



CIGNA PHARMACY COVERAGE POLICY

The following Coverage Policy applies to all plans administered by CIGNA Companies including plans administered by Great-West Healthcare, which is now a part of CIGNA.

Subject Granulocyte Colony Stimulating Factor Therapy [Filgrastim (Neupogen®), Pegfilgrastim (Neulasta®)]

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Table of Contents

Coverage Policy	1
General Background	2
Coding/Billing Information	6
References	6
Policy History.....	8

Hyperlink to Related Coverage Policies

INSTRUCTIONS FOR USE

Coverage Policies are intended to provide guidance in interpreting certain **standard** CIGNA HealthCare benefit plans as well as benefit plans formerly administered by Great-West Healthcare. Please note, the terms of a participant's particular benefit plan document [Group Service Agreement (GSA), Evidence of Coverage, Certificate of Coverage, Summary Plan Description (SPD) or similar plan document] may differ significantly from the standard benefit plans upon which these Coverage Policies are based. For example, a participant's benefit plan document may contain a specific exclusion related to a topic addressed in a Coverage Policy. In the event of a conflict, a participant's benefit plan document **always supercedes** the information in the Coverage Policies. In the absence of a controlling federal or state coverage mandate, benefits are ultimately determined by the terms of the applicable benefit plan document. Coverage determinations in each specific instance require consideration of 1) the terms of the applicable group benefit plan document in effect on the date of service; 2) any applicable laws/regulations; 3) any relevant collateral source materials including Coverage Policies and; 4) the specific facts of the particular situation. Coverage Policies relate exclusively to the administration of health benefit plans. Coverage Policies are not recommendations for treatment and should never be used as treatment guidelines. Proprietary information of CIGNA. Copyright ©2011 CIGNA

Coverage Policy

CIGNA covers granulocyte colony stimulating factor therapy [filgrastim (Neupogen®), pegfilgrastim (Neulasta®)] as medically necessary for ANY of the of the following indications when the associated criteria are met:

- primary prophylaxis of febrile neutropenia (FN) for **EITHER** of the following:
 - individual receiving myelosuppressive chemotherapy that results in an FN rate of 20% or higher
 - individual receiving non-myelosuppressive chemotherapy who is at increased risk for FN or infection, regardless of the anticipated FN rate due to **ANY** of the following (this list may not be all-inclusive):
 - age greater than 65 years
 - poor performance status
 - previous episodes of FN
 - extensive prior chemotherapy or radiation treatment
 - cytopenias due to bone marrow involvement by tumor
 - poor nutritional status
 - presence of open wounds or active infections
 - presence of more advanced cancer
 - other serious comorbidities

- secondary prophylaxis of febrile neutropenia (FN) for **ANY** of the following:
 - febrile neutropenia from a prior cycle of chemotherapy for which primary prophylaxis was not received
 - individuals for whom chemotherapy dose reduction as an alternative means of preventing febrile neutropenia is not a viable option
 - when prolonged neutropenia is creating delay in chemotherapy treatment
- febrile, neutropenic individual with **ANY** of the following indications:
 - expected prolonged (> 10 days) and profound (absolute neutrophil count < 0.1 x 10⁹/L) neutropenia
 - age > 65 years
 - uncontrolled primary disease
 - pneumonia
 - hypotension
 - multi-organ dysfunction (sepsis syndrome)
 - invasive fungal infection
 - development of fever while hospitalized
- individual with acute myeloid leukemia (AML) receiving induction chemotherapy
- individual with acute lymphoblastic leukemia (ALL) after completion of the first few days of chemotherapy of the initial induction or first post-remission course
- intermittent use in myelodysplastic syndromes for severe neutropenia [absolute neutrophil count (ANC) < 500 per microliter (µL) or recurrent infections]
- radiation therapy alone when prolonged delays in treatment secondary to neutropenia are anticipated
- individual age 65 and older with lymphoma treated with chemotherapy [e.g. CHOP (cyclophosphamide, doxorubicin, vincristine, prednisone) or more aggressive regimens]
- treatment for radiation injury at doses of 3–10 Grays (Gy) or above
- **Filgrastim (Neupogen[®]) for ANY of the following when the associated criteria are met:**
 - individual with acute myeloid leukemia (AML) receiving consolidation chemotherapy
 - as an adjunct to progenitor cell-transplantation to mobilize peripheral-blood progenitor-cells (PBPC) often in conjunction with chemotherapy after autologous (but not allogenic) transplantation
 - individual who has undergone allogeneic or autologous BMT in whom engraftment is delayed or has failed, in the presence or absence of infection
 - treatment of myeloid engraftment following hematopoietic stem cell transplantation
 - treatment of severe chronic neutropenia, including congenital neutropenia (Kostmann's syndrome), idiopathic neutropenia, and cyclic neutropenia
 - HIV and/or AIDs associated neutropenia secondary to the disease itself, infection with opportunistic organisms, or antiretroviral agents
 - drug-induced neutropenia
 - aplastic anemia, hairy cell leukemia, congenital agranulocytosis, or Alloimmune Neonatal neutropenia

