Articles (LCAs) may exist and compliance with these policies is required where applicable. They can be found at: <http://www.cms.gov/medicare-coverage-database/search/advanced-search.aspx> (<http://www.cms.gov/medicare-coverage-database/search/advanced-search.aspx>). Additional indications may be covered at the discretion of the health plan.

Medicare Part B Covered Diagnosis Codes (applicable to existing NCD/LCD/LCA):

Jurisdiction(s): 6, K	NCD/LCD/LCA Document (s): A52408
<a href="https://www.cms.gov/medicare-coverage-database/search/document-id-search-results.aspx?DocID=A52408&amp;bc=gAAAAAAAAAAAA&amp;">https://www.cms.gov/medicare-coverage-database/search/document-id-search-results.aspx?DocID=A52408&amp;bc=gAAAAAAAAAAAA&amp;</a> ( <a href="https://www.cms.gov/medicare-coverage-database/search/document-id-search-results.aspx?DocID=A52408&amp;bc=gAAAAAAAAAAAA&amp;">https://www.cms.gov/medicare-coverage-database/search/document-id-search-results.aspx?DocID=A52408&amp;bc=gAAAAAAAAAAAA&amp;</a> )	
Jurisdiction(s): N	NCD/LCD/LCA Document (s): A57725
<a href="https://www.cms.gov/medicare-coverage-database/search/article-date-search.aspx?DocID=A57725&amp;bc=gAAAAAAAAAAAA">https://www.cms.gov/medicare-coverage-database/search/article-date-search.aspx?DocID=A57725&amp;bc=gAAAAAAAAAAAA</a> ( <a href="https://www.cms.gov/medicare-coverage-database/search/article-date-search.aspx?DocID=A57725&amp;bc=gAAAAAAAAAAAA">https://www.cms.gov/medicare-coverage-database/search/article-date-search.aspx?DocID=A57725&amp;bc=gAAAAAAAAAAAA</a> )	
Jurisdiction(s): J, M	NCD/LCD/LCA Document (s): A56748
<a href="https://www.cms.gov/medicare-coverage-database/search/article-date-search.aspx?DocID=A56748&amp;bc=gAAAAAAAAAAAA">https://www.cms.gov/medicare-coverage-database/search/article-date-search.aspx?DocID=A56748&amp;bc=gAAAAAAAAAAAA</a> ( <a href="https://www.cms.gov/medicare-coverage-database/search/article-date-search.aspx?DocID=A56748&amp;bc=gAAAAAAAAAAAA">https://www.cms.gov/medicare-coverage-database/search/article-date-search.aspx?DocID=A56748&amp;bc=gAAAAAAAAAAAA</a> )	
Jurisdiction(s): J, M	NCD/LCD/LCA Document (s): A54682
<a href="https://www.cms.gov/medicare-coverage-database/search/article-date-search.aspx?DocID=A54682&amp;bc=gAAAAAAAAAAAA">https://www.cms.gov/medicare-coverage-database/search/article-date-search.aspx?DocID=A54682&amp;bc=gAAAAAAAAAAAA</a> ( <a href="https://www.cms.gov/medicare-coverage-database/search/article-date-search.aspx?DocID=A54682&amp;bc=gAAAAAAAAAAAA">https://www.cms.gov/medicare-coverage-database/search/article-date-search.aspx?DocID=A54682&amp;bc=gAAAAAAAAAAAA</a> )	

Medicare Part B Administrative Contractor (MAC) Jurisdictions		
Jurisdiction	Applicable State/US Territory	Contractor
E (1)	CA, HI, NV, AS, GU, CNMI	Noridian Healthcare Solutions, LLC
F (2 & 3)	AK, WA, OR, ID, ND, SD, MT, WY, UT, AZ	Noridian Healthcare Solutions, LLC
5	KS, NE, IA, MO	Wisconsin Physicians Service Insurance Corp (WPS)
6	MN, WI, IL	National Government Services, Inc. (NGS)
H (4 & 7)	LA, AR, MS, TX, OK, CO, NM	Novitas Solutions, Inc.
8	MI, IN	Wisconsin Physicians Service Insurance Corp (WPS)
N (9)	FL, PR, VI	First Coast Service Options, Inc.
J (10)	TN, GA, AL	Palmetto GBA, LLC
M (11)	NC, SC, WV, VA (excluding below)	Palmetto GBA, LLC
L (12)	DE, MD, PA, NJ, DC (includes Arlington & Fairfax counties and the city of Alexandria in VA)	Novitas Solutions, Inc.
K (13 & 14)	NY, CT, MA, RI, VT, ME, NH	National Government Services, Inc. (NGS)
15	KY, OH	CGS Administrators, LLC