Policy Number	**RX501.134**
Policy Effective Date	**02/01/2025**
Policy End Date	**12/31/2025**

Oncologic Uses of White Blood Cell Colony Stimulating Factors

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Related Policies (if applicable)
None

Disclaimer

Medical policies are a set of written guidelines that support current standards of practice. They are based on current peer-reviewed scientific literature. A requested therapy must be proven effective for the relevant diagnosis or procedure. For drug therapy, the proposed dose, frequency and duration of therapy must be consistent with recommendations in at least one authoritative source. This medical policy is supported by FDA-approved labeling and/or nationally recognized authoritative references to major drug compendia, peer reviewed scientific literature and acceptable standards of medical practice. These references include, but are not limited to: MCG care guidelines, DrugDex (IIa level of evidence or higher), NCCN Guidelines (IIb level of evidence or higher), NCCN Compendia (IIb level of evidence or higher), professional society guidelines, and CMS coverage policy.

Carefully check state regulations and/or the member contract.

Each benefit plan, summary plan description or contract defines which services are covered, which services are excluded, and which services are subject to dollar caps or other limitations, conditions or exclusions. Members and their providers have the responsibility for consulting the member's benefit plan, summary plan description or contract to determine if there are any exclusions or other benefit limitations applicable to this service or supply. **If there is a discrepancy between a Medical Policy and a member's benefit plan, summary plan description or contract, the benefit plan, summary plan description or contract will govern.**

Legislative Mandates

EXCEPTION: New Mexico: For plans delivered, or issued for delivery or renewal on or after January 1, 2025, NMSA 1978 §59A-22B-8 (SB 135) prohibits step therapy requirements before authorizing coverage for medication approved by the U.S. Food and Drug Administration (FDA) that is prescribed for the treatment of an autoimmune disorder, cancer, or a substance use disorder, pursuant to a medical necessity determination, except in cases in which a biosimilar, interchangeable biologic or generic version is available. Any approved step therapy exception may be continued for no less than the duration of the therapeutic effect of the drug. This does not prevent a requirement of a member trying biosimilars, interchangeable biologics or generics of a prescription drug before providing coverage for the equivalent brand name prescription drug. This applies to the following: fully insured group business; Individual and Family Market plans, both on- and off-exchange; the State's Medicaid Plan; and the

mandatory coverage for IBAC plans (i.e., State of New Mexico, Public Schools Insurance Authority, Albuquerque Public Schools and the New Mexico Retiree Health Care Authority).

EXCEPTION: For HCSC members residing in the state of Ohio, § 3923.60 requires any group or individual policy (Small, Mid-Market, Large Groups, Municipalities/Counties/Schools, State Employees, Fully-Insured, PPO, HMO, POS, EPO) that covers prescription drugs to provide for the coverage of any drug approved by the U. S. Food and Drug Administration (FDA) when it is prescribed for a use recognized as safe and effective for the treatment of a given indication in one or more of the standard medical reference compendia adopted by the United States Department of Health and Human Services or in medical literature even if the FDA has not approved the drug for that indication. Medical literature support is only satisfied when safety and efficacy has been confirmed in two articles from major peer-reviewed professional medical journals that present data supporting the proposed off-label use or uses as generally safe and effective. Examples of accepted journals include, but are not limited to, Journal of American Medical Association (JAMA), New England Journal of Medicine (NEJM), and Lancet. Accepted study designs may include, but are not limited to, randomized, double blind, placebo controlled clinical trials. Evidence limited to case studies or case series is not sufficient to meet the standard of this criterion. Coverage is never required where the FDA has recognized a use to be contraindicated and coverage is not required for non-formulary drugs.

EXCEPTION: For HCSC members residing in the state of Arkansas, § 23-79-147 relating to cancer drug step therapy, requires any policy that covers prescription drugs and which provides coverage for the treatment of metastatic cancer to not limit or exclude coverage under the health benefit plan for a drug approved by the United States Food and Drug Administration that is on the prescription drug formulary of the insurance policy by mandating that a covered person with metastatic cancer undergo step therapy unless the preferred drug is consistent with best practices and have an approved indication for the treatment of metastatic cancer or associated conditions by US FDA or the National Comprehensive Cancer Network Drugs and Biologics Compendium or based on evidence-based, peer-reviewed, recognized medical literature. This applies to the following: Fully Insured Group, Student, Small Group, Mid-Market, Large Group, HMO, EPO, PPO, POS. Unless indicated by the group, this mandate or coverage will not apply to ASO groups.

Coverage

This medical policy has become inactive as of the end date above. There is no current active version and this policy is not to be used for current claims adjudication or business purposes.

See RX502.061 Oncology Medications for dates of service 01/01/2026 and after.

Continuation Therapy:
Continuation of therapy with non-preferred agents **is considered medically necessary** for all members (including new members):

- Who are currently receiving the requested medication for an indication listed below, AND
- Who are experiencing benefit from therapy as evidenced by disease stability or disease improvement; AND
- When dosing is in accordance with an authoritative source.

Initial Therapy:
Coverage for non-preferred agents will be provided contingent to the criteria in this section. For individuals initiating therapy, the following criteria would apply prior to non-preferred agent use:

- Individual has tried and failed, is intolerant to, or has a clinical contraindication to the preferred agent; AND
- Physician attests that in their clinical opinion, the same intolerance, contraindications, lack of clinical efficacy, or adverse event would not be expected to occur with non-preferred agents;

OR

- The preferred drugs are experiencing documented drug shortages or recalls from a wholesaler, manufacturer, the ASHP (American Hospital of Health-System Pharmacist) Drug Shortage web page or the US Food and Drug Administration.

State specific drug criteria my apply.

Preferred Drugs	Non-Preferred Drugs
Nivestym Zarxio	Neupogen Granix Releuko Nypozi
Fulphila Nyvepria	Neulasta Neulasta Onpro Udenyca Udenyca Onbody Ziextenzo Stimufend Fylnetra Rolvedon Ryzneuta

Additionally, coverage for Neulasta® Onpro® or **Udenyca Onbody may be considered** when the following criteria are also met:

- The individual has an inability to physically or cognitively adhere to the treatment schedule and ALL of the following:
  - Inability to self-administer the medication; AND
  - Lack of caregiver or support system for assistance with medication administration.

Primary Prophylaxis of Febrile Neutropenia
The following criteria apply to:

- Filgrastim/filgrastim biosimilars;
- Peg-filgrastim/peg-filgrastim biosimilars;
- Tbo-filgrastim;

- Eflapegrastim-xnst.

Consideration should be given to equally effective and safe alternative chemotherapy treatment options that do not require colony stimulating factor (CSF) support, when available.

One white blood cell (WBC) growth factor agent **may be considered medically necessary** for primary prophylaxis of chemotherapy-induced febrile neutropenia when **ALL** of the following are met:

1. The individual has a **non-myeloid malignancy** and is **NOT** receiving chemotherapy with radiation concurrently; AND
2. Chemotherapy intent must include ONE of the following:
    a. Curative intent (adjuvant treatment for early stage disease, for example); 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 clinically significant risk categories for febrile neutropenia (where chemotherapy risk is per Carelon Febrile Neutropenia Risk Guideline https://guidelines.carelonmedicalbenefitsmanagement.com/febrile-neutropenia-risk:
    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:
        i. Age >65;
        ii. Poor performance status (Eastern Cooperative Oncology Group [ECOG] 3 or 4, but chemotherapy still indicated);
        iii. Preexisting neutropenia, for example resulting from bone marrow damage or tumor infiltration (absolute neutrophil count [ANC] <1500mm^3);
        iv. Previous febrile neutropenia episode;
        v. Liver dysfunction, with bilirubin ≥1.0 or liver enzymes ≥2x upper limit of normal;
        vi. Presence of open wounds or active infections when chemotherapy cannot be delayed to accommodate recovery;
        vii. Renal dysfunction with creatinine clearance of less than 50 mL/min;
        viii. Poor nutritional status (baseline albumin ≤3.5 g/dL or body mass index [BMI] less than 20)
        ix. HIV (human immunodeficiency virus) infection (active) requiring ongoing antiviral therapy;
        x. High tumor volume and/or high symptom burden from disseminated or unresectable malignancy;
        xi. Multiple serious comorbid conditions in addition to the treated malignancy.

Secondary Prophylaxis of Febrile Neutropenia
The following criteria apply to:

- Filgrastim/filgrastim biosimilars;
- Peg-filgrastim/peg-filgrastim biosimilars;
- Sargramostim;
- Tbo-filgrastim;
- Eflapegrastim-xnst.

Secondary prophylaxis of febrile neutropenia **maybe considered medically necessary** 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)
The following criteria apply to:
- Filgrastim/filgrastim biosimilars;
- Peg-filgrastim/peg-filgrastim biosimilars;
- Sargramostim;
- Tbo-filgrastim;
- Eflapegrastim-xnst.

Adjunctive treatment of febrile neutropenia **may be considered medically necessary** when any of the following risk factors are present:
1. Age >65;
2. Neutrophil recovery is expected to be delayed (greater than 10 days);
3. Neutropenia is profound (less than 0.1×10^9);
4. Active pneumonia;
5. Sepsis syndrome (hypotension and/or multi-organ damage/dysfunction noted);
6. Invasive fungal or opportunistic infection;
7. Onset of fever during inpatient stay.

NOTE 1: Febrile neutropenia is defined an absolute neutrophil count (ANC) less than $1000/mm^3$ and a single temperature of >38.3° C (101° F) or a sustained temperature of ≥38° C (100.4° F) for more than one hour.

The use of multiple white blood cell (WBC) growth factor agents for prophylaxis and/or adjunctive treatment within a given chemotherapy cycle **is considered not medically necessary.**

Other Oncologic Uses for WBC Growth Factors
The following indications by growth factor type **may be considered medically necessary** when the requirements are met:

Filgrastim/filgrastim biosimilars	
Indication	**Requirements**

Acute lymphocytic leukemia (ALL)	• After start of induction or first post-remission chemotherapy course; OR • As an alternate or adjunct to donor leukocyte infusions (DLI) for relapsed disease after transplant.
Acute myeloid leukemia (AML)	• After induction, reinduction or consolidation; OR • As an alternate or adjunct to donor leukocyte infusions (DLI) for relapsed disease after transplant.
Aplastic anemia, moderate or severe	None
Hairy cell leukemia	• To treat severe neutropenia.
Hematopoietic stem cell transplant	• To promote bone marrow myeloid recovery; OR • To treat delayed or failed engraftment; OR • To mobilize stem cells for collection by pheresis.
Myelodysplastic syndrome (MDS)	• To treat recurrent infection; OR • To treat neutrophil count <500 mm^3; OR • MDS: Treatment of lower risk disease [(defined as IPSS-R (Very Low, Low, Intermediate), IPSS (Low/Intermediate-1), WPSS (Very Low, Low, Intermediate)] associated with symptomatic anemia without del(5q), with or without cytogenetic abnormalities, with serum erythropoietin ≤500 mU/mL and either of the following: ○ Ring sideroblasts ≥15% in combination with an erythropoiesis-stimulating agent (ESA); OR ○ Ring sideroblasts ≤15% in combination with lenalidomide and an ESA following no response (despite adequate iron stores) or loss of response to an iron store.
Radiation exposure	• Following radiation therapy in the absence of chemotherapy if prolonged delays are expected; OR • After accidental or intentional body irradiation of doses greater than 2 Gy (hematopoietic syndrome of acute radiation syndrome).
Support for dose dense or dose intensive chemotherapy in any of these scenarios	• Adjuvant treatment of high-risk breast cancer with combination therapy that includes anthracycline (doxorubicin or epirubicin)/cyclophosphamide followed by paclitaxel; OR • High-dose intensity methotrexate, vinblastine, doxorubicin, and cisplatin (HD-M-VAC) in urothelial cancer; OR • Chemotherapy intensification for newly diagnosed, localized Ewing sarcoma.

