Clinical Policy: Pegfilgrastim (Neulasta, Neulasta Onpro), Pegfilgrastim-jmdb (Fulphila), Pegfilgrastim-pbbk (Fylnetra), Pegfilgrastim-apgf (Nyvepria), Eflapegrastim-xnst (Rolvedon), Pegfilgrastim-fpgk (Stimufend), Pegfilgrastim-cbqv (Udenyca), Pegfilgrastim-bmez (Ziextenzo)

Reference Number: ERX.SPA.59
Effective Date: 09.01.17
Last Review Date: 08.22
Line of Business: Commercial, Medicaid

Revision Log

See Important Reminder at the end of this policy for important regulatory and legal information.

Description
Pegfilgrastim (Neulasta®, Neulasta® Onpro®) and its biosimilars, pegfilgrastim-jmdb (Fulphila™), pegfilgrastim-pbbk (Fylnetra®), pegfilgrastim-apgf (Nyvepria™), eflapegrastim-xnst (Rolvedon™), pegfilgrastim-fpgk (Stimufend®), pegfilgrastim-cbqv (Udenyca™), and pegfilgrastim-bmez (Ziextenzo™), are leukocyte growth factors.

FDA Approved Indication(s)
Neulasta, Neulasta Onpro, Fulphila, Fylnetra, Nyvepria, Rolvedon, Stimufend, Udenyca, and Ziextenzo 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 significant incidence of febrile neutropenia (FN).

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

Limitation(s) of use: Neulasta, Fulphila, Fylnetra, Nyvepria, Rolvedon, Stimufend, Udenyca, and Ziextenzo are not indicated for the mobilization of peripheral blood progenitor cells for hematopoietic stem cell transplantation.

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

Health plan approved formularies should be reviewed for all coverage determinations. Requirements to use preferred alternative agents apply only when such requirements align with the health plan approved formulary.

It is the policy of health plans affiliated with Envolve Pharmacy Solutions™ that Neulasta, Neulasta Onpro, Fulphila, Fylnetra, Nyvepria, Rolvedon, Stimufend, Udenyca, and Ziextenzo are **medically necessary** when the following criteria are met:

I. Initial Approval Criteria

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

1. Diagnosis of non-myeloid malignancy (i.e., solid tumor and lymphoid malignancies);
2. Prescribed for use following myelosuppressive chemotherapy;
3. For members receiving palliative chemotherapy, provider attestation that chemotherapy dose reduction has been considered;
4. Member meets one of the following (a or b):
   a. Member must use Ziextenzo*, unless clinically significant adverse effects are experienced or all are contraindicated;
      **Prior authorization may be required*
   b. Request is for the treatment associated with cancer for a State with regulations against step therapy in certain oncology settings *(see Appendix E)*;

5. Confirmation that there is at least 12 days between pegfilgrastim/eflapegrastim-xnst dose and the next cycle of chemotherapy;
6. The requested medication will not be prescribed concurrently with other colony stimulating factors (e.g., filgrastim, Leukine®) within any chemotherapy cycle;
7. Dose does not exceed one of the following (a or b):
   a. For pegfilgrastim: 6 mg (1 syringe) per chemotherapy cycle;
   b. For eflapegrastim: 13.2 mg (1 syringe) per chemotherapy cycle.

Approval duration: 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. Request is not for Rolvedon;
3. Member meets one of the following (a or b):
   a. Member must use Ziextenzo*, unless clinically significant adverse effects are experienced or all are contraindicated;
      **Prior authorization may be required*
   b. Request is for the treatment associated with cancer for a State with regulations against step therapy in certain oncology settings *(see Appendix E*);
4. The requested medication will not be prescribed concurrently with other colony stimulating factors (e.g., filgrastim, Leukine) within any chemotherapy cycle;
5. Dose does not exceed two 6 mg doses administered one week apart.

