Blue Cross Blue Shield Blue Care Network of Michigan

Nonprofit corporations and independent licensees of the Blue Cross and Blue Shield Association

Medical benefit drug policies are a source for BCBSM and BCN medical policy information only. These documents are not to be used to determine benefits or reimbursement. Please reference the appropriate certificate or contract for benefit information. This policy may be updated and therefore subject to change.

Effective Date: 08/08/2024

Colony Stimulating Factors (CSFs)

Fulphila™ (pegfilgrastim-jmbd)
Fylnetra® (pegfilgrastim-pbbk)
Granix® (tbo-filgrastim)
Leukine® (sargramostim)
Neulasta® (pegfilgrastim)
Neulasta On-Pro® (pegfilgrastim)
Neupogen® (filgrastim)
Nivestym™ (filgrastim-aafi)
Nypozi™ (filgrastim-txid)
Nyvepria™ (pegfilgrastim-apgf)
Releuko™ (filgrastim-ayow)
Rolvedon™ (eflapegrastim-xnsxt)
Ryzneuta® (efbemalenograstim alfa-vuxw)
Stimufend® (pegfilgrastim-fpgk)
Udenyca™ (pegfilgrastim-cbqv)
Udenyca Onbody™ (pegfilgrastim-cbqv)
Zarxio® (filgrastim-sndz)
Ziextenzo™ (pegfilgrastim-bmez)

HCPCS: Fulphila: Q5108; Fylnetra; Q5130; Granix: J1447; Leukine: J2820; Neupogen: J1442; Neulasta: J2506; Nivestym: Q5110; Nypozi: J3590; Nyvepria: Q5122; Releuko: Q5125; Rolvedon: J1449; Ryzneuta: J9361; Stimufend: Q5127; Udenyca: Q5111; Udenyca Onbody: Q5111; Zarxio: Q5101; Ziextenzo: Q5120

Policy:

Requests must be supported by submission of chart notes and patient specific documentation.

A. Coverage of the requested drug is provided when all the following are met:
   a. Primary prophylaxis of chemotherapy-induced febrile neutropenia is considered clinically appropriate when ALL of the following are met:
      i. The individual has a non-myeloid malignancy
      ii. The individual falls into one of the following risk categories for febrile neutropenia:
         1. High risk of febrile neutropenia (≥ 20%) based on chemotherapy regimen; OR

2. Intermediate risk of febrile neutropenia (≥ 10% but < 20%) based on chemotherapy regimen, and at least ONE of the following significant risk factors:
    a) Age > 65
    b) Poor performance status (ECOG 3 or 4, but chemotherapy still indicated)
    c) Preexisting neutropenia, for example resulting from bone marrow damage or tumor infiltration (ANC < 1500 mm^3)
    d) Previous febrile neutropenia episode from a prior treatment regimen
    e) Liver dysfunction, with bilirubin ≥ 1.0 or liver enzymes ≥ 2x upper limit of normal
    f) Presence of open wounds or active infections, when chemotherapy cannot be delayed to accommodate recovery
    g) Renal dysfunction with creatinine clearance of less than 50 mL/min
    h) Poor nutritional status (baseline albumin less ≤ 3.5 g/dL or BMI less than 20)
    i) HIV infection
    j) Advanced cancer (i.e. metastatic or stage IV, unresectable disease).
    k) Multiple (5 or more) chronic conditions or at least two serious comorbidities
3. Low risk of febrile neutropenia (>10%) based on chemotherapy regimen, and
    a) Dose reduction is not clinically appropriate
    b) Member has at least TWO of the following significant risk factors:
        1) Age > 65
        2) Poor performance status (ECOG 3 or 4, but chemotherapy still indicated)
        3) Preexisting neutropenia, for example resulting from bone marrow damage or tumor infiltration (ANC < 1,500 mm^3)
        4) Previous febrile neutropenia episode from a prior treatment regimen
        5) Liver dysfunction, with bilirubin ≥ 1.0 or liver enzymes ≥ 2x upper limit of normal
        6) Presence of open wounds or active infections, when chemotherapy cannot be delayed to accommodate recovery
        7) Renal dysfunction with creatinine clearance of less than 50 mL/min
        8) Poor nutritional status (baseline albumin less ≤ 3.5 g/dL or BMI less than 20)
        9) HIV infection
        10) Advanced cancer (i.e. metastatic or stage IV, unresectable disease).
        11) Multiple (5 or more) chronic conditions or at least two serious comorbidities