IPSS: International Prognostic Scoring System; IPSS-R: Revised International Prognostic Scoring System; WPSS: World Health Organization (WHO) classification-based Prognostic Scoring System (6)

Peg-filgrastim/peg-filgrastim biosimilars	
Indication	**Requirements**
Acute lymphocytic leukemia (ALL)	• After start of induction or first post-remission chemotherapy course.
Hematopoietic stem cell transplant	• To promote bone marrow myeloid recovery; OR • To treat delayed or failed engraftment.
Myelodysplastic syndrome (MDS)	• To treat recurrent infection; OR • To treat neutrophil count <500mm^3.
Radiation exposure	• After accidental or intentional body irradiation of doses greater than 2 Gy (hematopoietic syndrome of acute radiation syndrome).
Support of dose dense chemotherapy in any of these scenarios	• Adjuvant treatment of high-risk breast cancer with combination therapy that includes anthracycline (doxorubicin or epirubicin)/cyclophosphamide followed by paclitaxel; OR • High-dose intensity methotrexate, vinblastine, doxorubicin, and cisplatin (HD-M-VAC) in urothelial cancer; OR • Chemotherapy intensification for newly diagnosed, localized Ewing sarcoma.

Sargramostim	
Indication	**Requirements**
Acute lymphocytic leukemia (ALL)	• After start of induction or first post-remission chemotherapy course.
Acute myeloid leukemia (AML)	• After induction, reinduction, for individuals over 55 years of age.
Hematopoietic stem cell transplant	• To promote bone marrow myeloid recovery; OR • To treat delayed or failed engraftment; OR • To mobilize stem cells for collection by pheresis.
Myelodysplastic syndrome (MDS)	• To treat recurrent infection; OR • To treat neutrophil count <500mm^3.
Radiation exposure	• After radiation therapy in the absence of chemotherapy, if prolonged delays are expected; OR • After accidental or intentional body irradiation of doses greater than 2 Gy (hematopoietic syndrome of acute radiation syndrome).
Support for dose dense chemotherapy in any of these scenarios	• Adjuvant treatment of high-risk breast cancer with combination therapy that includes anthracycline (doxorubicin or epirubicin)/cyclophosphamide followed by paclitaxel; OR

	• High-dose intensity methotrexate, vinblastine, doxorubicin, and cisplatin (HD-M-VAC) in urothelial cancer; OR • Chemotherapy intensification for newly diagnosed, localized Ewing sarcoma.
Relapsed or refractory high-risk neuroblastoma in the bone or bone marrow	• In combination with naxitamab (Danyelza) 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. (**NOTE 2**: Included in the FDA labeling for Danyelza).

Tbo-filgrastim	
Indication	**Requirements**
Hematopoietic stem cell transplant	• To promote bone marrow myeloid recovery; OR • To treat delayed or failed engraftment; OR • To mobilize stem cells for collection by pheresis
Myelodysplastic syndrome (MDS)	• MDS: Treatment of lower risk disease [(defined as IPSS-R (Very Low, Low, Intermediate), IPSS (Low/Intermediate-1), WPSS (Very Low, Low, Intermediate)] associated with symptomatic anemia without del(5q), with or without cytogenetic abnormalities, with serum erythropoietin ≤500 mU/mL and either of the following: ○ Ring sideroblasts ≥15% in combination with an erythropoiesis-stimulating agent (ESA); OR ○ Ring sideroblasts ≤15% in combination with lenalidomide and an ESA following no response (despite adequate iron stores) or loss of response to an iron store.
Radiation exposure	• After accidental or intentional body irradiation of doses greater than 2 Gy (hematopoietic syndrome of acute radiation syndrome).

IPSS: International Prognostic Scoring System; IPSS-R: Revised International Prognostic Scoring System; WPSS: World Health Organization (WHO) classification-based Prognostic Scoring System (6)

Eflapegrastim-xnst	
Indication	**Requirements**
Not applicable (N/A)	Not applicable (N/A)

Policy Guidelines

None.

Description

Neutropenia
Neutropenia is an abnormally low level of neutrophils, a type of white blood cell, in the blood. It can be a side effect of the treatment of cancer with chemotherapy or radiation therapy. If severe, it can significantly increase the risk of life-threatening infections.

Neutrophils serve as the body's major defense against acute bacterial and fungal infections. They usually make up about 45-75% of all white blood cells; and without the key defense provided by neutrophils, people have problems controlling infections and are at risk of dying from an infection. Chemotherapy and radiation therapy can impair neutrophil production. Neutropenia is asymptomatic until infection develops. Fever is often the only indication of an infection. (1)

Leukopenia (low total white blood cell count) and granulocytopenia (reduced number of all granulocytes – neutrophils, eosinophils and basophils) are sometimes used interchangeably with neutropenia. Agranulocytosis literally means the absence of granulocytes but may be used in the literature to indicate very severe or profound neutropenia. (3)

Neutropenic Fever
Neutropenic fever is the most common and serious complication associated with hematopoietic cancers or with patients receiving chemotherapeutic regimens for cancer. In an immunocompromised state, patients lose or have weakened immunity to fend off infections, and they can encounter an infectious pathogen, leading to neutropenic fever. About 1% of patients undergoing chemotherapy and radiation experience this complication. (2)

It is defined by the U.S. Department of Health and Human Services Common Terminology Criteria for Adverse Events (CTCAE) as a single oral temperature of greater than 101°F, or a sustained temperature greater than or equal to 100.4°F for more than an hour, with an absolute neutrophilic count (ANC) of less than 1000 cells/microliter (1000/mm^3). (4)

Granulocyte Colony Stimulating Factors (G-CSF)
In an attempt to decrease infectious complications, recombinant human granulocyte colony stimulating factor (G-CSF: filgrastim and pegylated filgrastim) and granulocyte-macrophage colony stimulating factor (GM-CSF: sargramostim) have been used to reduce the duration and degree of neutropenia. (3) CSFs stimulate the stem cells in the bone marrow to produce more white blood cells which migrate into the blood and fight infection.

Also known as myeloid growth factors, G-CSFs have been evaluated for prophylactic use following the administration of chemotherapy when neutropenia is anticipated (primary prophylaxis), as well as during retreatment after a previous cycle of chemotherapy that caused neutropenic fever (secondary prophylaxis). They have also been evaluated to shorten the duration of severe chemotherapy-induced neutropenia in patients who have neutropenia

without fever (afebrile neutropenia). They are generally not recommended for routine use in patients with established fever and neutropenia. (3)

Primary Prophylaxis

Primary prophylaxis refers to the initiation of G-CSFs during the first cycle of myelosuppressive chemotherapy, with the goal of preventing neutropenic complications throughout all of the chemotherapy cycles. It may be used to decrease the incidence of neutropenic fever and need for hospitalization. Primary prophylaxis is recommended when the anticipated evidence of neutropenic fever is approximately 20% or higher with a given regimen. (3)

Secondary Prophylaxis

Secondary prophylaxis refers to the administration of a G-CSF in subsequent chemotherapy cycles after neutropenic fever has occurred in a prior cycle. A prior episode of fever during neutropenia is a risk factor for developing fever during neutropenia in later cycles, with recurrences noted in 50-60% of patients. Secondary prophylaxis reduces this risk by approximately one-half with CSFs. (3)

Eastern Cooperative Oncology Group Performance Status

The Eastern Cooperative Oncology Group performance status or ECOG are criteria used by physicians and researchers to assess how a patient's disease is progressing, assess how the disease affects the daily living abilities of the patient, and to determine appropriate treatment and prognosis. Table 1 shows the ECOG grade and status. (5)

Table 1. Eastern Cooperative Oncology Group Performance Status (ECOG)

Grade	ECOG
0	Fully active, able to carry on all pre-disease performance without restriction.
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light housework, office work.
2	Ambulatory and capable of all selfcare but unable to carry out any work activities. Up and about more than 50% of waking hours.
3	Capable of only limited selfcare, confined to bed or chair more than 50% of waking hours.
4	Completely disabled. Cannot carry out any selfcare. Totally confined to bed or chair.
5	Dead.

Scoring System for Myelodysplastic Syndrome (6)

Several factors may affect the prognosis or likely outcome of patients with myelodysplastic syndrome (MDS). These factors can help physicians determine when to start treatment and how intensive the treatment should be. The factors include:

- MDS subtype;
- Number and severity of cytopenias (low blood cell counts);
- Percent of blast cells in the bone marrow; and

- Type and number of chromosome changes.

By using these factors, doctors assign a risk score and risk group. Each prognostic factor is given a number based on its severity. A lower score can generally indicate a better outlook. The scores for all the factors are added together to create the overall risk score, which describes how fast the disease is likely to progress and is used to assign the patient to a particular risk group. The risk group is used to choose a treatment approach for the patient. Tables 2, 3, and 4 below provide the scores for each of the scoring systems; Table 5 provides the categorization for the risk groups.

There are three main prognostic scoring systems:
- IPSS (International Prognostic Scoring System);
- IPSS-R (Revised International Prognostic Scoring System);
- WPSS (WHO classification-based Prognostic Scoring System).

International Prognostic Scoring System (IPSS)
The most commonly used prognostic scoring system, IPSS uses three prognostic factors to predict the course of the patient's disease:
- The percentage of leukemic blast cells in the marrow;
- The type of chromosomal changes, if any, in the marrow cells (cytogenetics);
- The presence of one or more low blood cell counts (cytopenias).

Table 2. International Prognostic Scoring System (IPSS)

Prognostic Factors Scored	Risk Groups Based on Total Risk Score
Percent of blast cells in bone marrow • Less than 5 = 0 points • 5 to 10 = 0.5 points • 11 to 20 = 1.5 points • 21 to 30 = 2 points	• 0 points = Low • 0.5 to 1 point = Intermediate-1 • 1.5 to 2 points = Intermediate-2 • 2.5 or more points = High
Cytogenetics (chromosome changes) • None, del (5q), del (20q) = 0 points • 3 or more abnormalities, abnormal chromosome 7 = 1 point • Other abnormalities = 0.5 points	
Number of cytopenias (anemia, neutropenia or thrombocytopenia) • None or 1 = 0 points • 2 or 3 = 0.5 points	

Key: del: deletion

Revised International Prognostic Scoring System (IPSS-R)
The IPSS-R includes the same disease factors as the IPSS, but they are identified in more detail. The IPSS-R disease factors are:

- Blasts;
- Cytogenetics;
- Hemoglobin;
- Platelet count;
- Absolute neutrophil count.

Table 3. Revised International Prognostic Scoring System (IPSS-R)

Prognostic Factors Scored	Risk Groups Based on Total Risk Score
Percent of blast cells in bone marrow • Less than or equal to 2 = 0 points • Greater than 2 to less than 5 = 1 point • 5 to 10 = 2 points • Greater than 10 = 3 points	• 1.5 or less points = Very Low • 2 to 3 points = Low • 3.5 to 4.5 points = Intermediate • 5 to 6 = High • 6.5 or more points = Very High
Cytogenetics (chromosome changes) • -Y, del (11q) = 0 points • Normal, del (5q), del (12p), del(20q), double including del(5q)[a] = 1 point • del (7q), +8, +19, i(17q), any other single or double independent clone[b] = 2 points • -7, inv(3), +(3q), del(3q), double including -7/del(7q), complex: 3 abnormalities = 3 points • More than 3 abnormalities = 4 points	
Hemoglobin concentration (g/dL) • Equal to or greater than 10 = 0 points • 8 to less than 10 = 1 point • Less than 8 = 1.5 points	
Platelet count (x 10^9/L of blood) • Equal to or greater than 100 = 0 points • 50 to less than 100 = 0.5 points • Less than 50 = 1 point	
Absolute neutrophil count ([AND] x 10^9/L of blood) • Equal to or greater than 0.8 = 0 points • Less than 0.8 = 0.5 points	

Key: del: deletion; g/dL: gram/deciliter; inv: an inversion in a chromosome.

[a] del(5q) plus another cytogenetic abnormality

[b] A single clone can have many abnormalities, all of them occurring simultaneously in the same cell.

<u>World Health Organization (WHO) classification-based Prognostic Scoring System (WPSS)</u>

The WPSS is not used as often as the IPSS and IPSS-R; and differs from the other two systems in that is includes the MDS subtype as a prognostic factor. A score is also assigned based on the presence or absence of severe anemia.

