

Corporate Medical Policy

White Blood Cell Growth Factors

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Description of Procedure or Service

White blood cell growth factors, also known as colony stimulating factors (CSF), are administered to enhance recovery of blood related functions in neutropenia (low white blood count) including febrile neutropenia (FN). CSFs are also utilized to decrease the incidence and severity of infection associated with select disease-related and drug-related myelosuppression (inhibition of bone marrow function).

Granulocyte colony stimulating factors (G-CSF) are glycoproteins which exert major control over the reproduction and maturation of certain white blood cells, which include the following U.S. Food & Drug Administration (FDA) approved products:

- Filgrastim (Neupogen[®], Amgen, Thousand Oaks, CA)
- Pegfilgrastim (Neulasta[®] and Neulasta[®] OnPro[®], Amgen, Thousand Oaks, CA)
- Pegfilgrastim-cbqv (Udenyca[™], Coherus BioSciences, Redwood City, CA)
- Pegfilgrastim-jmdb (Fulphila[™], Mylan, Rockford, IL)
- Filgrastim-aafi (Nivestym[™], Pfizer, Lake Forest, IL)
- Filgrastim-sndz (Zarxio[®], Sandoz, Princeton, NJ)
- Tbo-filgrastim (Granix[®], Sicor Biotech UAB/Teva Pharmaceuticals, North Wales, PA)

Granulocyte-macrophage colony stimulating factor (GM-CSF) is a hematopoietic growth factor which stimulates proliferation and differentiation of hematopoietic progenitor cells.

- Sargramostim (Leukine[®], Bayer Healthcare Pharmaceuticals, Seattle, WA)

*****Note: This Medical Policy is complex and technical. For questions concerning the technical language and/or specific clinical indications for its use, please consult your physician.**

Policy

BCBSNC will provide coverage for White Blood Cell Growth Factors when it is determined to be medically necessary because the medical criteria and guidelines shown below are met.

Benefits Application

This medical policy relates only to the services or supplies described herein. Please refer to the Member's Benefit Booklet for availability of benefits. Member's benefits may vary according to benefit design; therefore member benefit language should be reviewed before applying the terms of this medical policy.

When White Blood Cell Growth Factors are covered

For all indications, Pegfilgrastim (Neulasta, Neulasta OnPro), Pegfilgrastim-cbqv (Udenyca), Pegfilgrastim-jmdb (Fulphila), Filgrastim (Neupogen), Filgrastim-aafi (Nivestym), Filgrastim-

sndz (Zarxio), Tbo-filgrastim (Granix), and Sargramostim (Leukine) are considered medically necessary if the following criteria are met:

1. The request is for Neulasta, Neulasta OnPro, Fulphila, or Udenyca; **AND**
 - a. If the request is for Neulasta or Neulasta OnPro, the patient has tried and failed or has a clinical contraindication/intolerance to a biosimilar pegfilgrastim product (i.e. Fulphila, Udenyca); **AND**
 - b. If the request is for Neulasta OnPro, the patient has an inability to physically or cognitively adhere to the treatment schedule including all of the following:
 - i. Inability to self-administer the medication; **AND**
 - ii. Lack of caregiver or support system for assistance with medication administration; **AND**
 - iii. Inadequate access to a healthcare facility for assistance with medication administration; **OR**
2. The request is for Granix, Neupogen, Nivestym, or Zarxio; **AND**
 - a. If the request is for Neupogen, the patient has tried and failed or has a clinical contraindication/intolerance to a biosimilar filgrastim product (i.e. Granix, Nivestym, Zarxio); **AND**

Primary Prophylaxis of febrile neutropenia

One white blood cell (WBC) growth factor agent is considered clinically appropriate for primary prophylaxis of chemotherapy-induced febrile neutropenia when **ALL** of the following (1,2, and 3) are met:

