Clinical Policy Title:	pegfilgrastim, pegfilgrastim-apgf, pegfilgrastim-jmdb, pegfilgrastim-cbqv, pegfilgrastim-bmez
Policy Number:	RxA.131
Drug(s) Applied:	Neulasta®, Neulasta Onpro®, Nyvepria™, Fulphila®, Udenyca®, Ziextenzo™
Original Policy Date:	03/06/2020
Last Review Date:	03/09/2021
Line of Business Policy Applies to:	All lines of business

Background

Pegfilgrastim (Neulasta®) and its biosimilars, pegfilgrastim-apgf (Nyvepria™), pegfilgrastim-jmdb (Fulphila®), and pegfilgrastim- cbqv (Udenyca®), pegfilgrastim-bmez (Ziextenzo™) are leukocyte growth factors. FDA-approved indications for each are provided in the table below.

	pegfilgrastim (Neulasta®, Neulasta Onpro®)	pegfilgrastim-apgf (Nyvepria™)	pegfilgrastim-jmdb (Fulphila®)	pegfilgrastim-cbqv (Udenyca®)	pegfilgrastim-bmez (Ziextenzo™)
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 (FN)	x	x	x	x	x
Increase survival in patients acutely exposed to myelosuppressive doses of radiation (hematopoietic subsyndrome of acute radiation syndrome)	x				

Limitation(s) of use: Pegfilgrastim is not indicated for the mobilization of peripheral blood progenitor cells for hematopoietic stem cell transplantation.

Dosing Information

Drug Name	Indication	Dosing Regimen	Maximum Dose
All products	Myelosuppressive chemotherapy	6 mg administered SC once per chemotherapy cycle. Do not administer between 14 days before or 24 hours	6 mg/dose

		after administration of cytotoxic chemotherapy. Weight based dosing for pediatric patients: Less than 10kg: 0.1 mg/kg 10-20 kg: 1.5 mg 21-30 kg: 2.5 mg 31-44 kg: 4 mg	
pegfilgrastim (Neulasta®, Neulasta Onpro®)	Members acutely exposed to myelosuppressive doses of radiation	Two doses, 6 mg each, administered SC one week apart. Administer the first dose as soon as possible after suspected or confirmed exposure to myelosuppressive doses of radiation, and a second dose one week after Weight based dosing for pediatric patients: Less than 10kg: 0.1 mg/kg 10-20 kg: 1.5 mg 21-30 kg: 2.5 mg 31-44 kg: 4 mg	6 mg/dose

Dosage Forms

- pegfilgrastim (Neulasta®): Injection, 6 mg/0.6 mL solution in a single-dose prefilled syringe for manual use only
- pegfilgrastim (Neulasta Onpro®): Injection, 6 mg/0.6 mL solution in a single-dose prefilled syringe co-packaged with the on-body injector
- pegfilgrastim-apgf (Nyvepria™): Injection, 6 mg/0.6 mL solution in a single-dose prefilled syringe for manual use only
- pegfilgrastim- jmdb (Fulphila®): Injection, 6 mg/0.6 mL solution in a single-dose prefilled syringe for manual use only
- pegfilgrastim- cbqv (Udenyca®): Injection, 6 mg/0.6 mL solution in a single-dose prefilled syringe for manual use only
- pegfilgrastim-bmez (Ziextenzo™): Injection, 6 mg/0.6 mL solution in a single-dose prefilled syringe for manual use only

Clinical Policy

Provider must submit documentation (such as office chart notes, lab results or other clinical information) supporting that member has met all approval criteria.

I. Initial Approval Criteria

A. Chemotherapy- Induced Neutropenia (must meet all)**:**

1. Diagnosis of non-myeloid malignancy;
2. Prescribed for use following myelosuppressive chemotherapy;
3. Member is at risk for febrile neutropenia (a or b):
   a. Member is currently on a high-risk chemotherapy regimen (20% or greater) defined by NCCN; or
   b. Member is currently on an intermediate-risk chemotherapy regimen (10% to 20%) defined by NCCN and has one of the following risk factors (i, ii, iii, iv, v, vi, vii, or viii):
      i. Prior chemotherapy or radiation therapy;
      ii. Persistent neutropenia;
      iii. Bone marrow involvement by tumor;

iv. Recent surgery and/or open wounds;
v. Liver dysfunction (bilirubin greater than 2.0 mg/dL);
vi. Renal dysfunction (creatinine clearance less than 50 mL/min);
vii. Age 65 years of age or older receiving full chemotherapy dose intensity;