Table 4. World Health Organization (WHO) classification-based Prognostic Scoring System (WPSS)

Prognostic Factors Scored	Risk Groups Based on Total Risk Score
MDS subtype • MDS-SLD, MDS-RS, MDS with isolated del(5q) = 0 points • MDS-MLD = 1 point • MDS-EB1 = 2 points • MDS-EB2 = 3 points	• 0 points = Very Low • 1 point = Low • 2 points = Intermediate • 3 to 4 points = High • 5 to 6 points = Very High
Cytogenetics (chromosome changes) • Good: normal, -Y alone, del(5q) alone, del(20q) alone = 0 points • Intermediate: other abnormalities = 1 point • Poor: 3 or more abnormalities, chromosome 7 abnormalities = 2 points	
Presence of severe anemia (hemoglobin less than 9 g/dL in men or less than 8 g/dL in women) • Absent = 0 points • Present = 1 point	

Key: del: deletion; g/dL: gram/deciliter; MDS: myelodysplastic syndrome; MDS-EB: MDS with excess blasts; MDS-MLD: MDS with multilineage dysplasia; MDS-RS: MDS with ring sideroblasts.

Risk Groups

Doctors group the patient's condition into one of two risk categories based on the scores from one of the prognostic classification systems into either a "lower-risk" or "higher-risk" category of MDS. It is important to note that the prognostic systems and risk groups do not predict how MDS will respond to treatment, but instead, how MDS is likely to behave over time without treatment. Lower-risk MDS tends to grow and progress slowly and may not cause many or even severe symptom for some time. As a result, less intensive treatment is frequently used. Higher-risk MDS is likely to progress more quickly or become acute myeloid leukemia (AML) more quickly without treatment. It may cause more symptoms and complications in a shorter amount of time, requiring more intensive treatment.

Table 5. Risk Groups

Lower-risk Groups	Higher-risk Groups

• IPSS
  ○ Low and Intermediate-1
	• IPSS
	  ○ Intermediate-2 and High

• IPSS-R
  ○ Very Low, Low, Intermediate
• WPSS
  ○ Very Low, Low, Intermediate
	• IPSS-R
	  ○ Intermediate, High, Very High
	• WPSS
	  ○ High, Very High

Key: IPSS: International Prognostic Scoring System; IPSS-R: International Prognostic Scoring System-Revised; WPSS: World Health Organization (WHO) Classification-based Prognostic Scoring System.

Regulatory Status (7)

Filgrastim

The U.S. Food and Drug Administration (FDA) initially approved filgrastim (Neupogen®) in 1991. Filgrastim 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 with fever;
- Reduce the time to neutrophil recovery and the duration of fever, following induction or consolidation chemotherapy treatment of patients with acute myeloid leukemia;
- 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 bone marrow transplantation (BMT);
- Mobilize autologous hematopoietic progenitor cells into the peripheral blood for collection by leukapheresis;
- Reduce the incidence and duration of sequelae of severe neutropenia (e.g., fever, infections, oropharyngeal ulcers) 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).

Filgrastim Biosimilars

The FDA approved filgrastim-sndz (Zarxio®) in 2015; and filgrastim-aafi (Nivestym®) in 2018 as biosimilars to filgrastim. Biosimilar means that the biological product is approved based on data demonstrating that it is highly similar to an FDA-approved biological product, known as a reference product, and that there are no clinically meaningful differences between the biosimilar product and the reference product.

These filgrastim biosimilars are 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 with fever;
- Reduce the time to neutrophil recovery and the duration of fever, following induction or consolidation chemotherapy treatment of patients with acute myeloid leukemia;

- 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 bone marrow transplantation (BMT);
- Mobilize autologous hematopoietic progenitor cells into the peripheral blood for collection by leukapheresis;
- Reduce the incidence and duration of sequelae of severe neutropenia (e.g., fever, infections, oropharyngeal ulcers) in symptomatic patients with congenital neutropenia, cyclic neutropenia, or idiopathic neutropenia.

Pegfilgrastim

The FDA initially approved pegfilgrastim (Neulasta®) in 2002. It 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;
- Increase survival in patients acutely exposed to myelosuppressive doses of radiation (Hematopoietic Syndrome of Acute Radiation Syndrome).

Pegfilgrastim biosimilars

The FDA approved pegfilgrastim-cbqv (Udenyca®) and pegfilgrastim-jmdb (Fulphila®) in 2018; pegfilgrastim-bmez (Ziextenzo®) in 2019; and pegfilgrastim-apgf (Nyvepria™) in 2020 as biosimilars to pegfilgrastim.

These pegfilgrastim biosimilars are 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.

Pegfilgrastim and pegfilgrastim biosimilars are not indicated for the mobilization of peripheral blood progenitor cells for hematopoietic stem cell transplantation.

Sargramostim

The FDA approved sargramostim (Leukine®) in 1991 for the following indications:

- To shorten time to neutrophil recovery and to reduce the incidence of severe and life-threatening infections and infections resulting in death following induction chemotherapy in adult patients 55 years and older with acute myeloid leukemia (AML);
- For the mobilization of hematopoietic progenitor cells into peripheral blood for collection by leukapheresis and autologous transplantation in adult patients;
- For the acceleration of myeloid reconstitution following autologous bone marrow or peripheral blood progenitor cell transplantation in adult and pediatric patients 2 years of age and older;
- For the acceleration of myeloid reconstitution following allogeneic bone marrow transplantation in adult and pediatric patients 2 years of age and older;

- For treatment of delayed neutrophil recovery or graft failure after autologous or allogeneic bone marrow transplantation in adult and pediatric patients 2 years of age and older;
- 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 [H-ARS]).

NOTE 3: In November 2020, the FDA approved the use of granulocyte-macrophage colony-stimulating factor (GM-CSF) in combination with Danyelza® (naxitmab-gqgk) for the treatment of pediatric patients one year of age and older, and adult patients with relapsed or refractory high-risk neuroblastoma in the bone or bone marrow who have demonstrated a partial response, minor response, or stable disease in prior therapy. This indication is approved under accelerated approval based on overall response rate and duration of response. Continued approval for this indication may be contingent upon verification and description of clinical benefit in a confirmatory trial(s). (7)

Tbo-filgrastim

Tbo-filgrastim (Granix®) was approved by the FDA in 2012 for adult and pediatric patients 1 month and older for reduction in the duration of severe neutropenia in patients with non-myeloid malignancies receiving myelosuppressive anticancer drugs associated with a clinically significant incidence of febrile neutropenia.

Eflapegrastim-xnst

Eflapegrastim-xnst (Rolvedon®) was approved by the FDA in 2022 as a leukocyte growth factor indicated 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.

Rolvedon is not indicated for the mobilization of peripheral blood progenitor cells for hematopoietic stem cell transplantation.

Rationale

This medical policy was developed in February 2021 and is based in part on the studies provided to the U.S. Food and Drug Administration (FDA) during the approval process for these agents, as well as clinical guidelines from the American Society of Clinical Oncology and the National Cancer Comprehensive Network available at the time the policy was developed. The following is a summary of the key literature through March 25, 2024.

In 2011, Cooper et al. published a systematic review and meta-analysis assessing the effectiveness of granulocyte colony-stimulating factors (G-CSFs) in reducing febrile neutropenia (FN) in adults undergoing chemotherapy for solid tumors or lymphoma. The authors reviewed twenty studies comparing primary G-CSFs with no primary G-CSF prophylaxis – five studies of pegfilgrastim; ten of filgrastim; and five of lenograstim (not found in the U.S. Food and Drug

Administration database). They found that all three G-CSFs significantly reduced febrile neutropenia incidence, with relative risks of 0.30 (95% confidence interval [CI]: 0.14 to 0.65) for pegfilgrastim, 0.57 (95% CI: 0.48 to 0.69) for filgrastim, and 0.62 (95% CI: 0.44 to 0.88) for lenograstim. Overall, the relative risk of FN for any primary G-CSF prophylaxis versus no primary G-CSF prophylaxis was 0.51 (95% CI: 0.41 to 0.62). In terms of comparisons between different G-CSFs, five studies compared pegfilgrastim with filgrastim. FN incidence was significantly lower for pegfilgrastim than filgrastim, with a relative risk of 0.66 (95% CI: 0.44 to 0.98). The authors concluded primary prophylaxis with G-CSFs significantly reduced febrile neutropenia incidence in adults undergoing chemotherapy for solid tumors or lymphoma, with pegfilgrastim reducing the incidence to a significantly greater extent than filgrastim. (8)

A Cochrane Review published in 2014 by Mhaskar et al. evaluated the safety and efficacy of adding G-CSF or GM-CSF (granulocyte-macrophage CSF) to the standard treatment of antibiotics when treating chemotherapy-induced febrile neutropenia in individuals diagnosed with cancer. Fourteen randomized controlled trials (RCTs) (15 comparisons) including a total of 1553 participants addressing the role of CSF plus antibiotics in febrile neutropenia were included. They found overall mortality was not improved by the use of CSF plus antibiotics versus antibiotics alone (hazard ratio (HR) 0.74 (95% confidence interval (CI) 0.47 to 1.16) P = 0.19; 13 RCTs; 1335 participants; low quality evidence). A similar finding was seen for infection-related mortality (HR 0.75 (95% CI 0.47 to 1.20) P = 0.23; 10 RCTs; 897 participants; low quality evidence). Individuals who received CSF plus antibiotics were less likely to be hospitalized for more than 10 days (risk ratio (RR) 0.65 (95% CI 0.44 to 0.95) P = 0.03; 8 RCTs; 1221 participants; low quality evidence) and had a greater number of participants with a faster neutrophil recovery (RR 0.52 (95% CI 0.34 to 0.81) P = 0.004; 5 RCTs; 794 participants; moderate quality evidence) than those treated with antibiotics alone. Similarly, participants receiving CSF plus antibiotics had shorter duration of neutropenia (standardized mean difference (SMD) -1.70 (95% CI -2.65 to -0.76) P = 0.0004; 9 RCTs; 1135 participants; moderate quality evidence), faster recovery from fever (SMD -0.49 (95% CI -0.90 to -0.09) P value = 0.02; 9 RCTs; 966 participants; moderate quality evidence) and shorter duration of antibiotics use (SMD -1.50 (95% CI -2.83 to -0.18) P = 0.03; 3 RCTs; 457 participants; low quality evidence) compared with participants receiving antibiotics alone. The authors concluded that the use of a CSF plus antibiotics in individuals with chemotherapy-induced febrile neutropenia had no effect on overall mortality but reduced the amount of time participants spent in hospital and improved their ability to achieve neutrophil recovery. It was not clear whether CSF plus antibiotics had an effect on infection-related mortality. Participants receiving CSFs had shorter duration of neutropenia, faster recovery from fever and shorter duration of antibiotics use. (9)

Freyer et al. designed a prospective, multicenter and observational study to describe the prophylactic strategies – cycle delay, dose-reduction, G-CSF prescription – developed to prevent the recurrence of a neutropenic event (NE), subsequently to a previous episode in patients with solid tumors, and to evaluate their respective efficacy. The study included 548 patients 18 years of age and older who had experienced an NE in a previous chemotherapy cycle (cycle A) without G-CSF support which required cycle delay and/or dose reduction and/or prescription of prophylactic G-CSF in the subsequent cycle of the same chemotherapy. Patients were followed

up to four consecutive cycles (cycles B to E). Table 6 summarizes cycle duration, incidence of NE and prophylactic strategies by cycle. (10)

Table 6. Incidence of Neutropenic Events and Its Impact on the Prophylactic Strategies by Cycle (N=548, All Cycles)

	Cycle				
	A (No prophylactic G-CSF) N=548	**B (Initiation of G-CSF) N=548**	**C N=548**	**D N=442**	**E N=344**
Cycle Duration (days)					
Mean (±SD)	24.2±7.5	20.3±4.7	20.2±4.7	19.7±5.0	19.6±5.1
Median (range)	21 (7-68)	21 (7-35)	21 (7-42	21 (5; 37)	21 (7; 37)
Neutropenic events (NE) by cycle					
Number of patients with at least one NE N (%)	548 (100)	116 (21.2)	102 (18.6)	51 (11.5)	48 (12.9)
Febrile neutropenia N (%)	88 (16.1)	3 (0.5)	4 (0.7)	0	1 (0.3)
Median duration (days) (range)	-	8 (1-10)	10 (4-13)	-	4 (4-4)
Neutropenic fever N (%)	42 (7.7)	2 (0.4)	4 (0.7)	1 (0.2)	0
Median duration (days) (range)	-	5 (4-5)	3 (1-23)	5 (5-5)	-
Median worst grade (range)	3 (1-3)	2 (1-3)	3 (3-3)	3 (3-3)	-
Neutropenia without fever (N; %)	418 (76.3)	111 (20.3)	95 (17.3)	50 (11.3)	47 (13.7)
Grade 3-4 (N; %)	264 (63.2)	45 (40.5)	23 (24.2)	13 (26.0)	9 (19.2)
Prophylactic strategies [a] (by cycle)					
Cycle delay N (%)	-	244 (44.5)	44 (8.0)	23 (5.2)	18 (5.2)
Dose reduction N (%)	-	122 (22.3)	27 (409)	17 (3.8)	12 (3.5)
% of dose reduction±SD	-	23.7±13.3	24±13.7	19.2±10.3	24.8±4.9
Prophylactic G-CSF N (%)	-	466 (85.0)	413 (75.4)	332 (75.1)	247 (71.8)
Type of G-CSF N (%)					
Pegfilgrastim	-	278 (59.7)	253 (61.3)	211 (63.6)	152 (61.5)
Filgrastim	-	48 (10.3)	39 (9.4)	30 (9.0)	22 (8.9)
Lenograstim	-	127 (27.3)	11 (26.9)	84 (25.3)	67 (27.1)
Biosimilars	-	10 (2.1)	9 (2.2)	6 (1.8)	6 (2.4)
Number of G-CSF administrations (excluded pegfilgrastim)					
Mean (±SD)	-	4.4±1.6	46.±1.5	4.5±1.6	4.6±1.5