b. 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.
c. Adjunctive treatment of febrile neutropenia is considered clinically appropriate when any of the following risk factors are present:
    i. Age > 65
    ii. Neutrophil recovery is expected to be delayed (greater than 10 days)
    iii. Neutropenia is profound (less than 0.1 x 10^9)
    iv. Active pneumonia
    v. Sepsis syndrome (hypotension and/or multi-organ damage/dysfunction noted)
    vi. Invasive fungal or opportunistic infection
    vii. Onset of fever during inpatient stay
d. The following indications by growth factor type are also considered clinically appropriate when the requirements below are met:
    i. Filgrastim and filgrastim biosimilars

1. Acute lymphocytic leukemia (ALL)
    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 (AML)
    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. To treat severe neutropenia in hairy cell leukemia
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 (MDS)
    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

ii. Peg-filgrastim and peg-filgrastim biosimilars
1. Acute lymphocytic leukemia (ALL) after the start of induction of 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 (MDS)
    a) To treat recurrent infection; OR
    b) To treat neutrophil count < 500 mm^3
4. 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

iii. Sargramostim
1. Acute lymphocytic leukemia (ALL) after the start of induction or first post-remission chemotherapy course

2. Acute myeloid leukemia (AML) 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 mm^3
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
7. In combination with naxitamab for pediatric patients one year of age and older and adult patients with relapsed or refractory high-risk neuroblastoma in the bone or bone marrow demonstrating a partial response, minor response, or stable disease to prior therapy
8. In combination with dinutuximab, interleukin-2, and 13-cis-retinoic acid for the pediatric patients with high risk neuroblastoma who achieve at least a partial response to prior first line multiagent, multimodal therapy

iv. Tbo-filgrastim for use in hematopoietic stem cell transplant in any of the following scenarios:
1. To promote bone marrow myeloid recovery; OR
2. To treat delayed or failed engraftment; OR
3. To mobilize stem cells for collection by pheresis

e. Coverage will be provided for biosimilar products for FDA labeled indications of the innovator product when criteria are met
f. Trial and failure, contraindication, OR intolerance to the preferred drugs as listed in BCBSM/BCN's utilization management medical drug list and/or BCBSM/BCN's prior authorization and step therapy documents.

B. Quantity Limitations and Authorization Period
    a. Quantity Limits: Align with FDA approved dosing
    b. Initial Authorization Period: Aligns with FDA recommended or guideline supported treatment duration and provided for at least 60 days up to 6 months at a time

C. Renewal Criteria:
    a. Authorization may be reviewed at least annually to confirm that current criteria are met and that the medication is effective as demonstrated by a decrease in the interruption of chemotherapy cycles and reduced incidence of febrile neutropenia
    b. Renewal Authorization Period: Aligns with FDA recommended or guideline supported treatment duration and provided for at least 60 days up to 6 months at a time

***Note: Coverage and approval duration may differ for Medicare Part B members based on any applicable criteria outlined in Local Coverage Determinations (LCD) or National Coverage Determinations (NCD) as determined by Center for Medicare and Medicaid Services (CMS). See the CMS website at http://www.cms.hhs.gov/. Determination of coverage of Part B drugs is based on medically accepted indications which have supported citations included or approved for inclusion determined by CMS approved compendia.

Background Information:

- There are different types of colony stimulating factors (CSFs). Filgrastim-products, pegfilgrastim products and Leukine is the only sargramostim product. Filgrastim and pegfilgrastim products are human granulocyte colony-stimulating factors (G-CSFs). Leukine is a human granulocyte-macrophage CSF (GM-CSF).

- Filgrastim products:

    - Granix is FDA approved to reduce the duration of severe neutropenia in patients with non-myeloid malignancies receiving myelosuppressive anti-cancer medications associated with a clinically-significant incidence of febrile neutropenia. It is not technically considered a biosimilar because it was filed as a Biologics License Application since a biosimilars approval pathway had not been established at the time of FDA submission.