When coverage is available and medically necessary, the dosage, frequency, site of administration, and duration of therapy should be reasonable, clinically appropriate, and supported by evidence-based literature and adjusted based upon severity, alternative available treatments, and previous response to Granulocyte Colony Stimulating Factor Therapy [Filgrastim (Neupogen[®]), Pegfilgrastim (Neulasta[®])] therapy.

FDA Approved Indications

Neupogen:

- decrease the incidence of infection in cancer patients receiving myelosuppressive chemotherapy
- reducing the time to neutrophil recovery and the duration of fever patients with Acute Myeloid Leukemia receiving induction or consolidation chemotherapy
- reduce the duration of neutropenia and neutropenia-related clinical sequelae, eg, febrile neutropenia, in patients with nonmyeloid malignancies undergoing myeloablative chemotherapy followed by marrow transplantation
- for mobilization of hematopoietic progenitor cells into the peripheral blood for collection by leukapheresis in patients undergoing peripheral blood progenitor cell collection and therapy
- for chronic administration to reduce the incidence and duration of sequelae of neutropenia (eg, fever, infections, oropharyngeal ulcers) in symptomatic patients with congenital neutropenia, cyclic neutropenia, or idiopathic neutropenia

Neulasta

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

FDA Recommended Dosing

Neupogen

- Cancer patients receiving myelosuppressive chemotherapy: Recommended starting dose is 5 mcg/kg/day
- Cancer patients receiving bone marrow transplant: 10 mcg/kg/day given as an intravenous (IV) infusion of 4 or 24 hours, or as a continuous 24-hour subcutaneous (SC) infusion
- Peripheral blood progenitor cell collection and therapy in cancer patients: 10 mcg/kg/day SC, either as a bolus or a continuous infusion.
- Congenital Neutropenia: Recommended daily starting dose is 6 mcg/kg BID SC every day
- Idiopathic or cyclic neutropenia: Recommended daily starting dose is 5 mcg/kg as a single injection SC every day

Neulasta

A single subcutaneous injection of 6 mg administered once per chemotherapy cycle. It should be administered at least 24 hours after completion of chemotherapy cycle administration, and at least 14 days before the next chemotherapy cycle begins.

Drug Availability

Neupogen

Vials available in single-dose, preservative-free vials containing 300 mcg (1 mL) of Filgrastim (300 mcg/mL) in dispensing packs of 10 and single-dose, preservative-free vials containing 480 mcg (1.6 mL) of Filgrastim (300 mcg/mL) in dispensing packs of 10.

Prefilled syringes in single-dose, preservative-free, prefilled syringes containing 300 mcg (0.5 mL) of Filgrastim (600 mcg/mL) in dispensing packs of 10 and single-dose, preservative-free containing 480 mcg (0.8 mL) of Filgrastim (600 mcg/mL) in dispensing packs of 10.

Neulasta

Neulasta is supplied in a prefilled single use syringe containing 6 mg pegfilgrastim.