Approval duration: 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. Request is not for Rolvedon;
3. Failure of both of the following (a and b), unless contraindicated, clinically significant adverse effects are experienced, or request is for treatment associated with cancer for a State with regulations against step therapy in certain oncology settings *(see Appendix E*):
   a. Neupogen®, Nivestym™, Granix®, Releuko®, or Zarxio®;
   b. Leukine;
   **Prior authorization may be required for Neupogen, Nivestym, Granix, Zarxio, and Leukine*
4. Member meets one of the following (a or b):
   a. Member must use Ziextenzo*, unless clinically significant adverse effects are experienced or all are contraindicated;
      **Prior authorization may be required*
   b. Request is for the treatment associated with Stage IV or metastatic cancer for a State with regulations against step therapy in advanced oncology settings *(see Appendix E*);
5. The requested medication will not be prescribed concurrently with other colony stimulating factors (e.g., filgrastim, Leukine) within any chemotherapy cycle;
6. Request meets one of the following (a or b):
   a. Dose does not exceed 6 mg (1 syringe) 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: 6 months

D. Wilms Tumor (off-label) (must meet all)**:**
1. Diagnosis of Wilms tumor (nephroblastoma);
2. Request is not for Rolvedon;
3. Request is for supportive care for member receiving a regimen of cyclophosphamide and etoposide, or cyclophosphamide, doxorubicin, and vincristine in Regimen M and Regimen I (*see Appendix D*);

4. Member meets one of the following (a or b):
   a. Member must use Ziextenzo*, unless clinically significant adverse effects are experienced or all are contraindicated;
      **Prior authorization may be required*
   b. Request is for the treatment associated with cancer for a State with regulations against step therapy in certain oncology settings *(see Appendix E)*;
5. The requested medication will not be prescribed concurrently with other colony stimulating factors (e.g., filgrastim, Leukine) within any chemotherapy cycle;
6. Request meets one of the following (a or b):
   a. Dose does not exceed 6 mg (1 syringe) 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: 6 months

E. Other diagnoses/indications (must meet 1 and 2):
1. Member meets one of the following (a or b):
   a. Member must use Ziextenzo*, unless clinically significant adverse effects are experienced or all are contraindicated;
      **Prior authorization may be required*
   b. Request is for the treatment associated with cancer for a State with regulations against step therapy in certain oncology settings *(see Appendix E)*;
2. Refer to ERX.PA.01 if diagnosis is NOT specifically listed under section III (Diagnoses/Indications for which coverage is NOT authorized).

II. Continued Therapy

A. All Indications in Section I (must meet all)**:**
1. Currently receiving medication via a health plan affiliated with Envolve Pharmacy Solutions or member has previously met initial approval criteria;
2. Member is responding positively to therapy;
3. Member meets one of the following (a or b):
   a. Member must use Ziextenzo*, unless clinically significant adverse effects are experienced or all are contraindicated;
      **Prior authorization may be required*
   b. Request is for the treatment associated with cancer for a State with regulations against step therapy in certain oncology settings *(see Appendix E)*;
4. The requested medication will not be prescribed concurrently with other colony stimulating factors (e.g., filgrastim, Leukine) within any chemotherapy cycle;
5. If request is for a dose increase, new dose does not exceed one of the following (a, b, c, or d):
   a. Chemotherapy-induced neutropenia (i or ii):
      i. For pegfilgrastim: 6 mg (1 syringe) per chemotherapy cycle;
      ii. For eflapegrastim: 13.2 mg (1 syringe) per chemotherapy cycle;
   b. Acute radiation syndrome: two 6 mg doses administered one week apart;
   c. Bone marrow transplantation: 6 mg (1 syringe) per dose or dose is supported by practice guidelines or peer-reviewed literature for the relevant off-label use (*prescriber must submit supporting evidence*);
   d. Wilms tumor: 6 mg (1 syringe) administered once per chemotherapy cycle.

Approval duration: 6 months

B. Other diagnoses/indications (must meet 1 or 2)**:**
1. Member meets one of the following (a or b):
   a. Member must use Ziextenzo*, unless clinically significant adverse effects are experienced or all are contraindicated;
      **Prior authorization may be required*

b. Request is for the treatment associated with cancer for a State with regulations against step therapy in certain oncology settings *(see Appendix E)*;

2. One of the following (a or b):
   a. Currently receiving medication via a health plan affiliated with Envolve Pharmacy Solutions and documentation supports positive response to therapy. **Approval duration: Duration of request or 6 months (whichever is less)**; or
   b. Refer to ERX.PA.01 if diagnosis is NOT specifically listed under section III (Diagnoses/Indications for which coverage is NOT authorized).

III. Diagnoses/Indications for which coverage is NOT authorized:

A. Non-FDA approved indications, which are not addressed in this policy, unless there is sufficient documentation of efficacy and safety according to the off-label use policy – ERX.PA.01 or evidence of coverage documents.