Median (range)	-	5 (1-10)	5 (1-9)	5 (1-9)	5 (1-9)
Prophylactic antibiotics (N, %)		6 (1.1)	4 (0.7)	2 (0.5)	0

[a] Prophylactic strategy included cycle delay and/or dose reduction and/or prophylactic G-CSF.
G-CSF: granulocyte colony stimulating factors; SD: standard deviation

The authors concluded secondary G-CSF prophylaxis has significant efficacy in reducing the incidence of chemotherapy-induced neutropenic events and should be considered as a valuable option. (9)

Filgrastim (7)

Patients with Cancer Receiving Myelosuppressive Chemotherapy

The safety and efficacy of Neupogen to decrease the incidence of infection, as manifested by febrile neutropenia, in patients with non-myeloid malignancies receiving myelosuppressive anti-cancer drugs were established in a randomized, double-blind, placebo-controlled trial conducted in patients with small cell lung cancer (Study 1).

In Study 1, patients received up to 6 cycles of intravenous chemotherapy including intravenous cyclophosphamide and doxorubicin on day 1; and etoposide on days 1, 2, and 3 of 21-day cycles. Patients were randomized to receive Neupogen (n = 99) at a dose of 230 mcg/m^2 (4 to 8 mcg/kg/day) or placebo (n = 111). Study drug was administered subcutaneously daily beginning on day 4, for a maximum of 14 days. A total of 210 patients were evaluable for efficacy and 207 were evaluable for safety. The demographic and disease characteristics were balanced between arms with a median age of 62 (range 31 to 80) years; 64% males; 89% Caucasian; 72% extensive disease and 28% limited disease.

The main efficacy endpoint was the incidence of febrile neutropenia. Febrile neutropenia was defined as an absolute neutrophil count (ANC) < 1,000/mm^3 and temperature > 38.2°C. Treatment with Neupogen resulted in a clinically and statistically significant reduction in the incidence of infection, as manifested by febrile neutropenia, 40% for Neupogen-treated patients and 76% for placebo-treated patients ($p < 0.001$). There were also statistically significant reductions in the incidence and overall duration of infection manifested by febrile neutropenia; the incidence, severity and duration of severe neutropenia (ANC < 500/mm^3); the incidence and overall duration of hospital admissions; and the number of reported days of antibiotic use.

Patients with Acute Myeloid Leukemia Receiving Induction or Consolidation Chemotherapy

The safety and efficacy of Neupogen to reduce the time to neutrophil recovery and the duration of fever, following induction or consolidation chemotherapy treatment of patients with acute myeloid leukemia (AML) was established in a randomized, double-blind, placebo-controlled, multi-center trial in patients with newly diagnosed, de novo AML (Study 4).

In Study 4 the initial induction therapy consisted of intravenous daunorubicin days 1, 2, and 3; cytosine arabinoside days 1 to 7; and etoposide days 1 to 5. Patients were randomized to

receive subcutaneous Neupogen (n = 259) at a dose of 5 mcg/kg/day or placebo (n = 262) from 24 hours after the last dose of chemotherapy until neutrophil recovery (ANC ≥ 1,000/mm^3 for 3 consecutive days or ≥ 10,000/mm^3 for 1 day) or for a maximum of 35 days. The demographic and disease characteristics were balanced between arms with a median age of 54 (range 16 to 89) years; 54% males; initial white blood cell count (65% < 25,000/mm^3 and 27% > 100,000/mm^3); 29% unfavorable cytogenetics.

The main efficacy endpoint was median duration of severe neutropenia defined as neutrophil count < 500/mm^3. Treatment with Neupogen resulted in a clinically and statistically significant reduction in median number of days of severe neutropenia, Neupogen-treated patients 14 days, placebo-treated patients 19 days (p = 0.0001: difference of 5 days (95% CI: -6.0, -4.0)). There was a reduction in the median duration of intravenous antibiotic use, Neupogen-treated patients: 15 days versus placebo-treated patients: 18.5 days; a reduction in the median duration of hospitalization, Neupogen-treated patients: 20 days versus placebo-treated patients: 25 days.

There were no statistically significant differences between the Neupogen and the placebo groups in complete remission rate (69% -Neupogen, 68% -placebo), median time to progression of all randomized patients (165 days -Neupogen, 186 days -placebo), or median overall survival (380 days -Neupogen, 425 days -placebo).

Patients with Cancer Undergoing Bone Marrow Transplantation

The safety and efficacy of Neupogen to reduce the duration of neutropenia in patients with non-myeloid malignancies undergoing myeloablative chemotherapy followed by autologous bone marrow transplantation was evaluated in 2 randomized controlled trials of patients with lymphoma (Study 6 and Study 9). The safety and efficacy of Neupogen to reduce the duration of neutropenia in patients undergoing myeloablative chemotherapy followed by allogeneic bone marrow transplantation was evaluated in a randomized placebo-controlled trial (Study 10).

In Study 6, patients with Hodgkin's disease received a preparative regimen of intravenous cyclophosphamide, etoposide, and BCNU ("CVP"), and patients with non-Hodgkin's lymphoma received intravenous BCNU, etoposide, cytosine arabinoside and melphalan ("BEAM"). There were 54 patients randomized 1:1:1 to control, Neupogen 10 mcg/kg/day, and Neupogen 30 mcg/kg/day as a 24-hour continuous infusion starting 24 hours after bone marrow infusion for a maximum of 28 days. The median age was 33 (range 17 to 57) years; 56% males; 69% Hodgkin's disease and 31% non-Hodgkin's lymphoma.

The main efficacy endpoint was duration of severe neutropenia ANC < 500/mm^3. A statistically significant reduction in the median number of days of severe neutropenia (ANC < 500/mm^3) occurred in the Neupogen-treated groups versus the control group (23 days in the control group, 11 days in the 10 mcg/kg/day group, and 14 days in the 30 mcg/kg/day group [11 days in the combined treatment groups, p = 0.004]).

In Study 9, patients with Hodgkin's disease and non-Hodgkin's lymphoma received a preparative regimen of intravenous cyclophosphamide, etoposide, and BCNU ("CVP"). There were 43 evaluable patients randomized to continuous subcutaneous infusion Neupogen 10 mcg/kg/day (n = 19), Neupogen 30 mcg/kg/day (n = 10) and no treatment (n = 14) starting the day after marrow infusion for a maximum of 28 days. The median age was 33 (range 17 to 56) years; 67% males; 28% Hodgkin's disease and 72% non-Hodgkin's lymphoma.

The main efficacy endpoint was duration of severe neutropenia. There was statistically significant reduction in the median number of days of severe neutropenia (ANC < 500/mm^3) in the Neupogen-treated groups versus the control group (21.5 days in the control group versus 10 days in the Neupogen-treated groups, $p < 0.001$). The number of days of febrile neutropenia was also reduced significantly in this study (13.5 days in the control group versus 5 days in the Neupogen-treated groups, $p < 0.0001$).

In Study 10, 70 patients scheduled to undergo bone marrow transplantation for multiple underlying conditions using multiple preparative regimens were randomized to receive Neupogen 300 mcg/m^2/day (n = 33) or placebo (n = 37) days 5 through 28 after marrow infusion. The median age was 18 (range 1 to 45) years, 56% males. The underlying disease was: 67% hematologic malignancy, 24% aplastic anemia, 9% other. A statistically significant reduction in the median number of days of severe neutropenia occurred in the treated group versus the control group (19 days in the control group and 15 days in the treatment group, $p <0.001$) and time to recovery of ANC to ≥ 500/mm^3 (21 days in the control group and 16 days in the treatment group, $p < 0.001$).

<u>Patients Undergoing Autologous Peripheral Blood Progenitor Cell Collection and Therapy</u>
The safety and efficacy of Neupogen to mobilize autologous peripheral blood progenitor cells for collection by leukapheresis was supported by the experience in uncontrolled trials, and a randomized trial comparing hematopoietic stem cell rescue using Neupogen mobilized autologous peripheral blood progenitor cells to autologous bone marrow (Study 11). Patients in all these trials underwent a similar mobilization/collection regimen: Neupogen was administered for 6 to 7 days, in most cases the apheresis procedure occurred on days 5, 6, and 7. The dose of Neupogen ranged between 10 to 24 mcg/kg/day and was administered subcutaneously by injection or continuous intravenous infusion.

Engraftment was evaluated in 64 patients who underwent transplantation using Neupogen mobilized autologous hematopoietic progenitor cells in uncontrolled trials. Two of the 64 patients (3%) did not achieve the criteria for engraftment as defined by a platelet count ≥ 20,000/mm^3 by day 28. In clinical trials of Neupogen for the mobilization of hematopoietic progenitor cells, Neupogen was administered to patients at doses between 5 to 24 mcg/kg/day after reinfusion of the collected cells until a sustainable ANC (≥ 500/mm^3) was reached. The rate of engraftment of these cells in the absence of Neupogen post transplantation has not been studied.

Study 11 was a randomized, unblinded study of patients with Hodgkin's disease or non-Hodgkin's lymphoma undergoing myeloablative chemotherapy, 27 patients received Neupogen-mobilized autologous hematopoietic progenitor cells and 31 patients received autologous bone marrow. The preparative regimen was intravenous BCNU, etoposide, cytosine arabinoside and melphalan ("BEAM"). Patients received daily Neupogen 24 hours after stem cell infusion at a dose of 5 mcg/kg/day. The median age was 33 (range 1 to 59) years; 64% males; 57% Hodgkin's disease and 43% non-Hodgkin's lymphoma. The main efficacy endpoint was number of days of platelet transfusions. Patients randomized to Neupogen-mobilized autologous peripheral blood progenitor cells compared to autologous bone marrow had significantly fewer days of platelet transfusions (median 6 vs 10 days).

Patients with Severe Chronic Neutropenia

The safety and efficacy of Neupogen to reduce the incidence and duration of sequelae of neutropenia (that is fever, infections, oropharyngeal ulcers) in symptomatic adult and pediatric patients with congenital neutropenia, cyclic neutropenia, or idiopathic neutropenia was established in a randomized controlled trial conducted in patients with severe neutropenia (Study 7).

Patients eligible for Study 7 had a history of severe chronic neutropenia documented with an ANC < 500/mm^3 on three occasions during a 6-month period, or in patients with cyclic neutropenia 5 consecutive days of ANC < 500/mm^3 per cycle. In addition, patients must have experienced a clinically significant infection during the previous 12 months. Patients were randomized to a 4-month observation period followed by Neupogen treatment or immediate Neupogen treatment. The median age was 12 years (range 7 months to 76 years); 46% males; 34% idiopathic, 17% cyclic and 49% congenital neutropenia.

Neupogen was administered subcutaneously. The dose of Neupogen was determined by the category of neutropenia. Initial dose of Neupogen:

- Idiopathic neutropenia: 3.6 mcg/kg/day;
- Cyclic neutropenia: 6 mcg/kg/day;
- Congenital neutropenia: 6 mcg/kg/day divided 2 times per day.

The dose was increased incrementally to 12 mcg/kg/day divided 2 times per day if there was no response.

The main efficacy endpoint was response to Neupogen treatment. ANC response from baseline (< 500/mm^3) was defined as follows:

- Complete response: median ANC > 1,500/mm^3;
- Partial response: median ANC ≥ 500/mm^3 and ≤ 1,500/mm^3 with a minimum increase of 100%;
- No response: median ANC < 500/mm^3.

