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Policy Number: C10419-A

Rolvedon, Neulasta and Related Biosimilars

PRODUCTS AFFECTED

Neulasta (pegfilgrastim), Fylnetra (pegfilgrastim-pbbk), Fulphila (pegfilgrastim-jmdb), Udenyca (pegfilgrastim-cbqv), Ziextenzo (pegfilgrastim-bmez), Nyvepria (pegfilgrastim-apgf), Rolvedon (eflapegrastim-xnst), Stimufend (pegfilgrastim-fpgk)

COVERAGE POLICY

Coverage for services, procedures, medical devices, and drugs are dependent upon benefit eligibility as outlined in the member's specific benefit plan. This Coverage Guideline must be read in its entirety to determine coverage eligibility, if any.
This Coverage Guideline provides information related to coverage determinations only and does not imply that a service or treatment is clinically appropriate or inappropriate. The provider and the member are responsible for all decisions regarding the appropriateness of care. Providers should provide Molina Healthcare complete medical rationale when requesting any exceptions to these guidelines.

Documentation Requirements:
Molina Healthcare reserves the right to require that additional documentation be made available as part of its coverage determination; quality improvement; and fraud; waste and abuse prevention processes. Documentation required may include, but is not limited to, patient records, test results and credentials of the provider ordering or performing a drug or service. Molina Healthcare may deny reimbursement or take additional appropriate action if the documentation provided does not support the initial determination that the drugs or services were medically necessary, not investigational, or experimental, and otherwise within the scope of benefits afforded to the member, and/or the documentation demonstrates a pattern of billing or other practice that is inappropriate or excessive.

DIAGNOSIS:
Febrile neutropenia prophylaxis, Acute radiation syndrome

REQUIRED MEDICAL INFORMATION:
This clinical policy is consistent with standards of medical practice current at the time that this clinical policy was approved. If a drug within this policy receives an updated FDA label within the last 180 days, medical necessity for the member will be reviewed using the updated FDA label information along with state and federal requirements, benefit being administered and formulary preferencing. Coverage will be determined on a case-by case basis until the criteria can be updated through Molina Healthcare, Inc. clinical governance. Additional information may be required on a case-by-case basis to allow for adequate review. When the requested drug product for coverage is dosed by weight, body surface area or other member specific measurement, this data element is required as part of the medical necessity review.

FOR ALL INDICATIONS:
1. (a) IF THIS IS A PHARMACY BENEFIT REQUEST FOR A NON-FORMULARY/NON-PREFERRED PRODUCT: Documentation of trial/failure of or intolerance to a majority (not more than 3) of the

preferred formulary alternatives for the given diagnosis. Documentation of medication(s) tried, dates of trial(s) and reason for treatment failure(s) is required.
AND
(b) If request is for reference product with a biosimilar available for initial or continuation of therapy requests: Documentation of a trial and failure, intolerance or contraindication to a majority (not more than 3) biosimilar product(s) is required (unless otherwise specified per applicable state regulations and/or there is data demonstrating clinical superiority of reference drugs over the FDA approved biosimilar drugs).
[DOCUMENTATION REQUIRED: Document when the preferred biologic product or biosimilar was tried and the length of the trial period, Provide specific clinical documentation of therapeutic failure on the preferred biologic product or biosimilar whenever possible. Describe the medical problem caused by the preferred referenced biologic. Vague and non-descriptive symptoms are not adequate rationale (e.g., stomachache)]
OR

2. FOR INITIAL OR CONTINUATION OF THERAPY REQUESTS OF A PHYSICIAN ADMINISTERED MEDICATION: BIOSIMILAR DRUGS are preferred when requested as a physician administered drug per applicable state regulations and/or there is a lack of data demonstrating clinical superiority of reference drugs over the FDA approved biosimilar drugs. A reference medication is approved under the following conditions:
   a. Treatment with at least two (2) associated biosimilar drug(s) has been ineffective, not tolerated, or is contraindicated (i.e. an allergic reaction to a specific inactive ingredient in the preferred biologic product or biosimilar OR an adverse reaction to a specific inactive ingredient in the preferred biologic product or biosimilar OR therapeutic success while taking a non-preferred biologic product or biosimilar and therapeutic failure while taking the preferred biologic product or biosimilar documented by patient diary or medical charted notes)

