RXADVANCE
2 Park Central Drive
Southborough, MA 01772

**Clinical Policy Title:** **Pegfilgrastim (Neulasta®), Pegfilgrastim-jmdb (Fulphila™), Pegfilgrastim-cbqv (Udenyca®), Pegfilgrastim-bmez (Ziextenzo®)**
**Policy Number:** **RxA.131**
**Drug(s) Applied:** **Pegfilgrastim (Neulasta®), Pegfilgrastim-jmdb (Fulphila™), Pegfilgrastim-cbqv (Udenyca®), Pegfilgrastim-bmez (Ziextenzo®)**
**Last Review Date:** **05/2020**
**Line of Business:** **Commercial, Medicaid**

## Background

Pegfilgrastim (Neulasta®) and its biosimilars, pegfilgrastim-jmdb (Fulphila™) and pegfilgrastim- cbqv (Udenyca®), pegfilgrastim-bmez (Ziextenzo®) are leukocyte growth factors.

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 (FN). Neulasta® is also indicated to increase survival in patients acutely exposed to myelosuppressive doses of radiation (hematopoietic subsyndrome of acute radiation syndrome).

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

| Drug Name | Indication | Dosing Regimen | Maximum Dose |
|---|---|---|---|
| Pegfilgrastim (Neulasta®), pegfilgrastim- jmdb (Fulphila™), pegfilgrastim- cbqv (Udenyca®), pegfilgrastim-bmez (Ziextenzo®) | Myelosuppressive chemotherapy | 6 mg administered SC once per chemotherapy cycle. Do not administer between 14 days before or 24 hours after administration of cytotoxic chemotherapy.<br><br>Weight based dosing for pediatric patients < 45 kg | 6 mg/dose |
| Pegfilgrastim (Neulasta®) | 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<br>Weight based dosing for pediatric patients < 45 kg | 6 mg/dose |

| Drug Name | Availability |
|---|---|
| Pegfilgrastim (Neulasta®) | • Injection: 6 mg/0.6 mL solution in a single-dose prefilled syringe for manual use only<br>• Injection: 6 mg/0.6 mL solution in a single-dose prefilled syringe co-packaged with the on-body injector |
| 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
   b. Member is 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 > 2.0)
      vi. Renal dysfunction (creatinine clearance < 50)
      vii. Age > 65 years receiving full chemotherapy dose intensity
4. For members age ≥ 18 years, failure of filgrastim, unless one of the following (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 for assistance with administration;
      ii. Inadequate access to healthcare facility or home care interventions;
   c. Member requires ≥ 10 doses of filgrastim;
5. For members receiving palliative chemotherapy, provider attestation that chemotherapy dose reduction has been considered;
6. Pegfilgrastim is not given concurrently during chemotherapy (see dosing regimen);
7. Pegfilgrastim is not given concurrently with radiation therapy (see dosing regimen);
8. Dose does not exceed 6 mg (1 syringe) per chemotherapy cycle.

**Approval duration:**
**Medicaid –** 6 months
**Commercial –** 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 age ≥ 18 years, failure of filgrastim, unless one of the following (a, b, or c):
   a. Member has intolerance or contraindication to filgrastim;
   b. Documentation of member's inability to self-administer filgrastimdue to both of the following (i and ii):
      i. Lack of caregiver or support system for assistance with administration;
      ii. Inadequate access to healthcare facility or home care interventions;
   c. Member requires ≥ 10 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:**
**Medicaid/HIM –** 6 months
**Commercial –** 6 months

**C. Bone Marrow Transplantation (off-label)** (must meet all)**:**
1. Prescribed for one of the following (a or b):
   a. Supportive care post autologous hematopoietic cell transplantation;
   b. Mobilization of peripheral-blood progenitor cells prior to autologous transplantation;
2. Failure of sargramostim*, unless contraindicated or clinically significant adverse effects are experienced;
   **Prior authorization may be required*
3. For members age ≥ 18 years, failure of filgrastim, unless one of the following (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 for assistance with administration;
      ii. Inadequate access to healthcare facility or home care interventions;
   c. Member requires ≥ 10 doses 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:**
**Medicaid –** 6 months
**Commercial –** 6 months

**II. Continued Therapy**

**A. All Indications in Section I** (must meet all)**:**
1. 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 (*prescriber must submit supporting evidence*).

**Approval duration:**
**Medicaid/HIM –** 6 months
**Commercial –** 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*
*This table provides a listing of preferred alternative therapy recommended in the approval criteria. The drugs listed here may not be a formulary agent for all relevant lines of business and may require prior authorization.*

| 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**<br>10 mcg/kg IV or SC infusion QD<br><br>**Mobilization of peripheral-blood progenitor cells prior to autologous transplantation**<br>10 mcg/kg SC bolus or continuous infusion QD | 10 mcg/kg/day<br><br>10 mcg/kg/day |
| sargramostim (Leukine®) | **Supportive care post autologous hematopoietic cell transplantation**<br>250 mcg/m$^2$/day IV<br><br>**Mobilization of peripheral-blood progenitor cells prior to autologous transplantation**<br>250 mcg/m$^2$/day IV or SC QD | 500 mcg/m$^2$/day<br><br>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 Neulasta for supportive care post autologous hematopoietic cell transplant (category 2A).
- According to the ASCO, 2006 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.

**References**

1. Neulasta Prescribing Information. Thousand Oaks, CA: Amgen, Inc.; January 2020. Available at https://www.pi.amgen.com/~/media/amgen/repositorysites/pi-amgen-com/neulasta/neulasta_pi_hcp_english.pdf. Accessed May 8, 2020.
2. National Comprehensive Cancer Network. Myeloid Growth Factors Version 2.2020.. Available at: http://www.nccn.org/professionals/physician_gls/pdf/myeloid_growth.pdf. Accessed May 6, 2020.
3. Pegfilgrastim. In: National Comprehensive Cancer Network Drugs and Biologics Compendium. Available at NCCN.org. Accessed May 15, 2019; February 21, 2020.
4. DRUGDEX® System [Internet database]. Greenwood Village, Colo: Thomson Healthcare. Updated periodically. Accessed May 8, 2020.
5. Clinical Pharmacology [database online]. Tampa, FL: Gold Standard, Inc.; 2018. Available at: http://www.clinicalpharmacology-ip.com/. Accessed May 15, 2019.
6. Fulphila Prescribing Information. Zurich, Switzerland: Mylan GmbH; May 2019. Available at: www.fulphila.com. Accessed May 8, 2020.
7. Udenyca Prescribing Information. Redwood City, CA: Coherus BioSciences, Inc.; September 2019. Available at: www.udenyca.com. Accessed May 8, 2020.
8. Smith TJ, Khatcheressian J, Lyman GH, et al. 2006 Update of recommendations for the use of white blood cell growth factors: an evidence-based clinical practice guideline. JCO 2006 July. 24(19): 3187-3205.
9. 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. 2015 October. JCO 33(28): 3199-3212.
10. Product Information: Ziextenzo® subcutaneous injection, pegfilgrastim-bmez subcutaneous injection. Sandoz Inc, Princeton, NJ, 2019. Accessed on May 6, 2020.

| Review/Revision History | Review/Revised Date | P&T Approval Date |
|---|---|---|
| Policy was established | 03/2020 | 03/06/2020 |
| Added Ziextenzo to the following sections:<br>- Policy title<br>- Drugs applied<br>- Dosing<br>- Drug availability<br>Continued Therapy criteria II.A.1 was rephrased to " Currently receiving medication that has been authorized by RxAdvance…"<br>References were updated | 05/2020 | 05/21/2020 |