4. For members ages 18 years of age or older, member has tried and failed preferred filgrastim product(s), unless one of the following are present (a, b, or c):
   a. Member has intolerance or contraindication to filgrastim;
   b. Documentation of member's inability to self-administer filgrastim due to both of the following (i and ii):
      i. Lack of caregiver or support system to assist with administration;
      ii. Inadequate access to healthcare facility or home care interventions;
   c. Member requires 10 or more doses of filgrastim;
5. For members receiving palliative chemotherapy, provider attests that chemotherapy dose reduction has been considered;
6. Pegfilgrastim is not given concurrently during chemotherapy (see dosing regimen);
7. Dose does not exceed 6 mg (1 syringe) per chemotherapy cycle.

Approval Duration
Commercial: 6 months
Medicaid: 6 months

B. Acute Radiation Syndrome (must meet all)**:**

1. Prescribed for use following suspected or confirmed acute exposure to myelosuppressive doses of radiation;
2. For members ages 18 years of age or older, member has tried and failed preferred filgrastim product(s), unless one of the following are present (a, b, or c):
   a. Member has intolerance or contraindication to filgrastim;
   b. Documentation of member's inability to self-administer filgrastim due to both of the following (i and ii):
      i. Lack of caregiver or support system to assist with administration;
      ii. Inadequate access to healthcare facility or home care interventions;
   c. Member requires 10 or more doses of filgrastim;
3. Pegfilgrastim is not given concurrently during chemotherapy (see dosing regimen);
4. Dose does not exceed two 6 mg doses administered one week apart.

Approval duration
Commercial: 6 months
Medicaid: 6 months

C. Compendial Indications (off-label) (must meet all)**:**

1. Prescribed for one of the following (a, b, c, or d):
   a. Supportive care post autologous hematopoietic cell transplantation;
   b. Mobilization of peripheral-blood progenitor cells prior to autologous transplantation;
   c. Members with chronic myeloid leukemia for treatment of persistent neutropenia due to tyrosine kinase inhibitor therapy;
2. Member has tried and failed sargramostim*, unless contraindicated or clinically significant adverse effects are experienced;
   **Prior authorization may be required*
3. For members ages 18 years of age or older, member has tried and failed preferred filgrastim product(s), unless one of the following are present (a, b, or c):

a. Member has intolerance or contraindication to filgrastim;
b. Documentation of member's inability to self-administer filgrastim due to both of the following (i and ii):
   i. Lack of caregiver or support system to assist with administration;
   ii. Inadequate access to healthcare facility or home care interventions;
c. Member requires 10 doses or more of filgrastim;

**Prior authorization may be required*

4. Request meets one of the following (a or b):
   a. Dose does not exceed 6 mg per dose;
   b. Dose is supported by practice guidelines or peer-reviewed literature for the relevant off-label use (*prescriber must submit supporting evidence*).

Approval duration
Commercial: 6 months
Medicaid: 6 months

II. Continued Therapy Approval

A. All Indications in Section I (must meet all)**:**

1. Member is currently receiving medication that has been authorized by RxAdvance or member has previously met initial approval criteria listed in this policy;
2. Member is responding positively to therapy;
3. If request is for a dose increase, new dose does not exceed one of the following (a, b, or c):
   a. Chemotherapy-induced neutropenia: 6 mg administered once per chemotherapy cycle;
   b. Acute radiation syndrome: two 6 mg doses administered one week apart;
   c. Bone marrow transplantation: 6 mg per dose, or dose is supported by practice guidelines or peer-reviewed literature for the relevant off-label use (*provider must submit supporting evidence*).

Approval Duration
Commercial: 6 months
Medicaid: 6 months

III. Appendices

APPENDIX A: Abbreviation/Acronym Key
ANC: absolute neutrophil count
ASCO: American Society of Clinical Oncology
CSFs: colony-stimulating factors
FDA: Food and Drug Administration
FN: febrile neutropenia
NCCN: National Comprehensive Cancer Network

APPENDIX B: Therapeutic Alternatives
Below are suggested therapeutic alternatives based on clinical guidance. Please check drug formulary for preferred agents and utilization management requirements.