   [DOCUMENTATION REQUIRED: Document when the preferred biologic product or biosimilar was tried and the length of the trial period, Provide specific clinical documentation of therapeutic failure on the preferred biologic product or biosimilar whenever possible. Describe the medical problem caused by the preferred referenced biologic. Vague and non-descriptive symptoms are not adequate rationale (e.g., stomachache)]

A. FEBRILE NEUTROPENIA PROPHYLAXIS IN NON-MYELOID MALIGNANCIES:
   1. Documented diagnosis of non-myeloid malignancy
      AND
   2. Documentation that pegfilgrastim is being used following myelosuppressive chemotherapy [DOCUMENTATION REQUIRED of current chemotherapy regimen, any previous chemotherapy regimens, and anticipated treatment plan]
      AND
   3. (a) Member has a risk of febrile neutropenia (FN) of greater than 20% based on current chemotherapy regimen (as listed in current ASCO and NCCN guidelines for myeloid growth factors [See Appendix])
      OR
      (b) Member has a risk of febrile neutropenia of 10-20% based on chemotherapy regimen, and at least ONE of the following risk factors apply:
         (i) Prior chemotherapy or radiation therapy
         (ii) Persistent neutropenia (defined as neutrophil count less than 500 neutrophils/mcL or less than 1,000 neutrophils/mcL and a predicted decline to less than or equal to 500 neutrophils/mcL over next 48 hours)
         (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 greater than 65 receiving full chemotherapy dose intensity

      OR

(c) Previous neutropenic fever complication from a prior cycle of similar chemotherapy
OR
(d) The member is receiving a dose-dense chemotherapy regimen

B. HEMATOPOIETIC SUB SYNDROME OF ACUTE RADIATION SYNDROME (NEULASTA ONLY):
1. Documentation that member has had confirmed or suspected radiation injury due to accidental or intentional total body radiation of greater than 2 Grays (Gy) [DOCUMENTATION REQUIRED]

CONTINUATION OF THERAPY:

A. FEBRILE NEUTROPENIA PROPHYLAXIS IN NON-MYELOID MALIGNANCIES:
1. Documentation of clinical benefits to support continuation of treatment including positive response to therapy (i.e., member did not become neutropenic mid-cycle requiring G-CSF) [DOCUMENTATION REQUIRED]
AND
2. Prescriber attests to regular lab monitoring (i.e., CBC) as clinically appropriate
AND
3. Documentation that member continues to be treated with chemotherapy regimen which supports the need for G-CSF prophylaxis
AND
4. Prescriber attests to or clinical reviewer has found no evidence of intolerable adverse effects or drug toxicity

B. HEMATOPOIETIC SUB SYNDROME OF ACUTE RADIATION SYNDROME: NA

DURATION OF APPROVAL:

For Febrile Neutropenia Prophylaxis in Non-Myeloid Malignancies:
Initial authorization: One chemotherapy cycle or 12 weeks, Continuation of Therapy: for up to 6 months or up to length of chemotherapy approval date-whichever is shorter

For Hematopoietic Subsyndrome of Acute Radiation Syndrome (Neulasta only): Initial authorization: 1 month, Continuation of therapy: N/A

PRESCRIBER REQUIREMENTS:

Prescribed by or in consultation with a board-certified hematologist, oncologist, or transplant specialist. [If prescribed in consultation, consultation notes must be submitted with initial request and reauthorization requests]

AGE RESTRICTIONS:

Pegfilgrastim: None
Rolvedon (eflapegrastim-xnst): 18 years of age or older

QUANTITY:

Pegfilgrastim:

Febrile Neutropenia Prophylaxis: 6mg once per chemo cycle
Hematopoietic Sub Syndrome of Acute Radiation Syndrome: The recommended dose of Neulasta is two doses, 6 mg each, administered subcutaneously one week apart.
Dose is adjusted if weight is <45kg:
<10 kg: 0.1 mg/kg
10-20 kg: 1.5 mg
21-30 kg: 2.5 mg
31-44 kg: 4 mg

Up to 2 prefilled syringes (1.2mL) per 28 days (1 prefilled syringe per chemotherapy cycle), Up to 2 OnPro kits per 28 days (1 OnPro kit per chemotherapy cycle)

Rolvedon (eflapegrastim-xnst):
13.2 mg administered subcutaneously once per chemotherapy cycle

PLACE OF ADMINISTRATION:
The recommendation is that injectable medications in this policy will be for pharmacy or medical benefit coverage and the subcutaneous injectable products administered in a place of service that is a non- hospital facility-based location as per the Molina Health Care Site of Care program.

Note: Site of Care Utilization Management Policy applies for Fulphila (pegfilgrastim), Fylnetra (pegfilgrastim-pbbk), Neulasta (pegfilgrastim), Udenyca (pegfilgrastim-cbqv), Ziextenzo (pegfilgrastim- bmez), Nyvepria (pegfilgrastim-apgf injection), Rolvedon (eflapegrastim-xnst), Stimufend (pegfilgrastim-fpgk).
For information on site of care, See Specialty Medication Administration Site of Care Coverage Criteria (molinamarketplace.com)

DRUG INFORMATION

ROUTE OF ADMINISTRATION:
Subcutaneous

DRUG CLASS:
Granulocyte Colony-Stimulating Factors (G-CSF)

FDA-APPROVED USES:
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.

NEULASTA ONLY: Increase survival in patients acutely exposed to myelosuppressive doses of radiation (Hematopoietic Sub syndrome of Acute Radiation Syndrome).