1. The individual has a non-myeloid malignancy and is **NOT** receiving chemotherapy with radiation concurrently;
2. Chemotherapy intent **must include ONE** of the following:
 - a. Curative intent, such as adjuvant treatment for early stage disease ; **OR**
 - b. Intent is survival prolongation, and the use of a different regimen or dose reduction would reduce the likelihood of reaching the treatment goal; **OR**
 - c. Intent is symptom management, and the use of a different regimen or dose reduction would reduce the likelihood of reaching the treatment goal.
3. The individual falls into one of the following risk categories for febrile neutropenia:
 - a. High risk of febrile neutropenia (> 20%) based on chemotherapy regimen; **OR**
 - b. Intermediate risk of febrile neutropenia (> 10% but < 20 %) based on chemotherapy regimen **and at least ONE** of the following significant risk factors:
 - Age > 65;
 - Poor performance status (ECOG 3 or 4, but chemotherapy still indicated);
 - Preexisting neutropenia, for example resulting from bone marrow damage or tumor infiltration (ANC < 1500 mm³);
 - Previous febrile neutropenia episode;
 - Bone marrow infiltration by tumor;
 - Liver dysfunction, with bilirubin > 1.0 or liver enzymes > 2x upper limit of normal;
 - Presence of open wounds or active infections, when chemotherapy cannot be delayed to accommodate recovery;
 - Renal dysfunction, with creatinine clearance less than 50 ml/min;
 - Poor nutritional status (baseline albumin less 3.5 g/dl or BMI < 20);
 - HIV infection (active);
 - Advanced cancer

Secondary Prophylaxis of febrile neutropenia

Secondary prophylaxis of febrile neutropenia is considered clinically appropriate when there has been a previous neutropenic complication (in the absence of primary prophylaxis), **and a change to the regimen (including dose reduction, schedule change, or change in therapy) would be expected to compromise patient outcome**, particularly in the setting of curative intent.

Adjunctive treatment of febrile neutropenia (primary prophylaxis not given)

Adjunctive treatment of febrile neutropenia is considered clinically appropriate when **any** of the following risk factors are present:

- Age > 65
- Neutrophil recovery is expected to be delayed (greater than 10 days)
- Neutropenia is profound (less than 0.1×10^9)
- Active pneumonia
- Sepsis syndrome (hypotension and/or multi-organ damage/dysfunction noted)
- Invasive fungal or opportunistic infection
- Onset of fever during inpatient stay

Note: Febrile neutropenia is defined as an oral temperature > 38.3°C (101.0°F) or 2 consecutive readings of 38.0°C (100.4°F) for 1 hour, with an absolute neutrophil count less than 500 cells/microL ($0.5 \times 10^9/L$) or less than 1000 cells/microL and expected to fall below 500 cells/microL over the next 48 hours.

Other oncologic uses for WBC growth factors

The following indications by growth factor type are also considered clinically appropriate when the requirements below are met:

Filgrastim/filgrastim-aafi/filgrastim-sndz/Tbo-filgrastim

1. Acute lymphocytic leukemia
 - a. After start of induction or first post-remission chemotherapy course; **OR**
 - b. As an alternate or adjunct to donor leukocyte infusions (DLI) for relapsed disease after transplant.
2. Acute myeloid leukemia
 - a. After induction, reinduction, or consolidation; **OR**
 - b. As an alternate or adjunct to donor leukocyte infusions (DLI) for relapsed disease after transplant.
3. Aplastic anemia, moderate or severe
4. Hairy cell leukemia
 - a. To treat severe neutropenia
5. Hematopoietic stem cell transplant
 - a. To promote bone marrow myeloid recovery; **OR**
 - b. To treat delayed or failed engraftment; **OR**
 - c. To mobilize stem cells for collection by pheresis
6. Myelodysplastic syndrome
 - a. To treat recurrent infection; **OR**
 - b. To treat neutrophil count < 500 mm^3
7. Radiation exposure
 - a. Following radiation therapy in the absence of chemotherapy, if prolonged delays are expected; **OR**
 - b. After accidental or intentional body irradiation of doses greater than 2 Gy (hematopoietic syndrome of acute radiation syndrome).
8. Support for dose dense or dose intensive chemotherapy in **any** of the following scenarios:
 - a. Adjuvant treatment of high-risk breast cancer with combination therapy that includes anthracycline (doxorubicin or epirubicin)/cyclophosphamide followed by paclitaxel; **OR**
 - b. High-dose intensity methotrexate, vinblastine, doxorubicin, and cisplatin (HD-M-VAC) in urothelial cancer; **OR**
 - c. Chemotherapy intensification for newly diagnosed, localized Ewing sarcoma