General Background

Pharmacology

Granulocyte colony stimulating factors (G-CSF), such as filgrastim, are an important part of modern cancer treatment. Filgrastim is the active moiety in pegfilgrastim and, as such, the two entities share the same mechanism of action. Both agents act by increasing neutrophil production and enhancing end-cell function.

Pegfilgrastim is a covalent conjugate of filgrastim and polyethylene glycol. Pegylation of filgrastim extends the drug's half-life and duration of action. Consequently, pegfilgrastim requires less frequent dosing than filgrastim. The presence of neutrophil progenitor cells is necessary for pegfilgrastim therapy to be efficacious at normal doses. The CD34+ cell count is a common indicator of the number of peripheral blood progenitor cells available. In general, patients who have received prolonged chemotherapy or excessive radiation have lower levels of progenitor cells and are less likely to respond favorably to pegfilgrastim therapy.

Guidelines

The following recommendations are based on the American Society of Clinical Oncology (ASCO) 2006 update of recommendations for the use of white blood cell growth factors, an evidence-based clinical practice guideline (Smith, 2006), published in the Journal of Clinical Oncology. These recommendations should be followed in most cases; however, they cannot always account for individual variation among patients. They are not intended to replace physician judgment with respect to particular patients or special clinical situations.

Accepted off-label indications for filgrastim (Neupogen) listed in compendia, American Society of Health-Systems Pharmacists (AHFS), 2009 include: Myeloid engraftment following BMT failure or delay, Myeloid engraftment following hematopoietic stem cell transplant, Neutropenia associated with AIDS, severe chronic neutropenia, including congenital neutropenia (Kostmann's syndrome), idiopathic neutropenia, and cyclic neutropenia, Myelodysplastic syndromes, moderate to severe aplastic anemia, hairy cell leukemia, congenital agranulocytosis, and drug-induced neutropenia.

Clinical Efficacy

The clinical effects of pegfilgrastim and filgrastim in patients receiving myelosuppressive chemotherapy were demonstrated in two published trials and four abstracts. In these trials, various doses of pegfilgrastim were compared to a standard 5 mcg/kg daily dose of filgrastim. Absolute neutrophil count (ANC) at nadir, peak ANC, incidence of severe neutropenia, mean duration of severe neutropenia, incidence of febrile neutropenia, and time to ANC recovery were among the parameters examined in these trials. At pegfilgrastim doses similar to those recommended in the product labeling, its efficacy with regard to these parameters was similar to filgrastim.

Primary Prophylaxis of Febrile Neutropenia (FN)

Primary prophylaxis with CSFs is recommended and essential for the prevention of FN in patients who have a high risk of FN based on age, medical history, disease characteristics, and myelotoxicity of the chemotherapy regimen. Based on the new clinical trial data in patients treated with myelosuppressive chemotherapy regimens, the use of CSFs, when the risk of FN is in the range of approximately 20% or higher, have been proven to be effective and are recommended.

High-risk patients treated with non-myelosuppressive chemotherapy may have potential risk factors for febrile neutropenia or infection because of bone marrow compromise or comorbidity. In such situations, primary prophylaxis with CSF is often appropriate even with regimens with FN rates less than 20%. Certain clinical factors predispose to increased complications from prolonged neutropenia, including: patient age greater than 65 years; poor performance status; previous episodes of FN; extensive prior treatment, including large radiation ports; administration of combined chemoradiotherapy; cytopenias due to bone marrow involvement by tumor; poor nutritional status; the presence of open wounds or active infections; more advanced cancer, as well as other serious comorbidities.

Secondary Prophylaxis of Febrile Neutropenia

CSFs are recommended as secondary prophylaxis in patients who experienced a neutropenic complication from a prior cycle of chemotherapy for which primary prophylaxis was not received, and a reduced dose may compromise disease-free or overall survival or treatment outcome. However, it should be noted that in many clinical situations, dose reduction or delay may be a reasonable alternative.