COMPENDIAL APPROVED OFF-LABELED USES:
None

APPENDIX

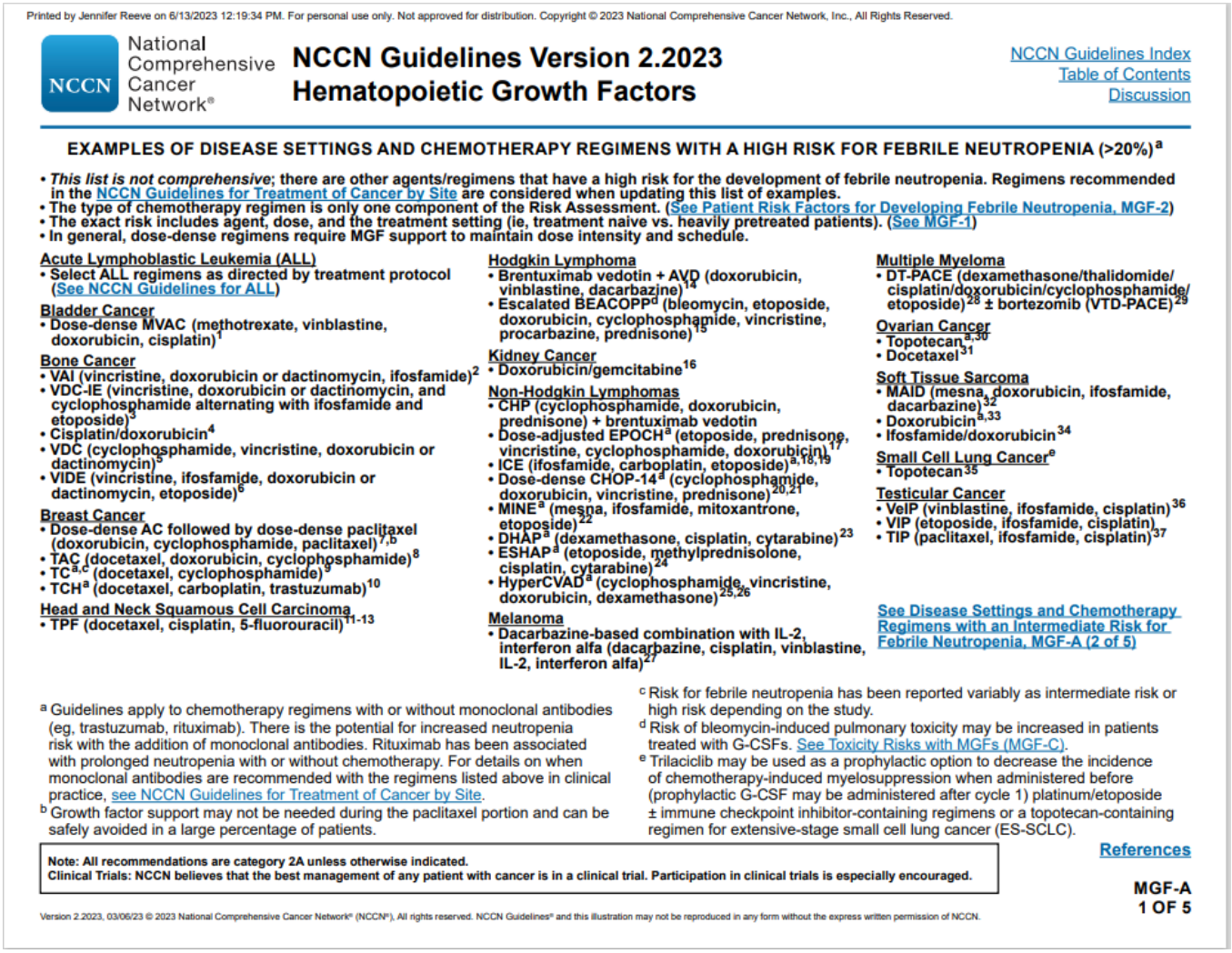
APPENDIX:
A biosimilar is highly similar version of a brand name biological drug that meets strict controls for structural, pharmaceutical, and clinical consistency. A biosimilar manufacturer must demonstrate that there are no meaningful clinical differences (i.e., safety and efficacy) between the biosimilar and the reference product. Clinical performance is demonstrated through human pharmacokinetic (exposure)and pharmacodynamic (response) studies, an assessment of clinical immunogenicity, and, if needed, additional clinical studies.[1] As costs for biological specialty drugs continue to rise, the growing biosimilar market will benefit providers and patients by broadening biological treatment options and expanding access to these medications at lower costs.
Molina Healthcare, Inc. continues to be committed to continually reevaluating Preferred strategies and applying innovative cost-controls to ensure patients receive safe, effective, and quality healthcare. This commitment includes potentially creating a preference for biosimilars when value can be added without compromising patient satisfaction and safety.

1. Food and Drug Administration. Biosimilar and Interchangeable Products. Retrieved from https://www.fda.gov/drugs/biosimilars/biosimilar-and-interchangeable-products. Accessed October 8, 2019.

High risk for chemotherapy induced FN infectious complications because of bone marrow compromise OR co-morbidity with any of the following risk factors (not an all-inclusive list):
Age >65 years

Drug and Biologic Coverage Criteria

- Poor performance status
- Previous episodes of FN
- History of previous chemotherapy or radiation therapy
- Completion of combined chemoradiotherapy
- Bone marrow involvement by tumor producing cytopenia
- Pre-existing neutropenia
- Poor nutritional status
- Poor renal function
- Liver dysfunction (i.e., elevated bilirubin)
- Presence of open wound(s) or active infection
- Recent surgery (within the past 12 weeks)
- More advanced cancer
- Other serious co-morbidities



National Comprehensive Cancer Network®

NCCN Guidelines Version 2.2023
Hematopoietic Growth Factors

NCCN Guidelines Index
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Discussion

EXAMPLES OF DISEASE SETTINGS AND CHEMOTHERAPY REGIMENS WITH A HIGH RISK FOR FEBRILE NEUTROPENIA (>20%)[a]

- ***This list is not comprehensive***; there are other agents/regimens that have a high risk for the development of febrile neutropenia. Regimens recommended in the NCCN Guidelines for Treatment of Cancer by Site are considered when updating this list of examples.
- The type of chemotherapy regimen is only one component of the Risk Assessment. (See Patient Risk Factors for Developing Febrile Neutropenia, MGF-2)
- The exact risk includes agent, dose, and the treatment setting (ie, treatment naive vs. heavily pretreated patients). (See MGF-1)
- In general, dose-dense regimens require MGF support to maintain dose intensity and schedule.

