CLINICAL GUIDELINES FOR MEDICAL NECESSITY

MEDICAL POLICY

Pegfilgrastim and Biosimilars (Fulphila®, Fylnetra®, Neulasta®, Neulasta-OnPro®, Nyvepria®, Stimufend®, Udenyca®, Ziextenzo®)

Version: 1.0

EFFECTIVE DATE: 1/1/2024

Please note the following:

Pegfilgrastim (Neulasta®, Neulasta-OnPro®); Pegfilgrastim-apgf (Nyvepria®); Pegfilgrastim-bmez (Ziextenzo®); Pegfilgrastim-cbqv (Udenyca®); Pegfilgrastim-fpgk (Stimufend®); Pegfilgrastim-jmdb (Fulphila®); Pegfilgrastim-pbbk (Fylnetra®)

Note: For Medicare members/enrollees, to ensure consistency with the Medicare National Coverage Determinations (NCD) and Local Coverage Determinations (LCD), all applicable NCDs, LCDs, and Medicare Coverage Articles should be reviewed prior to applying the criteria set forth in this clinical policy. Please refer to the CMS website at http://www.cms.gov for additional information.

Note: For Medicaid members/enrollees, circumstances when state Medicaid coverage provisions conflict with the coverage provisions within 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.

Pegfilgrastim (Neulasta, Neulasta-OnPro); Pegfilgrastim-apgf (Nyvepria); Pegfilgrastim-bmez (Ziextenzo); Pegfilgrastim-cbqv (Udenyca); Pegfilgrastim-fpgk (Stimufend); Pegfilgrastim-jmdb (Fulphila); Pegfilgrastim-pbbk (Fylnetra): Discussion

This policy addresses the use of the following FDA-approved granulocyte colony-stimulating factors (G-CSF), also known as white blood cell growth factors.

Some types of cancer chemotherapy can cause myelosuppression, a condition where the bone marrow's ability to produce blood cells is greatly reduced. One type of blood cell is called neutrophils, which are an important part of the body's immune system and assist in the fight against infection. Having an abnormally low number of neutrophils (neutropenia) increases vulnerability to infection. Developing a fever when neutropenic (febrile neutropenia), can be a life-threatening condition, often requiring prolonged hospitalizations and treatment with broad-spectrum antibiotics. [1] Neutropenic infections are dose-limiting events that can occur during chemotherapy which results in increased treatment costs, delays in cancer treatment, and/or reduction in chemotherapy dose intensity, which may negatively impact disease control and treatment outcomes. [2]

Pegfilgrastim and its biosimilars are granulocyte colony-stimulating factors (G-CSF). These are proteins that are involved in the production and regulation of neutrophils. The administration of a G-CSF drug stimulates the bone marrow to increase the production of neutrophils and is often given as part of myelosuppressive chemotherapy treatment to counteract chemotherapy-induced neutropenia and reduce the risk of developing febrile neutropenia.

Same-day administration of pegfilgrastim or any of its biosimilars is not recommended by the FDA or NCCN. [3,4,5,6,7,8,9,10]

Pegfilgrastim and its biosimilars are long-acting G-CSFs. A single dose of pegfilgrastim, or one of its biosimilars, can be given the day after myelosuppressive chemotherapy as an alternative to several doses of a short-acting G-CSF. Pegfilgrastim or any of its biosimilars may be given up to 3 to 4 days following myelosuppressive chemotherapy, and there should be at least 12 days between the dose of pegfilgrastim and the next cycle of chemotherapy. If the treatment cycle includes chemotherapy administration on days 1 and 15, pegfilgrastim or one of its biosimilars may be given after each chemotherapy treatment. [10]

For those individuals who cannot return to the clinic for pegfilgrastim the day following their chemotherapy, the FDA has approved an on-body injector device, which is programmed to deliver a full dose of pegfilgrastim approximately 27 hours after it is placed onto the skin. This device is currently only available for pegfilgrastim and is commercially available as Neulasta On-Pro. [3,10]

Pegfilgrastim, pegfilgrastim-apgf, pegfilgrastim-bmez, pegfilgrastim-cbqv, pegfilgrastim-fpgk, pegfilgrastim-jmdb, and pegfilgrastim-pbbk have all been approved by the FDA for use in adults and children with non-myeloid cancers receiving myelosuppressive chemotherapy that is associated with a clinically significant rate of febrile neutropenia. [3,4,5,6,7,8,9]

Note: Pegfilgrastim and its biosimilars are not indicated for the mobilization of peripheral blood progenitor cells for hematopoietic stem cell transplantation. [3,4,5,6,7,8,9]

Pegfilgrastim is endorsed by the National Comprehensive Cancer Network's (NCCN) guidelines for hematopoietic growth factors for the prevention of chemotherapy-induced febrile neutropenia or other dose-limiting neutropenic events as follows:

1. Individuals with solid tumors and non-myeloid malignancies undergoing myelosuppressive chemotherapy with a high risk of febrile neutropenia (>20% overall risk) in the curative/adjuvant or palliative settings (category 1)
2. Individuals with solid tumors and non-myeloid malignancies undergoing myelosuppressive chemotherapy with an intermediate risk of febrile neutropenia (10% to 20% overall risk) in the curative/adjuvant or palliative settings who have one or more patient risk factors (category 2A)
3. Individuals with solid tumors and non-myeloid malignancies undergoing myelosuppressive chemotherapy with a low risk of febrile neutropenia (<10% overall risk) in the curative/adjuvant or palliative settings who have 2 or more patient-related risk factors. The use of granulocyte colony-stimulating factors in this setting is based on clinical judgment (category 2A)

NCCN allows the substitution of pegfilgrastim with an FDA-approved biosimilar (category 2A endorsement).

