Clinical Policy: Pegfilgrastim (Neulasta, Neulasta Onpro), Pegfilgrastim-jmdb (Fulphila), Pegfilgrastim-pbbk (Fylnetra), Pegfilgrastim-apgf (Nyvepria), Eflapegrastim-xnst (Rolvedon), Pegfilgrastim-fpgk (Stimufend), Pegfilgrastim-apgf (Nyvepria), Pegfilgrastim-cbqv (Udenyca), Pegfilgrastim-bmez (Ziextenzo)
Reference Number: MDN.CP.PHAR.296
Effective Date: 04.01.22
Last Review Date: 6.6.24 Coding Implications
Line of Business: Meridian IL 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®, Udenyca® Autoinjector, Udenyca Onbody™), pegfilgrastim-bmez (Ziextenzo™), and are leukocyte growth factors.

FDA Approved Indication(s)
Neulasta, Nyvepria, Fulphila, Udenyca, Udenyca Autoinjector, Udenyca Onbody, 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 clinically significant incidence of febrile neutropenia (FN).

Neulasta and Udenyca (*Autoinjector and syringe only*), and Ziextenzo are also indicated to increase survival in patients acutely exposed to myelosuppressive doses of radiation (hematopoietic subsyndrome of acute radiation syndrome).

Limitation(s) of use: Neulasta, Neulasta Onpro, Fulphila, Nyvepria, Stimufend, Rolvedon, Udenyca products, 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.

It is the policy of health plans affiliated with Centene Corporation® that Neulasta, Neulasta Onpro, Fulphila, Nyvepria, Stimufend, Rolvedon, Udenyca, Udenyca Autoinjector 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;
2. Prescribed for use following myelosuppressive chemotherapy;

3. Failure of Neupogen, unless contraindicated or clinically significant adverse effects are experienced:
4. Confirmation that there is at least 12 days between pegfilgrastim dose and the next cycle of chemotherapy;
5. For members receiving palliative chemotherapy, provider attestation that chemotherapy dose reduction has been considered;
6. Dose does not exceed 6 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 Neulasta Onpro or Udenyca Onbody;
3. Failure of ONE of the following, unless contraindicated or clinically significant adverse effects are experienced: Neupogen, Leukine;
4. 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 ONE of the following, unless contraindicated or clinically significant adverse effects are experienced: Neupogen, Leukine;
3. 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. Failure of ONE of the following, unless contraindicated or clinically significant adverse effects are experienced: Neupogen, Leukine;
5. Request meets one of the following (a or b):
   a. Dose does not exceed 6 mg (1 syringe) per chemotherapy cycle;
   b. Dose is supported by practice guidelines or peer-reviewed literature for the relevant off-label use (*prescriber must submit supporting evidence*).

   Approved duration: 6 months

E. Other diagnoses/indications (must meet 1 and 2):

1. Failure of ONE of the following, unless contraindicated or clinically significant adverse effects are experienced: Neupogen, Leukine;
2. One of the following (a or b):
   a. If this drug has recently (within the last 6 months) undergone a label change (e.g., newly approved indication, age expansion, new dosing regimen) that is not yet reflected in this policy, refer to one of the following policies (i or ii):
      i. For drugs on PDL (Medicaid), the no coverage criteria policy for the relevant line of business: CP.PMN.255 for Medicaid; or
      ii. For drugs NOT on the PDL (Medicaid), the non-formulary policy for the relevant line of business: CP.PMN.16 for Medicaid; or
   b. If the requested use (e.g., diagnosis, age, dosing regimen) is NOT specifically listed under section III (Diagnoses/Indications for which coverage is NOT authorized) AND criterion 1 above does not apply, refer to the off-label use policy for the relevant line of business: CP.PMN.53 for Medicaid.

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II. Continued Therapy

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

1. Member meets one of the following (a or b):
   a. Currently receiving medication via Centene benefit or member has previously met initial approval criteria;
   b. Member is currently receiving medication and is enrolled in a state and product with continuity of care regulations (*refer to state specific addendums for CC.PHARM.03A and CC.PHARM.03B);*

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, Wilms tumor: 6 mg (1 syringe) administered once 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*).
4. The requested medication will not be prescribed concurrently with other colony stimulating factors (e.g., filgrastim, Leukine®) within any chemotherapy cycle;
5. Wilms tumor: 6 mg (1 syringe) administered once per chemotherapy cycle.

Approval duration: 6 months

B. Other diagnoses/indications (must meet 1 and 2)**:**

1. Failure of ONE of the following, unless contraindicated or clinically significant adverse effects are experienced: Neupogen, Leukine;
2. One of the following (a or b):

a. If this drug has recently (within the last 6 months) undergone a label change (e.g., newly approved indication, age expansion, new dosing regimen) that is not yet reflected in this policy, refer to one of the following policies (i or ii):
   i. For drugs on the PDL (Medicaid), the no coverage criteria policy for the relevant line of business: , CP.PMN.255 for Medicaid; or
   ii. For drugs NOT on the PDL (Medicaid), the non-formulary policy for the relevant line of business: CP.PMN.16 for Medicaid; or
b. If the requested use (e.g., diagnosis, age, dosing regimen) is NOT specifically listed under section III (Diagnoses/Indications for which coverage is NOT authorized) AND criterion 1 above does not apply, refer to the off-label use policy for the relevant line of business: CP.PMN.53 for Medicaid
therapy.

III. Diagnoses/Indications for which coverage is NO T 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 policies – CP.PMN.53 for Medicaid, 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 for all relevant lines of business and may require prior authorization.