Acute Lymphoblastic Leukemia (ALL)
- Select ALL regimens as directed by treatment protocol (See NCCN Guidelines for ALL)

Bladder Cancer
- Dose-dense MVAC (methotrexate, vinblastine, doxorubicin, cisplatin)[1]

Bone Cancer
- VAI (vincristine, doxorubicin or dactinomycin, ifosfamide)[2]
- VDC-IE (vincristine, doxorubicin or dactinomycin, and cyclophosphamide alternating with ifosfamide and etoposide)[3]
- Cisplatin/doxorubicin[4]
- VDC (cyclophosphamide, vincristine, doxorubicin or dactinomycin)[5]
- VIDE (vincristine, ifosfamide, doxorubicin or dactinomycin, etoposide)[6]

Breast Cancer
- Dose-dense AC followed by dose-dense paclitaxel (doxorubicin, cyclophosphamide, paclitaxel)[7,b]
- TAC (docetaxel, doxorubicin, cyclophosphamide)[8]
- TC[a,c] (docetaxel, cyclophosphamide)[9]
- TCH[a] (docetaxel, carboplatin, trastuzumab)[10]

Head and Neck Squamous Cell Carcinoma
- TPF (docetaxel, cisplatin, 5-fluorouracil)[11-13]

Hodgkin Lymphoma
- Brentuximab vedotin + AVD (doxorubicin, vinblastine, dacarbazine)[14]
- Escalated BEACOPP[d] (bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, prednisone)[15]

Kidney Cancer
- Doxorubicin/gemcitabine[16]

Non-Hodgkin Lymphomas
- CHP (cyclophosphamide, doxorubicin, prednisone) + brentuximab vedotin
- Dose-adjusted EPOCH[a] (etoposide, prednisone, vincristine, cyclophosphamide, doxorubicin)[17]
- ICE (ifosfamide, carboplatin, etoposide)[a,18,19]
- Dose-dense CHOP-14[a] (cyclophosphamide, doxorubicin, vincristine, prednisone)[20,21]
- MINE[a] (mesna, ifosfamide, mitoxantrone, etoposide)[22]
- DHAP[a] (dexamethasone, cisplatin, cytarabine)[23]
- ESHAP[a] (etoposide, methylprednisolone, cisplatin, cytarabine)[24]
- HyperCVAD[a] (cyclophosphamide, vincristine, doxorubicin, dexamethasone)[25,26]

Melanoma
- Dacarbazine-based combination with IL-2, interferon alfa (dacarbazine, cisplatin, vinblastine, IL-2, interferon alfa)[27]

Multiple Myeloma
- DT-PACE (dexamethasone/thalidomide/cisplatin/doxorubicin/cyclophosphamide/etoposide)[28] ± bortezomib (VTD-PACE)[29]

Ovarian Cancer
- Topotecan[a,30]
- Docetaxel[31]

Soft Tissue Sarcoma
- MAID (mesna, doxorubicin, ifosfamide, dacarbazine)[32]
- Doxorubicin[a,33]
- Ifosfamide/doxorubicin[34]

Small Cell Lung Cancer[e]
- Topotecan[35]

Testicular Cancer
- VeIP (vinblastine, ifosfamide, cisplatin)[36]
- VIP (etoposide, ifosfamide, cisplatin)
- TIP (paclitaxel, ifosfamide, cisplatin)[37]

See Disease Settings and Chemotherapy Regimens with an Intermediate Risk for Febrile Neutropenia, MGF-A (2 of 5)

[a] Guidelines apply to chemotherapy regimens with or without monoclonal antibodies (eg, trastuzumab, rituximab). There is the potential for increased neutropenia risk with the addition of monoclonal antibodies. Rituximab has been associated with prolonged neutropenia with or without chemotherapy. For details on when monoclonal antibodies are recommended with the regimens listed above in clinical practice, see NCCN Guidelines for Treatment of Cancer by Site.