There were 112 of 123 patients who demonstrated a complete or partial response to Neupogen treatment.

Additional efficacy endpoints included a comparison between patients randomized to 4 months of observation and patients receiving Neupogen of the following parameters:

- Incidence of infection;
- Incidence of fever;
- Duration of fever;
- Incidence, duration, and severity of oropharyngeal ulcers;
- Number of days of antibiotic use.

The incidence for each of these 5 clinical parameters was lower in the Neupogen arm compared to the control arm for cohorts in each of the 3 major diagnostic categories. An analysis of variance showed no significant interaction between treatment and diagnosis, suggesting that efficacy did not differ substantially in the different diseases. Although Neupogen substantially reduced neutropenia in all patient groups, in patients with cyclic neutropenia, cycling persisted but the period of neutropenia was shortened to 1 day.

Patients Acutely Exposed to Myelosuppressive Doses of Radiation (Hematopoietic Syndrome of Acute Radiation Syndrome)

Efficacy studies of Neupogen could not be conducted in humans with acute radiation syndrome for ethical and feasibility reasons. Approval of this indication was based on efficacy studies conducted in animals and data supporting the use of Neupogen for other approved indications.

Because of the uncertainty associated with extrapolating animal efficacy data to humans, the selection of human dose for Neupogen is aimed at providing exposures to filgrastim that exceed those observed in animal efficacy studies. The 10 mcg/kg daily dose is selected for humans exposed to myelosuppressive doses of radiation because the exposure associated with such a dose is expected to exceed the exposure associated with a 10 mcg/kg dose in non-human primates. The safety of Neupogen at a daily dose of 10 mcg/kg has been assessed on the basis of clinical experience in approved indications.

The efficacy of Neupogen was studied in a randomized, blinded, placebo-controlled study in a non-human primate model of radiation injury. The planned sample size was 62 animals, but the study was stopped at the interim analysis with 46 animals because efficacy was established. Rhesus macaques were randomized to a control (n = 22) or treated (n = 24) group. Animals were exposed to total body irradiation of 7.4 ± 0.15 Gy delivered at 0.8 ± 0.03 Gy/min, representing a dose that would be lethal in 50% of animals by 60 days of follow-up (LD50/60). Starting on day 1 after irradiation, animals received daily subcutaneous injections of placebo (5% dextrose in water) or filgrastim (10 mcg/kg/day). Blinded treatment was stopped when one of the following criteria was met: ANC ≥ 1,000/mm^3 for 3 consecutive days, or ANC ≥ 10,000/mm^3 for more than 2 consecutive days within study day 1 to 5, or ANC ≥ 10,000/mm^3 any time after study day 5. Animals received medical management consisting of intravenous fluids, antibiotics, blood transfusions, and other support as required.

Filgrastim significantly (at 0.023 level of significance) reduced 60-day mortality in the irradiated non-human primates: 21% mortality (5/24) in the filgrastim group compared to 59% mortality (13/22) in the control group.

Pegfilgrastim (7)

Patients with Cancer Receiving Myelosuppressive Chemotherapy

Neulasta was evaluated in three randomized, double-blind, controlled studies. Studies 1 and 2 were active-controlled studies that employed doxorubicin 60 mg/m^2 and docetaxel 75 mg/m^2 administered every 21 days for up to 4 cycles for the treatment of metastatic breast cancer. Study 1 investigated the utility of a fixed dose of Neulasta. Study 2 employed a weight-adjusted dose. In the absence of growth factor support, similar chemotherapy regimens have been reported to result in a 100% incidence of severe neutropenia (ANC < 0.5 x 10^9/L) with a mean duration of 5 to 7 days and a 30% to 40% incidence of febrile neutropenia. Based on the correlation between the duration of severe neutropenia and the incidence of febrile neutropenia found in studies with filgrastim, duration of severe neutropenia was chosen as the primary endpoint in both studies, and the efficacy of Neulasta was demonstrated by establishing comparability to filgrastim-treated patients in the mean days of severe neutropenia.

In Study 1, 157 patients were randomized to receive a single subcutaneous injection of Neulasta (6 mg) on day 2 of each chemotherapy cycle or daily subcutaneous filgrastim (5 mcg/kg/day) beginning on day 2 of each chemotherapy cycle. In Study 2, 310 patients were randomized to receive a single subcutaneous injection of Neulasta (100 mcg/kg) on day 2 or daily subcutaneous filgrastim (5 mcg/kg/day) beginning on day 2 of each chemotherapy cycle.

Both studies met the major efficacy outcome measure of demonstrating that the mean days of severe neutropenia of Neulasta-treated patients did not exceed that of filgrastim-treated patients by more than 1 day in cycle 1 of chemotherapy. The mean days of cycle 1 severe neutropenia in Study 1 were 1.8 days in the Neulasta arm compared to 1.6 days in the filgrastim arm [difference in means 0.2 (95% CI -0.2, 0.6)] and in Study 2 were 1.7 days in the Neulasta arm compared to 1.6 days in the filgrastim arm [difference in means 0.1 (95% CI -0.2, 0.4)].

A secondary endpoint in both studies was days of severe neutropenia in cycles 2 through 4 with results similar to those for cycle 1.

Study 3 was a randomized, double-blind, placebo-controlled study that employed docetaxel 100 mg/m^2 administered every 21 days for up to 4 cycles for the treatment of metastatic or non-metastatic breast cancer. In this study, 928 patients were randomized to receive a single subcutaneous injection of Neulasta (6 mg) or placebo on day 2 of each chemotherapy cycle. Study 3 met the major trial outcome measure of demonstrating that the incidence of febrile neutropenia (defined as temperature ≥ 38.2°C and ANC ≤ 0.5 x 10^9/L) was lower for Neulasta-treated patients as compared to placebo-treated patients (1% versus 17%, respectively, $p < 0.001$). The incidence of hospitalizations (1% versus 14%) and IV anti-infective use (2% versus

10%) for the treatment of febrile neutropenia was also lower in the Neulasta-treated patients compared to the placebo-treated patients.

Study 4 was a multicenter, randomized, open-label study to evaluate the efficacy, safety, and pharmacokinetics of Neulasta in pediatric and young adult patients with sarcoma. Patients with sarcoma receiving chemotherapy age 0 to 21 years were eligible. Patients were randomized to receive subcutaneous Neulasta as a single-dose of 100 mcg/kg (n = 37) or subcutaneous filgrastim at a dose 5 mcg/kg/day (n = 6) following myelosuppressive chemotherapy. Recovery of neutrophil counts was similar in the Neulasta and filgrastim groups. The most common adverse reaction reported was bone pain.

Patients with Hematopoietic Subsyndrome of Acute Radiation Syndrome

Efficacy studies of Neulasta could not be conducted in humans with acute radiation syndrome for ethical and feasibility reasons. Approval of this indication was based on efficacy studies conducted in animals and data supporting Neulasta's effect on severe neutropenia in patients with cancer receiving myelosuppressive chemotherapy.

The recommended dose of Neulasta is two doses, 6 mg each, administered one week apart for humans exposed to myelosuppressive doses of radiation. For pediatric patients weighing less than 45 kg, dosing of Neulasta is weight based and is provided in the Dosage and Administration Table of the FDA label. This dosing regimen is based on population modeling and simulation analyses. The exposure associated with this dosing regimen is expected to provide sufficient pharmacodynamic activity to treat humans exposed to myelosuppressive doses of radiation. The safety of Neulasta at a dose of 6 mg has been assessed on the basis of clinical experience in patients with cancer receiving myelosuppressive chemotherapy.

The efficacy of Neulasta for the acute radiation syndrome setting was studied in a randomized, placebo-controlled non-human primate model of radiation injury. Rhesus macaques were randomized to either a control (n = 23) or treated (n = 23) cohort. On study day 0, animals (n = 6 to 8 per irradiation day) were exposed to total body irradiation (TBI) of 7.50 ± 0.15 Gy delivered at 0.8 ± 0.03 Gy/min, representing a dose that would be lethal in 50% of animals by 60 days of follow-up (LD50/60). Animals were administered subcutaneous injections of a blinded treatment (control article [5% dextrose in water] or pegfilgrastim [300-319 mcg/kg/day]) on study day 1 and on study day 8. The primary endpoint was survival. Animals received medical management consisting of intravenous fluids, antibiotics, blood transfusions, and other support as required.

Pegfilgrastim significantly (at 0.0014 level of significance) increased 60-day survival in irradiated non-human primates: 91% survival (21/23) in the pegfilgrastim group compared to 48% survival (11/23) in the control group.

Sargramostim (7)

Following Induction Chemotherapy for Acute Myelogenous Leukemia

The efficacy of Leukine in the treatment of AML was evaluated in a multicenter, randomized, double-blind placebo-controlled trial (study 305) of 99 newly-diagnosed adult patients, 55-70 years of age, receiving induction with or without consolidation. A combination of standard doses of daunorubicin (days 1-3) and ara-C (days 1-7) was administered during induction and high dose ara-C was administered days 1-6 as a single course of consolidation, if given. Bone marrow evaluation was performed on day 10 following induction chemotherapy. If hypoplasia with <5% blasts was not achieved, patients immediately received a second cycle of induction chemotherapy. If the bone marrow was hypoplastic with <5% blasts on day 10 or four days following the second cycle of induction chemotherapy, Leukine (250 mcg/m^2/day) or placebo was given intravenously over four hours each day, starting four days after the completion of chemotherapy. Study drug was continued until an ANC ≥1500 cells/mm^3 for three consecutive days was attained or a maximum of 42 days. Leukine or placebo was also administered after the single course of consolidation chemotherapy if delivered (ara-C 3-6 weeks after induction following neutrophil recovery). Study drug was discontinued immediately if leukemic regrowth occurred.

Leukine significantly shortened the median duration of ANC <500 cells/mm^3 by 4 days and <1000 cells/mm^3 by 7 days following induction (see Table 7). Of patients receiving Leukine, 75% achieved ANC >500 cells/mm^3 by day 16, compared to day 25 for patients receiving placebo. The proportion of patients receiving one cycle (70%) or two cycles (30%) of induction was similar in both treatment groups. Leukine significantly shortened the median times to neutrophil recovery whether one cycle (12 vs. 15 days) or two cycles (14 vs. 23 days) of induction chemotherapy was administered. Median times to platelet (>20,000 cells/mm^3) and RBC transfusion independence were not significantly different between treatment groups.

Table 7. Hematological Recovery (in Days) in Patients with AML: Induction

Dataset	**Leukine n=52[a] Median (25%, 75%)**	**Placebo n=47 Median (25%, 75%)**	**p-value[b]**
ANC>500/mm^3 [c]	13 (11, 16)	17 (13, 25)	0.009
ANC>1000/mm^3 [d]	14 (12, 18)	21 (13, 34)	0.003
PLT>20,000/mm^3 [e]	11 (7, 14)	12 (9, >42)	0.10
RBC[f]	12 (9, 24)	14 (9, 42)	0.53

[a] Patients with missing data censored.
[b] p = Generalized Wilcoxon.
[c] 2 patients on Leukine and 4 patients on placebo had missing values.
[d] 2 patients on Leukine and 3 patients on placebo had missing values.
[e] 4 patients on placebo had missing values.
[f] 3 patients on Leukine and 4 patients on placebo had missing values.
AML: Acute Myelogenous Leukemia; ANC: absolute neutrophil count; PLT: platelets; RBC: red blood cell.

During the consolidation phase of treatment, Leukine did not shorten the median time to recovery of ANC to 500 cells/mm^3 (13 days) or 1000 cells/mm^3 (14.5 days) compared to placebo. There were no significant differences in time to platelet and RBC transfusion independence.

The incidence of severe infections and deaths associated with infections was significantly reduced in patients who received Leukine. During induction or consolidation, 27 of 52 patients receiving Leukine and 35 of 47 patients receiving placebo had at least one grade 3, 4 or 5 infection (p=0.02). Twenty-five patients receiving Leukine and 30 patients receiving placebo experienced severe and fatal infections during induction only. There were significantly fewer deaths from infectious causes in the Leukine arm (3 vs. 11, p=0.02). The majority of deaths in the placebo group were associated with fungal infections with pneumonia as the primary infection.