Peg-filgrastim/pegfilgrastim-cbqv/pegfilgrastim-jmdb

1. Acute lymphocytic leukemia
 - a. After start of induction or first post-remission chemotherapy course

2. Hematopoietic stem cell transplant
 - a. To promote bone marrow myeloid recovery; **OR**
 - b. To treat delayed or failed engraftment
3. Myelodysplastic syndrome
 - a. To treat recurrent infection; **OR**
 - b. To treat neutrophil count < 500 mm³
4. Radiation exposure
 - a. After accidental or intentional body irradiation of doses greater than 2 Gy (hematopoietic syndrome of acute radiation syndrome)
5. Support for dose dense chemotherapy in **any** of the following scenarios:
 - a. Adjuvant treatment of high-risk breast cancer with combination therapy that includes anthracycline (doxorubicin or epirubicin)/cyclophosphamide followed by paclitaxel; **OR**
 - b. High-dose intensity methotrexate, vinblastine, doxorubicin, and cisplatin (HD-M-VAC) in urothelial cancer; **OR**
 - c. Chemotherapy intensification for newly diagnosed, localized Ewing sarcoma.

Sargramostim

1. Acute lymphocytic leukemia
 - a. After start of induction or first post-remission chemotherapy course
2. Acute myeloid leukemia
 - a. After induction, reinduction, for individuals over 55 years of age
3. Hematopoietic stem cell transplant
 - a. To promote bone marrow myeloid recovery; **OR**
 - b. To treat delayed or failed engraftment; **OR**
 - c. To mobilize stem cells for collection by pheresis
4. Myelodysplastic syndrome (MDS)
 - a. To treat recurrent infection; **OR**
 - b. To treat neutrophil count < 500 mm³
5. Radiation exposure
 - a. After radiation therapy in the absence of chemotherapy, if prolonged delays are expected; **OR**
 - b. After accidental or intentional body irradiation of doses greater than 2 Gy (hematopoietic syndrome of acute radiation syndrome)
6. Support for dose dense chemotherapy in **any** of the following scenarios:
 - a. Adjuvant treatment of high-risk breast cancer with combination therapy that includes anthracycline (doxorubicin or epirubicin)/cyclophosphamide followed by paclitaxel; **OR**
 - b. High-dose intensity methotrexate, vinblastine, doxorubicin, and cisplatin (HD-M-VAC) in urothelial cancer; **OR**
 - c. Chemotherapy intensification for newly diagnosed, localized Ewing sarcoma.

Use of White Blood Cell Growth Factors may be considered medically necessary for clinical indications not listed above when the drug is prescribed for the treatment of cancer either:

- In accordance with FDA label (when clinical benefit has been established, see Policy Guidelines); **OR**
- In accordance with specific strong endorsement or support by nationally recognized compendia, when such recommendation is based on strong/high levels of evidence, and/or uniform consensus of clinical appropriateness has been reached.

When White Blood Cell Growth Factors are not covered

Pegfilgrastim (Neulasta, Neulasta OnPro), Pegfilgrastim-cbqv (Udenyca), Pegfilgrastim-jmdb (Fulphila), Filgrastim (Neupogen), Filgrastim-aafi (Nivestym), Filgrastim-sndz (Zarxio), Tbo-

filgrastim (Granix) and Sargramostim (Leukine) are considered not medically necessary and therefore not covered when above criteria are not met.

Pegfilgrastim (Neulasta, Neulasta OnPro), Pegfilgrastim-cbqv (Udenyca), and Pegfilgrastim-jmdb (Fulphila) are not medically necessary for the mobilization of peripheral blood progenitor cells for hematopoietic stem cell transplantation.

Indications outside of FDA labeling will be subject to medical necessity review against nationally recognized compendia (National Comprehensive Cancer Network, NCCN) for the highest level of evidence (Level 1, 2A)

White Blood Cell Growth Factors are considered investigational when used for:

1. Non-cancer indications; **OR**
2. When criteria are not met regarding FDA labeling **OR** strong endorsement/support by nationally recognized compendia, as stated under “When White Blood Cell Growth Factors are covered.”

Policy Guidelines

Indications outside of FDA labeling will be subject to medical necessity review against nationally recognized compendia (National Comprehensive Cancer Network, NCCN) for the highest level of evidence (Level 1, 2A).