    - Neupogen is approved 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 severe neutropenia and fever.

        - Reduce the time to neutrophil recovery and the duration of fever following induction or consolidation chemotherapy treatment of adults with AML.

        - Reduce the duration of neutropenia and neutropenia-related clinical sequelae (e.g., febrile neutropenia) in patients with non-myeloid malignancies undergoing myeloablative chemotherapy followed by BMT.

        - Mobilization of autologous hematopoietic progenitor cells into the peripheral blood for collection by leukapheresis.

        - Chronic administration to reduce the incidence and duration of sequelae of neutropenia in symptomatic patients with congenital neutropenia, cyclic neutropenia, or idiopathic neutropenia.

        - Increase survival in patients acutely exposed to myelosuppressive doses of radiation (hematopoietic syndrome of acute radiation syndrome).

    - All of Neupogen's biosimilars are approved for the same indications as Neupogen with the exception of use to increase survival in patients acutely exposed to myelosuppressive doses of radiation (hematopoietic syndrome of acute radiation syndrome). That indication is protected by Orphan Drug Exclusivity until March 30, 2022.

- Pegfilgrastim products:

    - Neulasta is approved 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. Limitation of Use: This agent is not indicated for mobilization of peripheral blood progenitor cells for HSCT.

    - Increase survival in patients acutely exposed to myelosuppressive doses of radiation (hematopoietic subsyndrome of acute radiation syndrome).

  - All of Neulasta' s biosimilars are approved for the same indications as Neulasta with the exception of increasing survival in patients acutely exposed to myelosuppressive doses of radiation. Stimufend, Udenyca, and Ziextenzo are approved for this indication.

- Sargramostim is approved:

  - To shorten time to neutrophil recovery and to reduce the incidence of severe, life-threatening or fatal infections following induction chemotherapy in adult patients ≥ 55 years of age with AML.

  - In adult patients with cancer undergoing autologous hematopoietic stem cell transplantation for the mobilization of hematopoietic progenitor cells into peripheral blood for collection by leukapheresis.

  - To accelerate myeloid reconstitution following autologous peripheral blood progenitor cell or bone marrow transplantation in adult and pediatric patients ≥ 2 years of age with non-Hodgkin's lymphoma, lymphoblastic leukemia, and Hodgkin's lymphoma.

  - For acceleration of myeloid reconstitution in adult and pediatric patients ≥ 2 years of age undergoing allogeneic bone marrow transplantation from HLA-matched related donors.

  - Treatment of adult and pediatric patients ≥ 2 years of age who have undergone allogeneic or autologous BMT in whom neutrophil recovery is delayed or failed.

  - To increase survival in adult and pediatric patients from birth to 17 years of age acutely exposed to myelosuppressive doses of radiation (hematopoietic syndrome of acute radiation syndrome).

- Eflapegrastim and efbemalenograstim alfa-vuxw are approved:

  - To decrease the incidence of infection, as manifested by febrile neutropenia, in adult patients with nonmyeloid malignancies receiving myelosuppressive anti-cancer drugs associated with clinically significant incidence of febrile neutropenia

- CSF products have an established role in the management of patients with non-myeloid malignancies who are receiving myelosuppressive anti-cancer agents, as well as for several other uses. Many studies have shown that the prophylactic use of these products reduces the incidence, duration, and severity of febrile neutropenia, decrease the subsequent rates of infection and hospitalization, and improves the delivery of full-dose intensity chemotherapy on schedule in patients with various cancers.

- The National Comprehensive Cancer Network (NCCN) guidelines for various cancer and myeloid growth factors provides recommendations on the use of these agents. The criteria reflects these recommendations along with expert opinion.

- Regarding biosimilars, the NCCN guidelines state an FDA approved biosimilar is an appropriate substitution for its reference products.