Autologous Peripheral Blood Progenitor Cell Mobilization and Collection

A retrospective review was conducted of data from adult patients with cancer undergoing collection of peripheral blood progenitor cells (PBPC) at a single transplant center. Mobilization of PBPC and myeloid reconstitution post-transplant were compared between four groups of patients (n=196) receiving Leukine for mobilization and a historical control group who did not receive any mobilization treatment [progenitor cells collected by leukapheresis without mobilization (n=100)]. Sequential cohorts received Leukine. The cohorts differed by dose (125 or 250 mcg/m^2/day), route (IV over 24 hours or SC) and use of Leukine post-transplant. Leukaphereses were initiated for all mobilization groups after the WBC reached 10,000 cells/mm^3. Leukaphereses continued until both a minimum number of mononucleated cells (MNC) were collected (6.5 or 8.0 × 108/kg body weight) and a minimum number of aphereses (5-8) were performed. Both minimum requirements varied by treatment cohort and planned conditioning regimen. If subjects failed to reach a WBC of 10,000 cells/mm^3 by day 5, another cytokine was substituted for Leukine.

Marked mobilization effects were seen in patients administered the higher dose of Leukine (250 mcg/m^2) either IV (n=63) or SC (n=41). PBPCs from patients treated at the 250 mcg/m^2/day dose had a significantly higher number of granulocyte-macrophage colony-forming units (CFU-GM) than those collected without mobilization. The mean value after thawing was 11.41 × 104 CFU-GM/kg for all Leukine-mobilized patients, compared to 0.96 × 104/kg for the non-mobilized group. A similar difference was observed in the mean number of erythrocyte burst-forming units (BFU-E) collected (23.96 × 104/kg for patients mobilized with 250 mcg/m^2 doses of Leukine administered SC vs. 1.63 × 104/kg for non-mobilized patients).

A second retrospective review of data from patients undergoing PBPC at another single transplant center was also conducted. Leukine was given SC at 250 mcg/m^2/day once a day (n=10) or twice a day (n=21) until completion of apheresis. Apheresis was begun on day 5 of Leukine administration and continued until the targeted MNC count of 9 × 108/kg or CD34+ cell count of 1 × 106/kg was reached. There was no difference in CD34+ cell count in patients receiving Leukine once or twice a day.

Autologous Peripheral Blood Progenitor Cell and Bone Marrow Transplantation

The efficacy of Leukine to accelerate myeloid reconstitution following autologous PBPC was established in the retrospective review above. After transplantation, mobilized subjects had

shorter times to neutrophil recovery and fewer days between transplantation and the last platelet transfusion compared to non-mobilized subjects. Neutrophil recovery (ANC >500 cells/mm^3) was more rapid in patients administered Leukine following PBPC transplantation with Leukine-mobilized cells (see Table 8). Mobilized patients also had fewer days to the last platelet transfusion and last RBC transfusion, and a shorter duration of hospitalization than did non-mobilized subjects.

Table 8. ANC and Platelet Recovery after PBPC Transplantation

	Leukine Route for Mobilization	**Post-transplant Leukine**	**Median Day ANC >500 cells/mm^3**	**Median Day of Last Platelet Transfusion**
No Mobilization	-	No	29	28
Leukine 250 mcg/m^2	IV	No	21	24
	IV	Yes	12	19
	SC	Yes	12	17

PBPC: peripheral blood progenitor cells; ANC: absolute neutrophil count; IV: intravenous; SC: subcutaneous.

The efficacy of Leukine on time to myeloid reconstitution following autologous BMT was established by three single-center, randomized, placebo-controlled and double-blinded studies (studies 301, 302, and 303) in adult and pediatric patients undergoing autologous BMT for lymphoid malignancies. A total of 128 patients (65 Leukine, 63 placebo) were enrolled in these three studies. The median age was 38 years (range 3-62 years), and 12 patients were younger than 18 years of age. The majority of the patients had lymphoid malignancy (87 NHL, 17 ALL), 23 patients had Hodgkin lymphoma, and one patient had AML. In 72 patients with NHL or ALL, the bone marrow harvest was purged with one of several monoclonal antibodies prior to storage. No chemical agent was used for in vitro treatment of the bone marrow. Preparative regimens in the three studies included cyclophosphamide (total dose 120-150 mg/kg) and total body irradiation (total dose 1,200-1,575 rads). Other regimens used in patients with Hodgkin's disease and NHL without radiotherapy consisted of three or more of the following in combination (expressed as total dose): cytosine arabinoside (400 mg/m^2) and carmustine (300 mg/m^2), cyclophosphamide (140-150 mg/kg), hydroxyurea (4.5 grams/m^2), and etoposide (375-450 mg/m^2).

Compared to placebo, administration of Leukine in two studies (study 301: 44 patients, 23 patients treated with Leukine, and study 303: 47 patients, 24 treated with Leukine) significantly improved the following hematologic and clinical endpoints: time to neutrophil recovery, duration of hospitalization and infection experience or antibacterial usage. In the third study (study 302: 37 patients who underwent autologous BMT, 18 treated with Leukine) there was a positive trend toward earlier myeloid engraftment in favor of Leukine. This latter study differed from the other two in having enrolled a large number of patients with Hodgkin lymphoma who had also received extensive radiation and chemotherapy prior to harvest of autologous bone marrow. In the following combined analysis of the three studies, these two subgroups (NHL and ALL vs. Hodgkin lymphoma) are presented separately.

Patients with Lymphoid Malignancy (Non-Hodgkin's Lymphoma and Acute Lymphoblastic Leukemia)

Neutrophil recovery (ANC ≥500 cells/mm3) in 54 patients with NHL or ALL receiving Leukine on Studies 301, 302 and 303 was observed on day 18, and on day 24 in 50 patients treated with placebo (see Table 9). The median duration of hospitalization was six days shorter for the Leukine group than for the placebo group. Median duration of infectious episodes (defined as fever and neutropenia; or two positive cultures of the same organism; or fever >38°C and one positive blood culture; or clinical evidence of infection) was three days less in the group treated with Leukine. The median duration of antibacterial administration in the post transplantation period was four days shorter for the patients treated with Leukine than for placebo-treated patients.

Table 9. Autologous BMT: Combined Analysis From Placebo-Controlled Clinical Trials of Responses in Patients with NHL and ALL Median Values (days)

	ANC≥500 cells/mm^3	**ANC≥1000 cells/mm^3**	**Duration of Hospitalization**	**Duration of Infection**	**Duration of Antibacterial Therapy**
Leukine N=54	1[a,b]	24[a,b]	25 [a]	1[a]	21[a]
Placebo N=50	24	32	31	4	25

[a] p<0.05 Wilcoxon or Cochran-Mantel-Haenszel RIDIT chi-squared.

[b] p<0.05 Log rank.

BMT: bone marrow transplant; NHL: Non-Hodgkin's Lymphoma; ALL: acute lymphoblastic leukemia. ANC: absolute neutrophil count.

Allogeneic Bone Marrow Transplantation

A multicenter, randomized, placebo-controlled, and double-blinded study (study 9002) was conducted to evaluate the safety and efficacy of Leukine for promoting hematopoietic reconstitution following allogeneic BMT. A total of 109 adult and pediatric patients (53 Leukine, 56 placebo) were enrolled in the study. The median age was 34.7 years (range 2.2- 65.1 years). Twenty-three patients (11 Leukine, 12 placebo) were 18 years old or younger. Sixty-seven patients had myeloid malignancies (33 AML, 34 CML), 17 had lymphoid malignancies (12 ALL, 5 NHL), three patients had Hodgkin's disease, six had multiple myeloma, nine had myelodysplastic disease, and seven patients had aplastic anemia. In 22 patients at one of the seven study sites, bone marrow harvests were depleted of T cells. Preparative regimens included cyclophosphamide, busulfan, cytosine arabinoside, etoposide, methotrexate, corticosteroids, and asparaginase. Some patients also received total body, splenic, or testicular irradiation. Primary GVHD prophylaxis was cyclosporine and a corticosteroid.

Accelerated myeloid engraftment was associated with significant laboratory and clinical benefits. Compared to placebo, administration of Leukine significantly improved the following:

time to neutrophil engraftment, duration of hospitalization, number of patients with bacteremia, and overall incidence of infection (see Table 10).

Table 10. Allogeneic BMT: Analysis of Data from Placebo-Controlled Clinical Trial Median Values (days or number of patients)

	ANC≥500/mm^3	ANC≥1000/mm^3	Number of Patients with Infections	Number of Patients with Bacteremia	Days of Hospitalization
Leukine N=53	13[a]	14[a]	30[a]	9[b]	25[a]
Placebo N=56	17	19	42	19	26

[a] p<0.05 generalized Wilcoxon test.
[b] p<0.05 simple chi-square test.
BMT: bone marrow transplant; ANC: absolute neutrophil count.

Median time to myeloid recovery (ANC ≥500 cells/mm^3) in 53 patients receiving Leukine was 4 four days less than in 56 patients treated with placebo (see Table 10). The numbers of patients with bacteremia and infection were significantly lower in the Leukine group compared to the placebo group (9/53 versus 19/56 and 30/53 versus 42/56, respectively). There were a number of secondary laboratory and clinical endpoints. Of these, only the incidence of severe (grade 3/4) mucositis was significantly improved in the Leukine group (4/53) compared to the placebo group (16/56) at p<0.05. Leukine-treated patients also had a shorter median duration of posttransplant IV antibiotic infusions, and a shorter median number of days to last platelet and RBC transfusions compared to placebo patients, but none of these differences reached statistical significance.

<u>Treatment of Delayed Neutrophil Recovery or Graft Failure After Allogeneic or Autologous Bone Marrow Transplantation</u>

A historically-controlled study (study 501) was conducted in patients experiencing graft failure following allogeneic or autologous BMT to determine whether Leukine improved survival after BMT failure.

Three categories of patients were eligible for this study:

1. Patients displaying a delay in neutrophil recovery (ANC ≤100 cells/mm^3 by day 28 post transplantation);
2. Patients displaying a delay in neutrophil recovery (ANC ≤100 cells/mm^3 by day 21 post transplantation) and who had evidence of an active infection; and
3. Patients who lost their marrow graft after a transient neutrophil recovery (manifested by an average of ANC ≥500 cells/mm^3 for at least one week followed by loss of engraftment with ANC <500 cells/mm^3 for at least one week beyond day 21 post transplantation).

A total of 140 eligible adult and pediatric patients from 35 institutions were treated with Leukine and evaluated in comparison to 103 historical control patients from a single institution. One hundred sixty-three patients had lymphoid or myeloid leukemia, 24 patients had NHL, 19 patients had Hodgkin's disease and 37 patients had other diseases, such as aplastic anemia, myelodysplasia or non-hematologic malignancy. The majority of patients (223 out of 243) had received prior chemotherapy with or without radiotherapy and/or immunotherapy prior to preparation for transplantation. The median age of enrolled patients was 27 years (range 1-66 years). Thirty-seven patients were younger than 18 years of age.

One-hundred-day survival was improved in favor of the patients treated with Leukine for graft failure following either autologous or allogeneic BMT. In addition, the median survival was improved by greater than two-fold. The median survival of patients treated with Leukine after autologous failure was 474 days versus 161 days for the historical patients. Similarly, after allogeneic failure, the median survival was 97 days with Leukine treatment and 35 days for the historical controls. Improvement in survival was better in patients with fewer impaired organs. The Multiple Organ Failure (MOF) score is a clinical and laboratory assessment of seven major organ systems: cardiovascular, respiratory, gastrointestinal, hematologic, renal, hepatic and neurologic. Median survival by MOF category is presented in Table 11.

Table 11. Median Survival by Multiple Organ Failure (MOF) Category Median Survival (days)

	MOF≤2 Organs	**MOF≥2 Organs**	**MOF (Composite of Both Groups)**
Autologous BMT			
Leukine	474 (n=58)	78.5 (n=10)	474 (n=68)
Historical	165 (n=14)	39 (n=3)	161 (n=17)
Allogeneic BMT			
Leukine	174 (n=50)	27 (n=22)	97 (n=72)
Historical	52.5 (n=60)	15.5 (n=26)	35 (n=86)

BMT: bone marrow transplantation

Acute Exposure to Myelosuppressive Doses of Radiation (H-ARS)

Efficacy studies of Leukine could not be conducted in humans with acute radiation syndrome for ethical and feasibility reasons. The use of Leukine in the H-ARS indication was based on efficacy studies conducted in animals and data supporting Leukine's effect on severe neutropenia in patients undergoing autologous or allogeneic BMT following myelosuppressive chemotherapy with or without total body irradiation, and in patients with acute myelogenous leukemia following myelosuppressive chemotherapy.