Drugs prescribed for treatment of cancer in accordance with FDA label may be considered medically necessary when clinical benefit has been established, and should not be determined to be investigational as defined in Corporate Medical Policy (CMP), “Investigational (Experimental) Services.”

Please refer to CMP “Investigational (Experimental) Services” for a summary of evidence standards from nationally recognized compendia.

Billing/Coding/Physician Documentation Information

This policy may apply to the following codes. Inclusion of a code in this section does not guarantee that it will be reimbursed. For further information on reimbursement guidelines, please see Administrative Policies on the Blue Cross Blue Shield of North Carolina web site at www.bcsnc.com. They are listed in the Category Search on the Medical Policy search page.

Applicable service codes: C9399, J1442, J2505, J2820, J3490, Q5101, Q5111, Q5108, Q5110, S0353, S0354

ICD-10 Codes: C00.0-C49.9, C4A.0-C4A.9, C50.011-C79.9, C7A.00-C7A.8, C7B.00-C7B.8, C80.0-C86.6, C88.2-C96.Z, D00.00-D09.9, Z51.11, Z51.12

BCBSNC may request medical records for determination of medical necessity. When medical records are requested, letters of support and/or explanation are often useful, but are not sufficient documentation unless all specific information needed to make a medical necessity determination is included.

Scientific Background and Reference Sources

U.S. Food and Drug Administration (FDA). Neulasta® (Pegfilgrastim).

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Leukine (sargramostim) product information. Sanofi-aventis. Bridgewater, NJ. April 2013

Neulasta (pegfilgrastim) product information. Amgen. Thousand Oaks, CA. April 2016

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Zarxio (filgrastim-sndz) product information. Sandoz, Inc. San Francisco, CA. March 2015.

Granix (Cotellic) product information. Teva. North Wales, PA. December 2014.

American Cancer Society. Available at: <http://www.cancer.org/>. Accessed September 11, 2016.

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U.S. Food and Drug Administration (FDA).
Neupogen [Product Information]. Thousand Oaks, CA. Amgen; July 30, 2015. Available at: http://www.accessdata.fda.gov/drugsatfda_docs/label/2015/103353s5186lbl.pdf. Accessed on June 19, 2017.

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Zarxio [Product Information]. Princeton, NJ. Sandoz Inc.; March 3, 2016. Available at: http://www.accessdata.fda.gov/drugsatfda_docs/label/2016/125553s001lbl.pdf. Accessed on June 19, 2017.

National Comprehensive Cancer Network (NCCN) Clinical Practice Guidelines in Oncology.
Myeloid Growth Factors, Version 1.2017- April 28, 2017. Available online at: https://www.nccn.org/professionals/physician_gls/pdf/myeloid_growth.pdf
Accessed August 9, 2017.

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National Comprehensive Cancer Network (NCCN) Clinical Practice Guidelines in Oncology. Myeloid Growth Factors, Version 1.2018 - March 2, 2018. Available online at: https://www.nccn.org/professionals/physician_gls/pdf/myeloid_growth.pdf Accessed June 2018.

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U.S. Food and Drug Administration (FDA). Fulphila (pegfilgrastim-jmdb) injection for subcutaneous use. Prescribing Information. Rockford, IL:FDA; 6/2018. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/761075s000lbl.pdf. Last accessed August 2018.

U.S. Food and Drug Administration (FDA). Nivestym (filgrastim-aafi) injection for subcutaneous or intravenous use. Prescribing Information. Lake Forest, IL:FDA; 7/2018. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/761080s000lbl.pdf. Last accessed September 2018.

U.S. Food and Drug Administration (FDA). Udenyca (pegfilgrastim-cbqv) injection for subcutaneous use. Prescribing Information. Redwood City, CA:FDA; 11/2018. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/761039s000lbl.pdf. Last accessed December 2018.