References:

1. Aapro MS, Bohlius J, Cameron DA, et al.; European Organisation for Research and Treatment of Cancer. 2010 update of EORTC guidelines for the use of granulocyte-colony stimulating factor to reduce the incidence of chemotherapy-induced febrile neutropenia in adult patients with lymphoproliferative disorders and solid tumours. Eur J Cancer. 2011; 47 (1): 8-32.
2. Bennett CL, Djulbegovic B, Norris LB, Armitage JO. Colony-stimulating factors for febrile neutropenia during cancer therapy. N Engl J Med. 2013; 368 (12): 1131-1139.
3. Clark OA, Lyman G, Castro AA, et al. Colony stimulating factors for chemotherapy induced febrile neutropenia. Cochrane Database Sys Rev. 2003; (3): CD003039.
4. Cooper KL, Madan J, Whyte S, Stevenson MD, Akehurst RL. Granulocyte colony-stimulating factors for febrile neutropenia prophylaxis following chemotherapy: systematic review and meta-analysis. BMC Cancer. 2011; 11: 404.
5. Crawford J, Armitage J, Balducci L, et al. Myeloid growth factors. J Natl Compr Canc Netw. 2013; 11 (10): 1266-1290.
6. Crawford J, Dale DC, Lyman GH. Chemotherapy-induced neutropenia: risks, consequences, and new directions for its management. Cancer. 2004; 100 (2): 228-237.
7. Freyer G, Jovenin N, Yazbek G, et al. Granocyte-colony stimulating factor (G-CSF) has significant efficacy as secondary prophylaxis of chemotherapy-induced neutropenia in patients with solid tumors: results of a prospective study. Anticancer Res. 2013; 33 (1): 301-307.
8. Hosmer W, Malin J, Wong M. Development and validation of a prediction model for the risk of developing febrile neutropenia in the first cycle of chemotherapy among elderly patients with breast, lung, colorectal, and prostate cancer. Support Care Cancer. 2011; 19 (3): 333-341.
9. Lyman GH, Abella E, Pettengell R. Risk factors for febrile neutropenia among patients with cancer receiving chemotherapy: a systemic review. Crit Rev Oncol Hematol. 2014; 90 (3): 190-199.
10. Lyman GH, Kuderer NM, Crawford J, et al. Predicting individual risk of neutropenic complications in patients receiving cancer chemotherapy. Cancer. 2011; 117 (9): 1917-1927.
11. Manko J, Walter-Croneck A, Jawniak D, et al. A clinical comparison of the efficacy and safety of biosimilar G-CSF and originator G-CSF in haematopoietic stem cell mobilization. Pharmacol Rep. 2014; 66 (2): 239-242.
12. Mhaskhar R, Clark OA, Lyman G, et al.; Colony-stimulating factors for chemotherapy-induced febrile neutropenia. Cochrane Database Syst Rev. 2014.
13. Sasse EC, Sasse AD, Brandalise SR, et al. Colony stimulating factors for prevention of myelosuppressive therapy induced febrile neutropenia in children with acute lymphoblastic leukaemia. Cochrane Database Syst Rev. 2005; (3): CD004139.
14. Schnipper LE, Smith TJ, Raghavan D, et al. American Society of Clinical Oncology identifies five key opportunities to improve care and reduce costs: the top five list for oncology. J Clin Oncol. 2012; 30 (14): 1715-1724.
15. Smith TJ, Khatcheressian J, Lyman G, et al. 2006 update of recommendations for the use of white blood cell growth factors: an evidence-based clinical practice guideline. J Clin Oncol. 2006; 24 (19): 3187-3205. Available at: http://www.jco.org/cgi/reprint/JCO.2006.06.4451v2.pdf.
16. Smith TJ, Bohlke K, Lyman G. et al. Recommendations for the Use of WBC growth factors: American Society of Clinical Oncology Clinical Practice Guideline Update. J Clin Oncol. 2015; 33 (28): 3199-3212.
17. Womer RB, West DC, Krailo MD, et al. Randomized controlled trial of interval-compressed chemotherapy for the treatment of localized Ewing sarcoma: A report from the Children's Oncology Group. J Clin Oncol. 2012; 30 (33): 4148-4154.
18. Facts & Comparisons. Wolters Kluwer Health, Inc. Riverwoods, IL. Available at: http://online.factsandcomparisons.com. Accessed March 8, 2022.
19. National Comprehensive Cancer Network. Hematopoietic growth factors (Version 3.2024). 2024 Jan 30. Available at: https://www.nccn.org/professionals/physician_gls/pdf/growthfactors.pdf. Accessed on July 2, 2024.