IV. Appendices/General Information

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 and may require prior authorization.

Drug Name	Dosing Regimen	Dose Limit/ Maximum Dose
Neupogen (filgrastim), Zarxio (filgrastim- sndz), Granix (tbo- filgrastim), Nivestym (filgrastim-aafi), Releuko (filgrastim-ayow)	**Supportive care post autologous hematopoietic cell transplantation** 10 mcg/kg IV or SC infusion QD **Mobilization of peripheral-blood progenitor cells prior to autologous transplantation** 10 mcg/kg SC bolus or continuous infusion QD	10 mcg/kg/day 10 mcg/kg/day
Leukine (sargramostim)	**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 QD	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 ≥ 38.8ºC orally or ≥ 38.0ºC 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 febrile neutropenia 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). The NCCN Compendiums 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 and its biosimilars for supportive care post autologous hematopoietic cell transplant and treatment for hematopoietic cell mobilization for autologous donors in combination with plerixafor, both category 2A recommendations.
- 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.
- Chemotherapy regimens used in the treatment of Wilms tumor for which pegfilgrastim supportive care may be considered:
    - Regimen M: 9 doses of vincristine, 5 doses of dactinomycin, 5 doses of doxorubicin (cumulative dose 150 mg/m2), 4 courses of 5 daily doses of cyclophosphamide, and 4 courses of 5 daily doses of etoposide over 24 weeks. Dactinomycin and doxorubicin are given together, and cyclophosphamide and etoposide are given together.
    - Regimen I: 9 doses of vincristine, 4 doses of doxorubicin (cumulative dose 180 mg/m2), 7 courses of 3 to 5 daily doses of cyclophosphamide, and 3 courses of 5 daily doses of etoposide. Doxorubicin and 3 daily doses of cyclophosphamide are given together, and 5 daily doses of cyclophosphamide and etoposide are given together.

Appendix E: States with Regulations against Redirections in Cancer

State	Step Therapy Prohibited?	Notes
FL	Yes	For stage 4 metastatic cancer and associated conditions.
GA	Yes	For stage 4 metastatic cancer. Redirection does not refer to review of medical necessity or clinical appropriateness.
IA	Yes	For standard of care stage 4 cancer drug use, supported by peer-reviewed, evidence-based literature, and approved by FDA.
LA	Yes	For stage 4 advanced, metastatic cancer or associated conditions. Exception if “clinically equivalent therapy, contains identical active ingredient(s), and proven to have same efficacy.
NV	Yes	Stage 3 and stage 4 cancer patients for a prescription drug to treat the cancer or any symptom thereof of the covered person
OH	Yes	**Applies to Commercial requests only** For stage 4 metastatic cancer and associated conditions
PA	Yes	For stage 4 advanced, metastatic cancer

State	Step Therapy Prohibited?	Notes
TN	Yes	For advanced metastatic cancer and associated conditions
TX	Yes	For stage 4 advanced, metastatic cancer and associated conditions

V. Dosage and Administration

Drug Name	Indication	Dosing Regimen	Maximum Dose
Pegfilgrastim (Neulasta), pegfilgrastim-jmdb (Fulphila), pegfilgrastim-pbbk (Fylnetra), pegfilgrastim-apgf (Nyvepria), pegfilgrastim-fpgk (Stimufend), pegfilgrastim-cbqv (Udenyca), pegfilgrastim-bmez (Ziextenzo)	Myelosuppressive chemotherapy	6 mg administered SC once per chemotherapy cycle. Do not administer between 14 days before and 24 hours after administration of cytotoxic chemotherapy. 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 Weight based dosing for pediatric patients < 45 kg	6 mg/dose
Eflapegrastim-xnst (Rolvedon)	Myelosuppressive chemotherapy	13.2 mg administered SC once per chemotherapy cycle. Do not administer between 14 days before and 24 hours after administration of cytotoxic chemotherapy.	13.2 mg/dose