Policy Implementation/Update Information

- 12/30/16 New policy developed. Pegfilgrastim (Neulasta), Filgrastim (Neupogen), Sargramostim (Leukine), Tbo-filgrastim (Granix) and Filgrastim-sndz (Zarxio) are considered medically necessary to enhance recovery of blood related functions in neutropenia. References added. Added HCPCS codes S0353, S0354 and ICD-10 diagnoses codes to “Billing/Coding” section. Medical Director review 12/2016. Notification 12/30/16 for effective date 4/1/17. (lpr)
- 5/26/17 Added the following statement to “When Covered” section: “Use of White Blood Cell Growth Factors may be considered medically necessary for clinical indications not listed above when the drug is prescribed for the treatment of cancer either: In accordance with FDA label (when clinical benefit has been established, see Policy Guidelines); OR In accordance with specific strong endorsement or support by nationally recognized compendia, when such recommendation is based on strong/high levels of evidence, and/or uniform consensus of clinical appropriateness has been reached”. Under “When Not Covered” section, added the statement “White Blood Cell Growth Factors are considered investigational when used for: 1)Non-cancer indications; **OR** 2) When criteria are not met regarding FDA labeling **OR** strong endorsement/ support by nationally recognized compendia, as stated under “When White Blood Cell Growth Factors are covered.” Added the following statements under “Policy Guidelines” section: 1)Drugs prescribed for treatment of cancer in accordance with FDA label may be considered medically necessary when clinical benefit has been established, and should not be determined to be investigational as defined in Corporate Medical Policy, Investigational (Experimental) Services.” 2) Please refer to CMP “Investigational (Experimental) Services” for a summary of evidence standards from nationally recognized compendia. Medical director review 3/2017. Specialty Matched Consultant Advisory Panel review 4/26/2017. No change to policy statement. (lpr)
- 6/30/17 Revised “When Covered” and When Not Covered” sections to reflect coverage by clinical condition rather than by individual agent, but no change to intent. References added. (lpr)
- 8/25/17 Added NCCN reference. No change to policy statement. (lpr)
- 10/13/17 Added HCPCS Q5101 to the Billing/Coding section. (lpr)

- 6/29/18 Specialty Matched Consultant Advisory Panel review 4/25/2018. Within “When Covered” section, added the following intermediate risk factors: “bone marrow infiltration by tumor” and “renal dysfunction, with creatinine clearance less than 50 ml/min.” Corrected typographical repetition error in “When Covered” section. No change to policy intent. References added. Medical Director review 6/2018. (krc)
- 8/10/18 Updated “Description”, “When Covered”, and “Policy Guidelines” sections to reflect addition of Fulphila (pegfilgrastim-jmdb), a biosimilar to Neulasta (pegfilgrastim), with same indications and coverage criteria as Neulasta. Added codes C9399 and J3490 to Billing/Coding section pertaining to Fulphila. Reference added. (krc)
- 9/28/18 Updated “Description”, “When Covered”, and “Policy Guidelines” sections to reflect addition of Nivestym (filgrastim-aafi), a biosimilar to Neupogen (filgrastim), with same indications and coverage criteria as Neupogen. Added the following to “When Covered” section: “For all indications, the following criteria are met: 1. The request is for Neulasta, Neulasta OnPro, or Fulphila; AND a. If the request is for Neulasta or Neulasta OnPro, the patient has tried and failed or has a clinical contraindication/intolerance to a biosimilar pegfilgrastim product (i.e. Fulphila); AND b. If the request is for Neulasta OnPro, the patient has an inability to physically or cognitively adhere to the treatment schedule; OR 2. The request is for Granix, Neupogen, Nivestym, or Zarxio; AND If the request is for Neupogen, the patient has tried and failed or has a clinical contraindication/intolerance to a biosimilar filgrastim product (i.e. Granix, Nivestym, Zarxio); AND.” Added code Q5110 to Billing/Coding section pertaining to Nivestym and code Q5108 pertaining to Fulphila. Reference added. **Notification given 10/1/18 for effective date 1/1/19.** (krc)
- 12/31/18 Updated “Description”, “When Covered”, and “Policy Guidelines” sections to reflect addition of Udenyca (pegfilgrastim-cbqv), a biosimilar to Neulasta (pegfilgrastim), with same indications and coverage criteria as Neulasta. Added HCPCS code Q5111 to Billing/Coding Section for effective date 1/1/19. (krc)

Medical policy is not an authorization, certification, explanation of benefits or a contract. Benefits and eligibility are determined before medical guidelines and payment guidelines are applied. Benefits are determined by the group contract and subscriber certificate that is in effect at the time services are rendered. This document is solely provided for informational purposes only and is based on research of current medical literature and review of common medical practices in the treatment and diagnosis of disease. Medical practices and knowledge are constantly changing and BCBSNC reserves the right to review and revise its medical policies periodically.