Drug Name	Dosing Regimen	Dose Limit/ Maximum Dose
filgrastim (Neupogen®), filgrastim-sndz (Zarxio®), tbo- filgrastim (Granix®), filgrastim-aafi (Nivestym®)	**Supportive care post autologous hematopoietic cell transplantation** 10 mcg/kg IV or SC infusion once daily **Mobilization of peripheral-blood progenitor cells prior to autologous transplantation** 10 mcg/kg SC bolus or continuous infusion once daily	10 mcg/kg/day
sargramostim (Leukine®)	**Supportive care post autologous hematopoietic cell transplantation** 250 mcg/m^2/day IV **Mobilization of peripheral-blood progenitor cells prior to autologous transplantation** 250 mcg/m^2/day IV or SC once daily	500 mcg/m^2/day 250 mcg/m^2/day

Therapeutic alternatives are listed as Brand name® (generic) when the drug is available by brand name only and generic (Brand name®) when the drug is available by both brand and generic.

APPENDIX C: Contraindications/Boxed Warnings

- Contraindication(s):
  - History of serious allergic reactions to human granulocyte colony- stimulating factors such as pegfilgrastim or filgrastim products.

- Boxed Warning(s):
  - None reported.

APPENDIX D: General Information

- Neutropenia is defined as an absolute neutrophil count (ANC) of < 500 neutrophils/mcL or an ANC of < 1,000 neutrophils/mcL and a predicted decline to ≤ 500 neutrophils/mcL over the next 48 hours. Neutropenia can progress to FN, defined as a single temperature of ≥ 38.8 C orally or ≥ 38.0 C over 1 hour.
- The development of FN is a common dose-limiting toxicity of many chemotherapy regimens. This risk is directly related to the intensity of the chemotherapy regimen. Chemotherapy regimens that have an incidence of FN greater than 20% in clinical trials in chemotherapy naïve patients are considered by the National Comprehensive Cancer Network (NCCN) panel at high risk. Prophylaxis with myeloid growth factors is recommended at this level of risk (category 1 recommendation). NCCN Compendium recommend prophylaxis be considered in intermediate-risk (10-20% overall risk of FN) patients (category 2A recommendation). In addition to chemotherapy regimens, other risk factors such as: treatment-related, patient related, cancer-related, and co-morbidities have also been associated with an increased risk of FN. Therefore, the type of chemotherapy regimen is only one component of the risk assessment.
- Harvesting of peripheral blood stem cells prior to autologous stem-cell transplantation has a recommendation of Class IIa in DRUGDEX.
- The NCCN Compendium recommends pegfilgrastim for supportive care post autologous hematopoietic cell transplant (category 2A).
- According to the ASCO Clinical Practice Guideline for the Use of White Blood Cell Growth Factors, dose reduction or delay remains an appropriate strategy for the palliative treatment of cancer, as there is no

evidence that dose maintenance or escalation improves clinically important outcomes in this setting. The 2015 updates to this guideline found no new data supporting the use of colony-stimulating factors (CSFs) to maintain dose-intensity in the treatment of metastatic disease, and the review found no demonstrable benefit in the use of myeloid growth factors to in patients with metastatic lung, small-cell lung, colorectal, hormone-refractory prostate, or breast cancer. To date, there have been no improvements in disease-free or OS reported for any common cancer with the use of CSFs to maintain dose-intensity, instead of dose reduction. The ASCO Panel recognizes that there may be individual patients who will not tolerate effective doses of chemotherapy without CSFs. Medical Oncologists making the decision to use prophylactic MGFs, or not, may need to consider not only the optimal chemotherapy regimen, but also the individual member risk factors and the intention of treatment; that is, curative, prolongation of life, or symptom control and palliation.

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Review/Revision History	Review/Revision Date	P&T Approval Date
Policy established.	03/2020	03/06/2020
Policy reviewed and updated. 1. Added Ziextenzo™ to the policy. 2. Continued Therapy criteria II.A.1 was rephrased to "Currently receiving medication that has been authorized by RxAdvance…" 3. References were updated.	05/2020	05/21/2020
Policy was reviewed and updated. 1. Nyvepria™ was added to the policy. 2. Clinical policy title and lines of business were updated. 3. Compendial uses updated. 4. Continued therapy criteria II.A.1 was rephrased to "Currently receiving medication that has been authorized by RxAdvance…". 5. References were reviewed and updated.	01/27/2021	03/09/2021