VI. Product Availability

Drug Name	Availability
Pegfilgrastim (Neulasta)	• Injection: 6 mg/0.6 mL solution in a single-dose prefilled syringe for manual use only • 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-pbbk (Fylnetra)	• Injection: 6 mg/0.6 mL solution in a single-dose prefilled syringe for manual use only
Pegfilgrastin-apgf (Nyvepria)	• Injection: 6 mg/0.6 mL solution in a single-dose prefilled syringe for manual use only
Pegfilgrastim-fpgk (Stimufend)	• Injection: 6 mg/0.6 mL solution in a single-dose prefilled syringe for manual use only
Pegfilgrastim-	• Injection: 6 mg/0.6 mL solution in a single-dose prefilled syringe for

Drug Name	Availability
cbqv (Udenyca)	manual use only
Pegfilgrastim-bmez (Ziextenzo)	• Injection: 6 mg/0.6 mL solution in a single-dose prefilled syringe for manual use only
Eflapegrastim-xnst (Rolvedon)	• Injection: 13.2 mg/0.6 mL solution in a single-dose prefilled syringe for manual use only

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Reviews, Revisions, and Approvals	Date	P&T Approval Date
3Q 2018 annual review: added off-label indications for mobilization of peripheral-blood progenitor cells and supportive care post autologous hematopoietic cell transplantation with redirection to FDA approved treatments Leukine and Neupogen, Granix, or Zarxio; references reviewed and updated.	05.08.18	08.18
Newly FDA-approved biosimilar added: Fulphila; references reviewed and updated.	07.31.18	11.18

Reviews, Revisions, and Approvals	Date	P&T Approval Date
Newly FDA-approved biosimilar added: Udenyca; references reviewed and updated.	12.05.18	
3Q 2019 annual review: no significant changes; added Nivestym to list of filgrastim products required for bone marrow transplant indication; references reviewed and updated.	05.15.19	08.19
RT4: added Ziextenzo to policy.	02.12.20	
3Q 2020 annual review: for chemotherapy-induced neutropenia criteria set, added "For members receiving palliative chemotherapy, provider attestation that chemotherapy dose reduction has been considered"; references reviewed and updated; for Ziextenzo and Fulphila requests added requirement for medical justification why Neulasta and Udenyca cannot be used with an allowed bypass of redirection if state regulations do not allow step therapy in Stage IV or metastatic cancer settings; RT4: added new biosimilar Nyvepria to policy.	04.30.20	08.20
Add requirement for confirmation that there is at least 12 days between pegfilgrastim dose and the next cycle of chemotherapy; added redirection for acute radiation syndrome to Neulasta and Udenyca to align with other indications; added bypass of redirection if state regulations do not allow step therapy in Stage IV or metastatic cancer settings for acute radiation syndrome and bone marrow transplant indications; removed AR from appendix E.	12.01.20	02.21
Updated appendix E to include Ohio.	02.08.21	
Updated GA language in appendix E.	03.10.21	
3Q 2021 annual review: removed redirection requirements for Ziextenzo; added Ziextenzo as a redirect option along with Neulasta and Udenyca for Nyvepria and Fulphila requests; added NCCN compendium supported off-label use in Wilms tumor; references reviewed and updated.	04.01.21	08.21
Added Nevada to Appendix E.	08.03.21	
3Q 2022 annual review: added requirement that requested medication will not be prescribed concurrently with other colony stimulating factors (e.g., pegfilgrastim, Leukine) within any chemotherapy cycle; clarified non-myeloid malignancy refers to solid tumor and lymphoid malignancies; for bone marrow transplantation redirection added bypass option if request is for a state with regulations against redirection in certain oncology settings; applied redirection to other diagnoses/indication criteria set requirements in both Section IE and IIB; RT4: added new biosimilar Fylnetra to policy; reference reviewed and updated.	04.27.22	08.22
RT4: added Stimufend and Rolvedon to policy; removed Neulasta and Udenyca as redirect option; for bone marrow transplantation, added Releuko to list of filgrastim products.	09.13.22	

Important Reminder

This clinical policy has been developed by appropriately experienced and licensed health care professionals based on a review and consideration of currently available generally accepted standards of medical practice; peer-reviewed medical literature; government agency/program approval status; evidence-based guidelines and positions of leading national health professional organizations; views of physicians practicing in relevant clinical areas affected by this clinical policy; and other available clinical information.

This Clinical Policy is not intended to dictate to providers how to practice medicine, nor does it constitute a contract or guarantee regarding payment or results. Providers are expected to exercise professional

medical judgment in providing the most appropriate care, and are solely responsible for the medical advice and treatment of members.