[b] Growth factor support may not be needed during the paclitaxel portion and can be safely avoided in a large percentage of patients.

[c] Risk for febrile neutropenia has been reported variably as intermediate risk or high risk depending on the study.

[d] Risk of bleomycin-induced pulmonary toxicity may be increased in patients treated with G-CSFs. See Toxicity Risks with MGFs (MGF-C).

[e] Trilaciclib may be used as a prophylactic option to decrease the incidence of chemotherapy-induced myelosuppression when administered before (prophylactic G-CSF may be administered after cycle 1) platinum/etoposide ± immune checkpoint inhibitor-containing regimens or a topotecan-containing regimen for extensive-stage small cell lung cancer (ES-SCLC).

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

References

MGF-A
1 OF 5

Recommendations for the Use of WBC Growth Factors (ASCO, 2015)
Primary prophylaxis with a CSF starting in the first cycle and continuing through subsequent cycles of chemotherapy is recommended in patients who have an approximately20%or higher risk for febrile neutropenia on the basis of patient-, disease-, and treatment related factors. Primary CSF prophylaxis should also be administered in patients receiving dose-dense chemotherapy when considered appropriate.

BACKGROUND AND OTHER CONSIDERATIONS

BACKGROUND:
None

CONTRAINDICATIONS/EXCLUSIONS/DISCONTINUATION:
All other uses of pegfilgrastim and its biosimilars are considered experimental/investigational and therefore, will follow Molina's Off-Label policy [Use in routine infection prophylaxis (e.g., adjunctive therapy to antibiotics in a member with uncomplicated febrile neutropenia, afebrile neutropenia). Continued use beyond 42 days with no response. Concurrent use with other CSF agents (Neupogen, Leukine). Known hypersensitivity to pegfilgrastim or any ingredient in the requested formulation. E. coli protein hypersensitivity. Receiving chemotherapy with a risk of febrile neutropenia <20% and no significant high risk for complications. Pegfilgrastim will be administered in the period between 14 days before and 24 hours after administration of cytotoxic chemotherapy]. Contraindications to pegfilgrastim and eflapegrastim include: Patients with a history of serious allergic reactions to human granulocyte colony-stimulating factors such as eflapegrastim, pegfilgrastim or filgrastim, administration between 14 days before and 24 hours after administration of cytotoxic chemotherapy.

OTHER SPECIAL CONSIDERATIONS:
None

CODING/BILLING INFORMATION

Note: 1) This list of codes may not be all-inclusive. 2) Deleted codes and codes which are not effective at the time the service is rendered may not be eligible for reimbursement

HCPCS CODE	DESCRIPTION
Q5111	Injection, pegfilgrastim-cbqv, biosimilar, (udenyca) 0.5mg
Q5108	Injection, pegfilgrastim-jmdb, biosimilar, (fulphila), 0.5mg
J2506	Injection, pegfilgrastim, excludes biosimilar, 0.5mg
Q5120	Injection, pegfilgrastim-bmez, biosimilar, (ziextenzo)0.5 mg
Q5122	Injection, pegfilgrastim-apgf, biosimilar, (nyvepria), 0.5 mg
Q5130	Injection, pegfilgrastim-pbbk (fylnetra), biosimilar, 0.5 mg
J1449	Injection, eflapegrastim-xnst, 0.1 mg
Q5127	Injection pegfilgrastim-fpgk (stimufend), biosimilar, 0.5 mg