NCCN defines febrile neutropenia as having an absolute neutrophil count (ANC) of less than 500 neutrophils/mcL, or an anticipated decline to ≤500 within the next 48 hours, accompanied by a single oral temperature of ≥38.3°C or a temperature ≥38.0°C for a duration of over 1 hour. [10]

Pegfilgrastim and Biosimilars: Definitions

- **Biosimilar drug -** A biological drug that is very much like another biological drug (called the reference drug) that has already been approved by the U.S. Food and Drug Administration (FDA). Biosimilar drugs and reference drugs are made from living organisms, but they may be made in different ways and of slightly different substances. To be called a biosimilar drug, a biological drug must be shown to be as safe as, work as well as, and work in the same way as its reference drug. It must also be used in the same way, at the same dose, and for the same condition as the reference drug. Biosimilar drugs must be approved by the FDA and may cost less than their reference drugs. [11]
- **Febrile neutropenia (FN) -** A condition marked by fever and a lower-than-normal number of neutrophils in the blood. [12]
- **Food and Drug Administration (FDA) -** The FDA is responsible for protecting the public health by assuring the safety, efficacy, and security of human and veterinary drugs, biological products, medical devices, our nation's food supply, cosmetics, and products that emit radiation.
- **National Comprehensive Cancer Network (NCCN) -** An alliance of thirty-two leading cancer centers devoted to patient care, research, and education. The NCCN guidelines are utilized for Radiation Therapy and Medical Oncology standards. NCCN consensus clinical standards are periodically updated and NantHealth, Inc. reviews these and updates its policies within a timely manner.

Pegfilgrastim, Pegfilgrastim-apgf, Pegfilgrastim-bmez, Pegfilgrastim-cbqv, Pegfilgrastim-fpgk, Pegfilgrastim-jmdb and Pegfilgrastim-pbbk: Policy

Pegfilgrastim and its biosimilars will be considered for coverage when the following criteria are met:

1. Pediatric or adult; AND
2. Prescribed by or in consultation with an oncologist; AND
3. May be used in cytotoxic chemotherapy regimens administered every 2 weeks or longer; AND
4. Prophylaxis of chemotherapy-induced febrile neutropenia or other dose-limiting neutropenic events is allowed for high-risk (>20% overall risk of febrile neutropenia) individuals with solid tumors and non-myeloid malignancies receiving treatment in the curative/adjuvant or palliative settings [10]; OR
5. Primary prophylaxis of chemotherapy-induced febrile neutropenia or other dose-limiting neutropenic events is allowed for intermediate-risk (10% to 20% overall risk of febrile neutropenia) individuals with solid tumors and non-myeloid malignancies receiving treatment in the curative/adjuvant or palliative settings who have one or more of the following risk factors:
    a) Prior chemotherapy or radiation therapy
    b) Persistent neutropenia

c) Bone marrow involvement by tumor
d) Recent surgery and/or open wounds
e) Liver dysfunction (bilirubin >2.0)
f) Renal dysfunction (creatinine clearance <50)
g) Age >65 years receiving full chemotherapy dose intensity
h) Poor performance status
i) Human immunodeficiency virus (HIV) infection (low CD4 counts)
j) Chronic immunosuppression in the post-transplant setting [10]; OR

6. Secondary prophylaxis of chemotherapy-induced febrile neutropenia or other dose-limiting neutropenic events is allowed for intermediate- or low-risk individuals with solid tumors and non-myeloid malignancies receiving treatment in the curative/adjuvant or palliative settings is permitted provided all of the following criteria are met:
    a) The individual has experienced an episode of febrile neutropenia or a dose-limiting neutropenic event
    b) There is a specific reason why there cannot be a modification of the chemotherapy dose, schedule, or treatment option (such as in the setting of curative intent). Documentation will be provided to the Nanthealth medical office
    c) The individual with an intermediate risk of febrile neutropenia did not receive primary prophylaxis with G-CSF

Note:

1. Pegfilgrastim and its biosimilars should not be given as prophylaxis in the setting of concurrent chemotherapy and radiation.
2. Pegfilgrastim and its biosimilars should not be used in cytotoxic chemotherapy regimens administered every week.
3. Requests for any G-CSF drug for the purposes of primary prophylaxis of chemotherapy-induced febrile neutropenia or other dose-limiting neutropenic events in low-risk (<10% overall risk of febrile neutropenia) individuals with solid tumors and non-myeloid malignancies receiving treatment in the curative/adjuvant or palliative settings will require further review.
4. Coverage of pegfilgrastim or any of its biosimilars will be provided for an FDA-approved indication or National Comprehensive Cancer Network (NCCN) guidelines when it is a Category 1, 2A, or 2B recommendation or when all criteria are met.