Policy History		
#	Date	Change Description
3.9	Effective Date: 08/08/2024	Updated to include Nypozi and add the statement that biosimilars will be approved for all indications of the innovator product when criteria is met
3.8	Effective Date: 07/18/2024	UM medical management system update for BCBS and BCN for Nypozi
3.7	Effective Date: 04/11/2024	Updated to remove the chemotherapy intent requirement and include criteria for use in low risk febrile neutropenia
3.6	Effective Date: 04/01/2024	UM medical management system update for MAPPO and BCNA for Ryzneuta and Udenyca Onbody
3.5	Effective Date: 03/05/2024	UM medical management system update for BCBS and BCN for Udenyca Onbody
3.4	Effective Date: 02/08/2024	Updated to include Ryzneuta and Udenyca Onbody
3.3	Effective Date: 01/01/2024	UM medical management system update for BCBS and BCN for Ryzneuta
3.2	Effective Date: 04/06/2023	Updated the authorization period to aligns with FDA recommended or guideline supported treatment duration and provided for at least 60 days up to 6 months at a time
3.1	Effective Date: 03/13/2023	UM medical management system update for Fylnetra and Rolvedon for BCBSM and BCN
3.0	Effective Date: 03/01/2023	UM medical management system update for Stimufend and Rolvedon for BCNA and MAPPO
2.9	Effective Date: 02/02/2023	UM medical management system update for Stimufend for BCBSM and BCN
2.8	Effective Date: 12/19/2022	UM medical management system update for Fylnetra for BCNA and MAPPO
2.7	Effective Date: 12/01/2022	Updated to include Rolvedon
2.6	Effective Date: 11/01/2022	UM medical management system update for Releuko for BCBSM and BCN
2.5	Effective Date: 10/06/2022	Updated to include Stimufend
2.4	Effective Date: 08/08/2022	UM medical management system update for Releuko for BCNA and MAPPO
2.3	Effective Date: 08/04/2022	Updated to include Fylnetra and add additional criteria for sargramostim supported by FDA labeling
2.2	Effective Date: 04/14/2022	Updated to include Releuko
2.1	Effective Date: 08/12/2021	Annual review performed, no changes to criteria
2.0	Effective Date: 10/01/2020	UM medical management system update for Neupogen and Granix for BCBSM
1.9	Effective Date: 08/13/2020	Added Nyvepria as a new drug
1.8	Effective Date: 12/05/2019	Added Ziextenzo as a new drug
1.7	Effective Date: 05/09/2019	Update per vendor recommendations

<table>
<tr><td>1.6</td><td>Effective Date: 12/06/2018</td><td>Added Udenyca</td></tr>
<tr><td>1.5</td><td>Effective Date: 08/09/2018</td><td>Adding change in indication for Leukine and added new approved biosimilars Fulphila and Nivestym</td></tr>
<tr><td>1.4</td><td>Effective Date: 11/09/2017</td><td>Annual review performed, no changes to criteria</td></tr>
<tr><td>1.3</td><td>Effective Date: 11/10/2016</td><td>Annual review performed, no changes to criteria</td></tr>
<tr><td>1.2</td><td>Effective Date: 05/05/2016</td><td>Updated due to new indication and dose for peg-filgrastim</td></tr>
<tr><td>1.1</td><td>Effective Date: 08/13/2015</td><td>Addition of Zarxio and added new indication to Neupogen</td></tr>
<tr><td>1.0</td><td>Effective Date: 05/08/2014</td><td>New policy
<table><tr><th>Line of Business</th><th>PA Required in Medical Management System (Yes/No)</th></tr><tr><td>BCBS</td><td>No</td></tr><tr><td>BCN</td><td>No</td></tr><tr><td>MAPPO</td><td>No</td></tr><tr><td>BCNA</td><td>No</td></tr></table></td></tr>
</table>

** The prescribing information for a drug is subject to change. To ensure you are reading the most current information it is advised that you reference the most updated prescribing information by visiting the drug or manufacturer website or http://dailymed.nlm.nih.gov/dailymed/index.cfm.*