The recommended dose of Leukine for adults exposed to myelosuppressive doses of radiation is 7 mcg/kg as a single daily SC injection. The 7 mcg/kg dosing regimen is based on population modeling and simulation analyses. The sargramostim exposure associated with the 7 mcg/kg adult dose is expected to be higher than sargramostim exposure in the nonclinical efficacy study and therefore are expected to provide sufficient pharmacodynamic activity to treat humans exposed to myelosuppressive doses of radiation. The safety of Leukine at a dose of 250

mcg/m^2/day (approximately 7 mcg/kg) has been assessed on the basis of clinical experience in myeloid reconstitution in patients after autologous or allogeneic BMT, and in patients with AML.

The efficacy of Leukine was studied in a randomized, blinded, placebo-controlled study in a nonhuman primate model of radiation injury. Rhesus macaques (50% male) were randomized to a control (n = 36) or treated (n = 36) group. Animals were exposed to total body irradiation at a dose that would be lethal in 50% to 60% of animals (655 cGy) by day 60 post irradiation (lethal dose $[LD]_{50\text{-}60/60}$). Starting 48 ± 1 hour after irradiation, animals received daily SC injections of placebo (sterile water for injection, USP) or Leukine (7 mcg/kg/day). Blinded treatment was stopped when one of the following criteria was met: ANC ≥1,000 cells/mm^3 for 3 consecutive days or if the ANC ≥10,000 cells/mm^3. Animals received minimal supportive care that included a prophylactic antibiotic, antiemetic, analgesics and parenteral fluids. No whole blood, blood products or individualized antibiotics were provided.

Leukine significantly (p=0.0018) increased survival at day 60 in irradiated nonhuman primates: 78% survival (28/36) in the Leukine group compared to 42% survival (15/36) in the control group.

In the same study, an exploratory cohort of 36 rhesus macaques randomized to control (n=18) or treated (n=18) was exposed to total body irradiation at a dose that would be lethal in 70-80% of animals (713 cGY) by day 60 post irradiation. Leukine increased survival at day 60 in irradiated nonhuman primates: 61% survival (11/18) in the Leukine group compared to 17% survival (3/18) in the control group.

Tbo-filgrastim (7)
The efficacy of Granix was evaluated in a multinational, multicenter, randomized and controlled Phase 3 study in 348 chemotherapy-naive patients with high-risk stage II, stage III, or stage IV breast cancer receiving doxorubicin (60 mg/m^2) and docetaxel (75 mg/m^2) comparing Granix to placebo and a non-US-approved filgrastim product as controls. The median age of the patients was 50 years (range 25 to 75 years) with 99% female and 86% Caucasian.

Granix, placebo, and the non-US-approved filgrastim product were administered at 5 mcg/kg subcutaneously once daily beginning one day after chemotherapy for at least five days and continued to a maximum of 14 days or until an ANC of ≥10,000 x 106/L after nadir was reached.

Granix was superior to placebo in duration of severe neutropenia (DSN) with a statistically significant reduction in DSN (1.1 days vs. 3.8 days, $p < 0.0001$).

Eflapegrastim-xnst (7)
The efficacy of Rolvedon to decrease the incidence of infection, as manifested by febrile neutropenia, in patients with nonmyeloid malignancies receiving myelosuppressive anti-cancer drugs was evaluated in two 1:1 randomized, open-label, active-controlled non-inferiority studies of similar design (Study 1 [NCT02643420] and Study 2 [NCT02953340]) that enrolled a

total of 643 patients with early-stage breast cancer. (5) Docetaxel 75 mg/m2 and cyclophosphamide 600 mg/m2 (TC) were administered intravenously every 21 days (on Day 1 of each cycle) for up to 4 cycles. A fixed dose of Rolvedon 13.2 mg/0.6 mL or pegfilgrastim (6 mg/0.6 mL) was administered subcutaneously on Day 2 of each cycle after TC chemotherapy.

The median age of patients enrolled in the two randomized studies was 60 years (Range: 24 to 88), the majority of patients were female (>99%), 77% were White and 12% were Black or African American.

Study 1 enrolled 406 patients; 196 patients to the Rolvedon arm and 210 patients to the pegfilgrastim arm. Study 2 enrolled 237 patients; 118 patients to the Rolvedon arm and 119 patients to the pegfilgrastim arm. Efficacy for both trials was based on the duration of severe neutropenia (DSN) in Cycle 1.

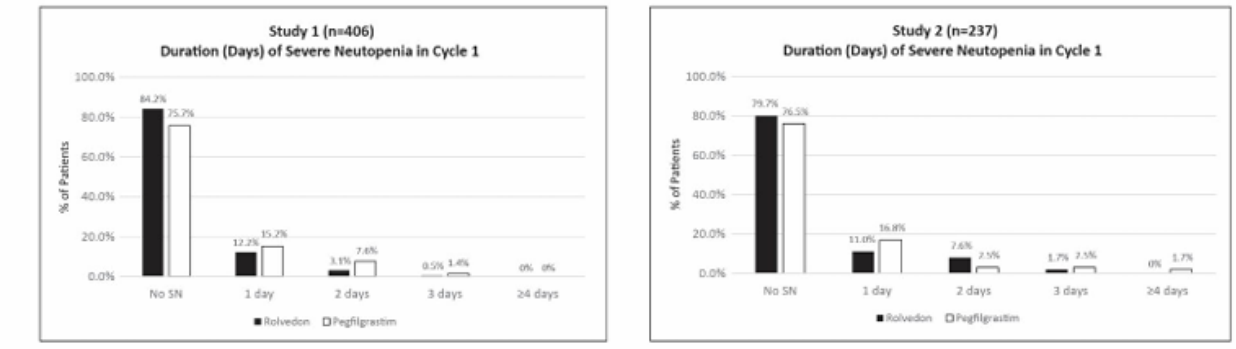
Efficacy results are shown in Table 2. In both studies, Rolvedon was non-inferior to pegfilgrastim. The distributions of the severe neutropenia events in percentage from Cycle 1 for Study 1 and Study 2 are presented in Figure 1.

Table 12. Duration of Severe Neutropenia (DSN) in Cycle 1 (Study 1 and Study 2)

	Study 1		**Study 2**	
	Rolvedon (n=196)	Pegfilgrastim (n=210)	Rolvedon (n-118)	Pegfilgrastim (n=119)
Mean DSN (SD) (Days)	0.20(0.503)	0.35(0.683)	0.31(0.688)	0.39(0.949)
Median DSN (Range) (Days)	0 (0, 3)	0 (0, 3)	0 (0, 3)	0 (0, 7)
Difference in DSN (Days)	-0.148		-0.073	
*95% Confidence Interval[a]	-0.265, -0.033		-0.292, 0.129	

[a]Confidence intervals were obtained using 2.5 percentile and 97.5 percentile of the 100,000 bootstrap samples with treatment as stratification factor.
*The non-inferiority of Rolvedon to pegfilgrastim was to be declared if the upper bound of 95% CI of the difference in mean DSN between the treatment arms was <0.62 days.

Figure 1. Duration of Severe Neutropenia (DSN) by Day in Cycle 1 (Study 1 and Study 2)



Summary of Evidence

Based on the review of literature as well as the studies provided to the U.S. Food and Drug Administration (FDA) for approval, the colony stimulating factors listed in this policy are considered medically necessary for the indications mentioned in the coverage statement for primary prophylaxis, secondary prophylaxis and adjunctive treatment of febrile neutropenia (FN). These agents may be considered medically necessary for other specific indications as stated in the coverage. The use of multiple white blood cell (WBC) growth factor agents for prophylaxis and/or adjunctive treatment within a given chemotherapy cycle is considered not medically necessary.

Professional Guidelines and Position Statements

European Organization for Research and Treatment of Cancer (EORTC)

In 2010 the EORTC updated their 2006 guidelines on the use of granulocyte-colony stimulating factors (G-CSFs) in adult cancer patients at risk of chemotherapy-induced febrile neutropenia. (11)

Recommendation 1: Patient-related risk factors should be evaluated in the overall assessment of febrile neutropenia (FN) risk before administering each cycle of chemotherapy. Particular consideration should be given to the elevated risk of FN for elderly patients (aged 65 and over). Other adverse risk factors that may influence FN risk include advanced stage of disease; experience of previous episode(s) of FN; lack of G-CSF use and absence of antibiotic prophylaxis. However, please note that the indiscriminate use of antibiotic prophylaxis for patients undergoing treatment for solid tumours or lymphoma is not recommended either by this working party or the EORTC Infectious Disease Group. Recommendation grade: B.

Recommendation 2: Consideration should be given to the elevated risk of FN when using certain chemotherapy regimens. Recommendation grade: A/B (depending on the evidence for each chemotherapy regimen).

Recommendation 3:

- In situations where dose-dense or dose-intense chemotherapy strategies have survival benefits, prophylactic G-CSF should be used as a supportive treatment. Recommendation grade: A.
- If reductions in chemotherapy dose intensity or density are known to be associated with a poor prognosis, primary G-CSF prophylaxis should be used to maintain chemotherapy. Examples of this could be when the patient is receiving adjuvant or potentially curative treatment or when the treatment intent is to prolong survival. Recommendation grade A.
- Where treatment intent is palliative, use of less myelosuppressive chemotherapy or dose/schedule modification should be considered. Recommendation grade: B.

Recommendation 4: The risk of complications related to FN should be assessed individually for each patient at the beginning of each cycle. When assessing FN risk, the clinician should take into account patient-related risk factors (recommendation 1), the chemotherapy regimen and associated complications (recommendations 2 and 3) and treatment intent (recommendation 3). Prophylactic G-CSF is recommended when there is a P20% overall risk of FN. When chemotherapy regimens associated with an FN risk of 10–20%, particular attention should be given to the assessment of patient characteristics that may increase the overall risk of FN. Recommendation grade: A.

Recommendation 5: Treatment with G-CSF for patients with solid tumours and malignant lymphoma and ongoing FN is indicated only in special situations. These are limited to those patients who are not responding to appropriate antibiotic management and who are developing life-threatening infectious complications (such as severe sepsis or septic shock). Recommendation grade: B.

Recommendation 6: Filgrastim, lenograstim and pegfilgrastim have clinical efficacy and we recommend the use of any of these agents, according to current administration guidelines, to prevent FN and FN-related complications, where indicated. Filgrastim biosimilars are now also a treatment option in Europe. Recommendation grade: A.