Authorization Period and Renewal Criteria

1. Initial Authorization Period: 12 months
2. Renewal Criteria: No evidence of disease progression or unacceptable toxicity
3. Renewal Authorization Period: 12 months

Pegfilgrastim and Biosimilars: References

1. Lyman GH, Kuderer NM. Epidemiology of febrile neutropenia. Supportive Cancer Therapy. 1:23-35;2003. https://pubmed.ncbi.nlm.nih.gov/18628128. Accessed June 12, 2023.
2. Lalami Y, Klastersky J. Impact of chemotherapy-induced neutropenia (CIN) and febrile neutropenia (FN) on cancer treatment outcomes: An overview about well-established and recently emerging clinical data. Crit Rev Oncol Hematol. 120:163-179;2017. https://pubmed.ncbi.nlm.nih.gov/29198330. Accessed June 12, 2023.
3. Pegfilgrastim (Neulasta, Neulasta-OnPro) Package Insert. https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/125031s203lbl.pdf. Accessed May 22, 2023.
4. Pegfilgrastim-apgf (Nyvepria) Package Insert. https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/761111s004lbl.pdf. Accessed May 22, 2023.
5. Pegfilgrastim-bmez (Ziextenzo) Package Insert. https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/761045s006lbl.pdf. Accessed May 22, 2023.
6. Pegfilgrastim-cbqv (Udenyca) Package Insert. https://www.accessdata.fda.gov/drugsatfda_docs/label/2023/761039s013lbl.pdf. Accessed May 22, 2023.
7. Pegfilgrastim-fpgk (Stimufend) Package Insert. https://www.accessdata.fda.gov/drugsatfda_docs/label/2022/761173Orig1s000correctedlbl.pdf. Accessed May 22, 2023.
8. Pegfilgrastim-jmdb (Fulphila) Package Insert. https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/761075s012lbl.pdf. Accessed May 22, 2023.
9. Pegfilgrastim-pbbk (Fylnetra) Package Insert. https://www.accessdata.fda.gov/drugsatfda_docs/label/2022/761084s000lbl.pdf. Accessed May 22, 2023.
10. National Comprehensive Cancer Network Guidelines. Hematopoietic Growth Factors (Version 2.2023). https://www.nccn.org/professionals/physician_gls/pdf/growthfactors.pdf. Accessed May 22, 2023.
11. National Cancer Institute. (n.d.) NCI Dictionary of Cancer Terms. https://www.cancer.gov/publications/dictionaries/cancer-terms/def/biosimilar-drug. Accessed May 22, 2023.
12. National Cancer Institute. (n.d.) NCI Dictionary of Cancer Terms. https://www.cancer.gov/publications/dictionaries/cancer-terms/def/febrile-neutropenia. Accessed May 22, 2023.

Pegfilgrastim and Biosimilars: Coding (CPT®, ICD 10 and HCPCS) *

*Procedure codes appearing in medical policy documents are only included as a general reference. This list may not be all-inclusive and is subject to updates. In addition, the codes listed are not a guarantee of payment. CPT codes are available through the AMA.

CPT CODE	DESCRIPTION
C00.0 - C41.9, C43.0 - C43.9, C4A.0 – C4A.9, C44.00 - C75.9, C7A.1 - C7A.8, C76.0 - C91.32, C91.50 - C91.92	Malignant neoplasms
J2506	Pegfilgrastim (Neulasta®, Neulasta OnPro®)
Q5108	Pegfilgrastim-jmdb (Fulphila®)
Q5111	Pegfilgrastim-cbqv (Udenyca®)
Q5120	Pegfilgrastim-bmez (Ziextenzo®)
Q5122	Pegfilgrastim-apgf (Nyvepria®)
Q5127	Pegfilgrastim-fpgk (Stimufend®)
Q5130	Pegfilgrastim-pbbk (Fylnetra®)
96377	Application of on-body injector (includes cannula insertion) for timed subcutaneous injection [Neulasta OnPro injector]
C00.0 - C41.9, C43.0 - C43.9, C4A.0 – C4A.9, C44.00 - C75.9, C7A.1 - C7A.8, C76.0 - C91.32, C91.50 - C91.92	Malignant neoplasms
J2506	Pegfilgrastim (Neulasta®, Neulasta OnPro®)

Pegfilgrastim and Biosimilars: Revision and Review History

No.	Description	Date(s)
1	Original Effective Date:	1/1/2024
2	Policy Review Dates:	7/7/2023
3	Policy Revision Dates:	
4	Department Owner:	Medical Affairs
5	NH Advisory Committee Approval Dates:	8/7/2023
6	Revision Changes:	