Drug Name	Dosing Regimen	Dose Limit/ Maximum Dose
Neupogen® (filgrastim), Zarxio® (filgrastim-sndz), Granix® (tbo-filgrastim), Nivestym® (filgrastim-aafi)	**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®	**Supportive care post autologous hematopoietic**	500 mcg/m^2/day

(sargramostim)	**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	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 eflapegrastim, 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.

- Chemotherapy regimens used in the treatment of Wilms Tumor for which filgrastim 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

V. Dosage and Administration

Drug Name	Indication	Dosing Regimen	Maximum Dose
Pegfilgrastim (Neulasta), pegfilgrastim-jmdb (Fulphila), pegfilgrastim-cbqv (Udenyca), pegfilgrastim-bmez (Ziextenzo), pegfilgrastin-apgf (Nyvepria)	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), pegfilgrastim-cbqv (Udenyca), pegfilgrastim-bmez (Ziextenzo)	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	13.2 mg/dose
Efbemalenograstim alfa-vuxw (Ryzneuta)	Myelosuppressive chemotherapy	20 mg administered SC once per chemotherapy cycle at least 24 hours after cytotoxic chemotherapy. Do not administer within 14 days before and < 24 hours after administration of cytotoxic chemotherapy.	20 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
Pegfilgrastin-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 Injection: 0.6 mg/0.6 mL solution in a single-dose prefilled autoinjector (not for use in pediatric patients < 45 kg) • Injection: 6 mg/0.6 mL solution in a single-dose prefilled syringe co-packaged with the on-body injector
Pegfilgrastim-bmez (Ziextenzo)	• 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
Eflapegrastim-xnst (Rolvedon)	Injection: 13.2 mg/0.6 mL solution in a single-dose prefilled syringe for manual use only

VII. References

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Coding Implications

Codes referenced in this clinical policy are for informational purposes only. Inclusion or exclusion of any codes does not guarantee coverage. Providers should reference the most up-todate sources of professional coding guidance prior to the submission of claims for reimbursement of covered services.

HCPCS Codes	Description
J2506	Injection, pegfilgrastim, excludes biosimilar, 0.5 mg
Q5111	Injection, pegfilgrastim-cbqv, biosimilar, (Udenyca), 0.5 mg
Q5108	Injection, pegfilgrastim-jmdb, biosimilar, (Fulphila), 0.5 mg
Q5120	Injection, pegfilgrastim-bmez, biosimilar, (Ziextenzo), 0.5 mg
Q5122	Injection, pegfilgrastim-apgf, biosimilar, (Nyvepria), 0.5 mg

J3590	Unclassified biologics

Reviews, Revisions, and Approvals	Date	P&T Approval Date
Policy created, adapted from CP.PHAR.296	04.01.22	04.22
RT4: added Stimufend and Rolvedon to policy; template changes applied to other diagnoses/indications and continued therapy section.	11.29.22	
RT4: added new indication of hematopoietic subsyndrome of acute radiation syndrome to Udenyca; added that request is not for Neulasta OnPro for acute radiation syndrome.	1.19.23	
RT4: added new formulation of Udenyca prefilled auto-injector; references reviewed and updated.	4.28.23	
2Q2024 Annual Review: for Stimufend, added new indication of hematopoietic subsyndrome of acute radiation syndrome to FDA approved indication section and section V; added newly FDA approved Ryzneuta; for acute radiation syndrome, removed "request is not for Rolvedon" as off-label use is supported on NCCN compendium and added standard off-label dosing language for Rolvedon and Ryzneuta; for Acute Radiation Syndrome, added "Request is not for Udenyca Onbody"; for Ziextenzo, added new indication for hematopoietic subsyndrome of acute radiation syndrome.	6.6.24	

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. The Health Plan makes no representations and accepts no liability with respect to the content of any external information used or relied upon in developing this clinical policy. This clinical policy is consistent with standards of medical practice current at the time that this clinical policy was approved. "Health Plan" means a health plan that has adopted this clinical policy and that is operated or administered, in whole or in part, by Centene Management Company, LLC, or any of such health plan's affiliates, as applicable.

The purpose of this clinical policy is to provide a guide to medical necessity, which is a component of the guidelines used to assist in making coverage decisions and administering benefits. It does not constitute a contract or guarantee regarding payment or results. Coverage decisions and the administration of benefits are subject to all terms, conditions, exclusions and limitations of the coverage documents (e.g., evidence of coverage, certificate of coverage,

policy, contract of insurance, etc.), as well as to state and federal requirements and applicable Health Plan-level administrative policies and procedures.

This clinical policy is effective as of the date determined by the Health Plan. The date of posting may not be the effective date of this clinical policy. This clinical policy may be subject to applicable legal and regulatory requirements relating to provider notification. If there is a discrepancy between the effective date of this clinical policy and any applicable legal or regulatory requirement, the requirements of law and regulation shall govern. The Health Plan retains the right to change, amend or withdraw this clinical policy, and additional clinical policies may be developed and adopted as needed, at any time.

This clinical policy does not constitute medical advice, medical treatment or medical care. It is not intended to dictate to providers how to practice medicine. 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. This clinical policy is not intended to recommend treatment for members. Members should consult with their treating physician in connection with diagnosis and treatment decisions.

Providers referred to in this clinical policy are independent contractors who exercise independent judgment and over whom the Health Plan has no control or right of control. Providers are not agents or employees of the Health Plan.

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Note: For Medicaid members, when state Medicaid coverage provisions conflict with the coverage provisions in this clinical policy, state Medicaid coverage provisions take precedence. Please refer to the state Medicaid manual for any coverage provisions pertaining to this clinical policy.