AVAILABLE DOSAGE FORMS:
Neulasta (pegfilgrastim) 6mg/0.6mL prefilled syringe, 6mg/0.6mL OnPro kit
Fulphila (pegfilgrastim-jmdb) 6mg/0.6mL prefilled syringe
Udenyca 6mg/0.6mL prefilled syringe, 6mg/0.6mL autoinjector
Ziextenzo SOSY 6MG/0.6ML prefilled syringe
Nyvepria 6 mg/0.6 mL prefilled syringe
Rolvedon 13.2 mg/0.6 mL solution in a single dose prefilled syringe
Stimufend SOSY 6MG/0.6ML solution in a single dose prefilled syringe
Fylnetra 6mg/0.6mL solution in a single dose prefilled syringe

REFERENCES

1. Neulasta [package insert]. Thousand Oaks, CA; Amgen Inc; February 2021.
2. Fulphila [package insert]. Morgantown, WV; Mylan GmbH; October 2021.
3. Udenyca [package insert]. Coherus Biosciences. Redwood City, CA; March 2023.

4. Ziextenzo [package insert]. Princeton, NJ; Sandoz Inc.; March 2021.
5. Nyvepria [package insert]. Lake Forest, IL; Hospira Inc., a Pfizer Company; March 2023.
6. Fylnetra [package insert]. Piscataway, NJ; Amneal Pharmaceuticals LLC; May 2022.
7. Rolvedon (eflapegrastim) [prescribing information]. Irvine, CA: Spectrum Pharmaceuticals Inc; September 2022.
8. Stimufend (pegfilgrastim-fpgk) [prescribing information]. Lake Zurich, IL: Fresenius Kabi USA, LLC; September 2022.
9. National Comprehensive Cancer Network. 2022. Hematopoietic Growth Factors (Version 1.2023). [online] Available at: < growthfactors.pdf (nccn.org)> [Accessed 8 December 2022]
10. Chemoradiotherapy with or without granulocyte-macrophage colony-stimulating factor in the treatment of limited-stage small-cell lung cancer: a prospective phase III randomized study of the Southwest Oncology Group Bunn PA Jr, Crowley J, Kelly K, Hazuka MB, Beasley K, Upchurch C, Livingston R, Weiss GR, Hicks WJ, Gandara DR. J Clin Oncol. 1995;13(7):1632
11. Intensified hyperfractionated accelerated radiotherapy limits the additional benefit of simultaneous chemotherapy--results of a multicentric randomized German trial in advanced head-and-neck cancer. Staar S, Rudat V, Stuetzer H, Dietz A, Volling P, Schroeder M, Flentje M, Eckel HE, Mueller RP. Int J Radiat Oncol Biol Phys. 2001;50(5):1161
12. Smith, T. J., Bohlke, K., Lyman, G. H., Carson, K. R., Crawford, J., Cross, S. J., … Armitage, J. O. (2015). Recommendations for the Use of WBC Growth Factors: American Society of Clinical Oncology Clinical Practice Guideline Update. Journal of Clinical Oncology, 33(28), 3199–3212. https://doi.org/10.1200/jco.2015.62.3488
13. National Comprehensive Cancer Network. 2023. Hematopoietic Growth Factors (Version 2.2023). [online] Available at: < growthfactors.pdf (nccn.org) > [Accessed 13 June 2023].

SUMMARY OF REVIEW/REVISIONS	DATE
REVISION- Notable revisions: Diagnosis Required Medical Information Continuation of Therapy Duration of Approval Appendix Contraindications/Exclusions/Discontinuation Coding/Billing Information Available Dosage Forms References	Q3 2023
REVISION- Notable revisions: Title Products Affected Age Restrictions Quantity Contraindications/Exclusions/Discontinuation Coding/Billing Information Available Dosage Forms References	Q1 2023
REVISION- Notable revisions: Products Affected Required Medical Information Continuation of Therapy Duration of Approval Quantity Contraindications/Exclusions/Discontinuation References	Q4 2022
Q2 2022 Established tracking in new format	Historical changes on file