National Comprehensive Cancer Network

Table 13 includes the recommendations for administration of colony stimulating factors from the National Comprehensive Cancer Network (NCCN) along with their corresponding category of evidence. (12)

Table 13. Hematopoietic Growth Factors

Agent	Recommendation	Category of Evidence
Filgrastim	Prophylaxis of chemotherapy-induced febrile neutropenia or other dose-limiting neutropenic events in high-risk (>20% overall risk of febrile neutropenia) patients with solid tumors and non-myeloid malignancies receiving treatment in the curative/adjuvant or palliative settings.	1

	Consider for prophylaxis of chemotherapy-induced febrile neutropenia or other dose-limiting neutropenic events in intermediate-risk (10% to 20% overall risk of febrile neutropenia) patients with solid tumors and non-myeloid malignancies receiving treatment in the curative/adjuvant or palliative settings who have one or more patient risk factors.	2A
	Treatment of chemotherapy-induced febrile neutropenia: • In patients who have been receiving prophylactic filgrastim. • Consider in patients who have not received prophylactic granulocyte colony-stimulating factors but who have risk factors for an infection-associated complication.	2A
	• Treatment for patients with radiation-induced myelosuppression following a radiological/nuclear incident (hematopoietic acute radiation syndrome [H-ARS]).	2A
	Used in hematopoietic cell transplant for: • Mobilization of hematopoietic progenitor cells in the autologous setting as a single agent, following combination chemotherapy, or in combination with sargramostim. • Mobilization of hematopoietic progenitor cells in combination with plerixafor in the autologous setting for patients with non-Hodgkin lymphoma or multiple myeloma mobilization of donor hematopoietic progenitor cells or for granulocyte transfusion in the allogeneic setting. • Supportive care in the posttransplant setting.	2A for all others 2B in combination with sargramostim
Pegfilgrastim	Prophylaxis of chemotherapy-induced febrile neutropenia or other dose-limiting neutropenic events in high-risk (>20% overall risk of febrile neutropenia) patients with solid tumors and non-myeloid malignancies receiving treatment in the curative/adjuvant or palliative settings.	1
	Consider for prophylaxis of chemotherapy-induced febrile neutropenia or other dose-limiting neutropenic events in intermediate-risk (10% to 20% overall risk of febrile neutropenia) patients with solid tumors and non-myeloid malignancies receiving treatment in the curative/adjuvant or palliative settings who have one or more patient risk factors.	2A

	Treatment for patients with radiation-induced myelosuppression following a radiological/nuclear incident (hematopoietic acute radiation syndrome [H-ARS]).	2A
	Used for supportive care post autologous hematopoietic cell transplant.	2A
Sargramostim	Consider for treatment of chemotherapy-induced febrile neutropenia in patients who have not received prophylactic granulocyte colony-stimulating factors but who have risk factors for an infection-associated complication.	2A
	Treatment for patients with radiation-induced myelosuppression following a radiological/nuclear incident (hematopoietic acute radiation syndrome [H-ARS]).	2A
	Used in hematopoietic cell transplant for mobilization of hematopoietic progenitor cells in combination with filgrastim or biosimilars in the autologous setting.	2A
Tbo-filgrastim	Prophylaxis of chemotherapy-induced febrile neutropenia or other dose-limiting neutropenic events in high-risk (>20% overall risk of febrile neutropenia) patients with solid tumors and non-myeloid malignancies receiving treatment in the curative/adjuvant or palliative settings.	1
	Consider for prophylaxis of chemotherapy-induced febrile neutropenia or other dose-limiting neutropenic events in intermediate-risk (10% to 20% overall risk of febrile neutropenia) patients with solid tumors and non-myeloid malignancies receiving treatment in the curative/adjuvant or palliative settings who have one or more patient risk factors.	2A
	Treatment of chemotherapy-induced febrile neutropenia: • In patients who have been receiving prophylactic tbo-filgrastim. • Consider in patients who have not received prophylactic granulocyte colony-stimulating factors but who have risk factors for an infection-associated complication.	2A
	Treatment for patients with radiation-induced myelosuppression following a radiological/nuclear incident (hematopoietic acute radiation syndrome [H-ARS]).	2A
	Used in hematopoietic cell transplant for: • Mobilization of hematopoietic progenitor cells in the autologous setting as a single agent or following combination chemotherapy. • Mobilization of hematopoietic progenitor cells in combination with plerixafor in the autologous setting	2A for all others 2B for mobilization of donor hematopoietic

	for patients with non-Hodgkin lymphoma or multiple myeloma • Mobilization of donor hematopoietic progenitor cells or for granulocyte transfusion in the allogeneic setting • Supportive care in the posttransplant setting.	progenitor cells or granulocyte transfusion in the allogeneic setting
Eflapegrastim-xnst	Prophylaxis of chemotherapy-induced febrile neutropenia or other dose-limiting neutropenic events in high-risk (>20% overall risk of febrile neutropenia) patients with solid tumors and non-myeloid malignancies receiving treatment in the curative/adjuvant or palliative settings.	1 for use of G-CSFs in the high-risk setting 2A for use of eflapegrastim-xnst
	Consider for prophylaxis of chemotherapy-induced febrile neutropenia or other dose-limiting neutropenic events in intermediate-risk (10% to 20% overall risk of febrile neutropenia) patients with solid tumors and non-myeloid malignancies receiving treatment in the curative/adjuvant or palliative settings who have one or more patient risk factors.	2A
	Consider for prophylaxis of chemotherapy-induced febrile neutropenia or other dose-limiting neutropenic events in low-risk (<10% overall risk of febrile neutropenia) patients with solid tumors and non-myeloid malignancies receiving treatment in the curative/adjuvant or palliative settings who have 2 or more patient-related risk factors. Use of granulocyte colony-stimulating factors in this setting is based on clinical judgment.	2A
	Treatment for patients with radiation-induced myelosuppression following a radiologic/nuclear incident (hematopoietic acute radiation syndrome [H-ARS]).	2A

American Society of Clinical Oncology

In 2015, the American Society of Clinical Oncology (ASCO) reviewed and updated their 2006 guidelines on the use of hematopoietic colony-stimulating factors (CSFs). (13)

- Primary prophylaxis with a CSF starting with the first cycle and continuing through subsequent cycles of chemotherapy is recommended in patients who have an approximately 20% or higher risk for febrile neutropenia based on patient-, disease- and treatment-related factors. Primary CSF prophylaxis should also be administered in patients receiving dose-dense chemotherapy when considered appropriate. Consideration should be given to alternative, equally effective, and safe chemotherapy regimens not requiring CSF

support when available. (Type: evidence based, benefits outweigh harms. Evidence quality: high. Strength of recommendation: strong.)

- Secondary prophylaxis with a CSF is recommended for patients who experienced a neutropenic complication from a prior cycle of chemotherapy (for which primary prophylaxis was not received), in which a reduced dose or treatment delay may compromise disease-free or overall survival or treatment outcome. In many clinical situations, dose reduction or delay may be a reasonable alternative. (Type: evidence based, benefits outweigh harms. Evidence quality: high. Strength of recommendation: strong.)
- CSFs should not be routinely used for patients with neutropenia who are afebrile. (Type: evidence based, benefits outweigh harms. Evidence quality: high. Strength of recommendation: strong.)
- CSFs should not be routinely used as adjunctive treatment with antibiotic therapy for patients with fever and neutropenia. However, CSFs should be considered in patients with fever and neutropenia who are at high risk for infection-associated complications or who have prognostic factors predictive of poor clinical outcomes. (Type: evidence based, benefits outweigh harms. Evidence quality: high. Strength of recommendation: strong.)
- Dose-dense regimens with CSF support should only be used if supported by convincing efficacy data or within an appropriately designed clinical trial. Efficacy data support the use of dose-dense chemotherapy in the adjuvant treatment of high-risk breast cancer and the use of high-dose intensity methotrexate, vinblastine, doxorubicin, and cisplatin in urothelial cancer. There are limited and conflicting data on the value of dose-dense regimens with CSF support in non- Hodgkin lymphoma, and it cannot routinely be recommended at this time. (Type: evidence based, benefits outweigh harms. Evidence quality: high for breast cancer and lymphoma; intermediate for urothelial cancer. Strength of recommendation: strong for breast cancer and lymphoma; moderate for urothelial cancer.)
- CSFs may be used alone, after chemotherapy, or in combination with plerixafor to mobilize peripheral-blood progenitor cells. Choice of mobilization strategy depends in part on type of cancer and type of transplantation. (Type: evidence based, benefits outweigh harms. Evidence quality: strong. Strength of recommendation: high.)
- CSFs should be administered after autologous stem-cell transplantation to reduce the duration of severe neutropenia. (Type: evidence based, benefits outweigh harms. Evidence quality: high. Strength of recommendation: strong.)
- CSFs may be administered after allogeneic stem-cell transplantation to reduce the duration of severe neutropenia. (Type: evidence based. Evidence quality: low. Strength of recommendation: weak).
- Prophylactic CSFs for patients with diffuse aggressive lymphoma age ≥ 65 years treated with curative chemotherapy (cyclophosphamide, doxorubicin, vincristine, prednisone, and rituximab) should be considered, particularly in the presence of comorbidities. (Type: evidence based, benefits outweigh harms. Evidence quality: intermediate. Strength of recommendation: moderate.)
- The use of CSFs in pediatric patients will almost always be guided by clinical protocols. As in adults, the use of CSFs is reasonable as primary prophylaxis for pediatric patients with a high likelihood of febrile neutropenia. Similarly, the use of CSFs for secondary prophylaxis or

for therapy should be limited to high-risk patients. (Type: evidence based, benefits outweigh harms. Evidence quality: high. Strength of recommendation: strong.)

- For pediatric indications in which dose-intense chemotherapy is known to have a survival benefit, such as Ewing sarcoma, CSFs should be used to enable the administration of these regimens. (Type: evidence based, benefits outweigh harms. Evidence quality: high. Strength of recommendation: strong.)
- CSFs should not be used in pediatric patients with non-relapsed acute lymphoblastic leukemia or non-relapsed acute myeloid leukemia who do not have an infection. (Type: informal consensus. Evidence quality: intermediate. Strength of recommendation: moderate.)
- Pegfilgrastim, filgrastim, tbo-filgrastim, and filgrastim-sndz (and other biosimilars, as they become available) can be used for the prevention of treatment-related febrile neutropenia. The choice of agent depends on convenience, cost, and clinical situation. There have been no additional data comparing granulocyte CSFs and granulocyte-macrophage CSFs since the 2006 update; therefore, there is no change in the recommendation regarding their therapeutic equivalency. (Type: evidence based, benefits outweigh harms. Evidence quality: high. Strength of recommendation: strong.)
- Current recommendations for the management of patients exposed to lethal doses of total-body radiotherapy, but not doses high enough to lead to certain death resulting from injury to other organs, include the prompt administration of CSFs or pegylated granulocyte CSFs. (Type: formal consensus [by others], benefits outweigh harms. Evidence quality: intermediate. Strength of recommendation: moderate.)

The Update Committee did not provide recommendations regarding the use of CSFs in adult patients with acute myeloid leukemia or myelodysplastic syndromes.

Coding

Procedure codes on Medical Policy documents are included **only** as a general reference tool for each policy. **They may not be all-inclusive.**

The presence or absence of procedure, service, supply, or device codes in a Medical Policy document has no relevance for determination of benefit coverage for members or reimbursement for providers. **Only the written coverage position in a Medical Policy should be used for such determinations.**

Benefit coverage determinations based on written Medical Policy coverage positions must include review of the member's benefit contract or Summary Plan Description (SPD) for defined coverage vs. non-coverage, benefit exclusions, and benefit limitations such as dollar or duration caps.

CPT Codes	96377
HCPCS Codes	C9173, C9399, J1442, J1447, J1449, J2506, J2820, J3490, J3590, J9999, Q5101, Q5108, Q5110, Q5111, Q5120, Q5122, Q5125, Q5127, Q5130, Q5148, [Deleted 10/2022: C9096]

*Current Procedural Terminology (CPT®) ©2024 American Medical Association: Chicago, IL.

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Centers for Medicare and Medicaid Services (CMS)

The information contained in this section is for informational purposes only. HCSC makes no representation as to the accuracy of this information. It is not to be used for claims adjudication for HCSC Plans.

The Centers for Medicare and Medicaid Services (CMS) does not have a national Medicare coverage position. Coverage may be subject to local carrier discretion.

A national coverage position for Medicare may have been developed since this medical policy document was written. See Medicare's National Coverage at <https://www.cms.hhs.gov>.

Policy History/Revision

Date	Description of Change
12/31/2025	Document became inactive.
02/01/2025	Document updated. The following change was made to Coverage: Added language regarding drug shortages/recalls to “Initial Therapy” criteria. No new references added.
01/01/2025	Document updated. The following change was made to Coverage: Revised preferred/non-preferred drug table.
12/01/2024	Document updated with literature review. Criteria for Udenyca Onbody added to coverage. No new references added; others updated.
07/01/2024	Document updated. The following change was made to Coverage: Added Udenyca Onbody and Ryzneuta to list of non-preferred drugs. No new references added.
06/01/2024	Document updated. The following change was made to Continuation Therapy in Coverage: removed “through a previously authorized pharmacy or medical benefit” in the statement “Continuation therapy with non-preferred agents is considered medically necessary for all members (including new members)…” No new references added.
11/01/2023	Document updated with literature review. The following changes were made to Coverage: 1) Added Stimufend, Fulnetra, and Rolvendon to list of non-

	preferred drugs; and 2) Added conditional coverage for eflapegrastim-xnst. References updated; no new references added.
08/01/2022	Document updated with preferred drug criteria included.
10/1/2021	New medical document. Primary prophylaxis, secondary prophylaxis and adjunctive treatment of febrile neutropenia, as well as other oncologic uses of white blood cell colony stimulating factors filgrastim and biosimilars, peg-filgrastim and biosimilars, sargramostim, and tbo-filgrastim may be considered medically necessary as outlined in the Coverage. The use of multiple white blood cell (WBC) growth factor agents for prophylaxis and/or adjunctive treatment within a given chemotherapy cycle is considered not medically necessary.