Therapeutic Use of CSF in Afebrile or Febrile, Neutropenic Patients

To date, there are no supportive published data that pertain to the use of CSF in patients who are afebrile and neutropenic. Therefore, CSFs should not be routinely used for patients with neutropenia who are afebrile.

Although CSF should not be routinely used as adjunctive treatment with antibiotic therapy for patients with fever and neutropenia; however, they are recommended in patients with fever and neutropenia who are at high risk for infection-associated complications, or who have prognostic factors that are predictive of poor clinical outcomes. High-risk factors include expected prolonged, meaning greater than 10 days, and profound, meaning less than $0.1 \times 10^9/L$, neutropenia, age greater than 65 years, uncontrolled primary disease, pneumonia, hypotension and multiorgan dysfunction (sepsis syndrome), invasive fungal infection, or being hospitalized at the time of the development of fever.

As Adjunct to Progenitor Cell Transplantation

The use of some CSFs (e.g. filgrastim) to mobilize peripheral blood progenitor cells (PBPC) and to shorten the period of neutropenia after cytoreduction and PBPC transplantation, is well established.

Filgrastim has FDA-approved indication for the mobilization of hematopoietic progenitor cells into the peripheral blood for collection by leukapheresis, and pegfilgrastim is being investigated in the setting of peripheral blood progenitor cells (PBPC) mobilization. The current standard of care is to use CSFs as adjunct to progenitor-cell transplantation to mobilize PBPC, often in conjunction with chemotherapy after autologous, but not allogenic, transplantation.

Acute Myeloid Leukemia (AML)

Several studies have shown the efficacy of CSF which can produce variable and modest decreases in the duration of neutropenia when begun shortly after completion of the initial induction chemotherapy. Because of the potential reduction in the incidence of infection and eliminating the likelihood of hospitalization, CSF use is recommended after the completion of consolidation chemotherapy in some patients receiving intensive post-remission chemotherapy. To date, the use of longer acting, pegylated CSFs for consolidation chemotherapy has not been studied and is not recommended outside clinical trials. In addition, the use of CSFs for priming of leukemia cells in patients with AML is not recommended.

Acute Lymphocytic Leukemia (ALL)

To shorten the duration of neutropenia in these patients, CSFs are recommended after the completion of the initial first few days of chemotherapy of the initial induction or first post-remission course. G-CSF can be given with the continued corticosteroid/antimetabolite therapy, without evidence that such concurrent therapy prolongs the myelosuppressive effects of the chemotherapy.

The expected efficacy of CSFs in patients with refractory or relapsed myeloid leukemia is only a few days of shortened neutropenia, and generally the use of CSFs in these patients should be used with caution, or not at all. Because the AML patients with relapsed or refractory disease have a very low response rate, and since there is concern that CSFs may stimulate the tumor cells to grow, it would be difficult to determine whether the persistence of leukemia after chemotherapy is due to a drug resistance or a stimulatory effect of the CSF.

Myelodysplastic Syndromes (MDS)

The long-term continuous use of CSFs in patients with MDS has not been established; however, it has been shown that CSFs can increase the absolute neutrophil count in neutropenic MDS patients. Therefore, the intermittent administration of CSFs may be considered in a subset of patients with severe neutropenia and recurrent infection. According to the American Cancer Society, an absolute neutrophil count (ANC) lower than 500 per microliter (μL) is considered severe neutropenia.

Radiotherapy With or Without Concurrent Chemotherapy

Patients receiving concomitant chemotherapy and radiation therapy should not be treated with CSFs. However, CSFs may be considered in patients receiving radiation therapy alone, if prolonged delays secondary to neutropenia are expected. To date, no studies have been published to support the use of CSFs in patients receiving concomitant chemotherapy and radiation therapy.

Older Patients With Lymphoma

Several studies have shown that the risk of neutropenia following chemotherapy increases with age. In addition, the mortality rate resulting from neutropenic infections is also higher for older patients with lymphoma. Several prospective studies of combination chemotherapy similar to CHOP (cyclophosphamide, doxorubicin, vincristine, prednisone) in patients aged 60 and older have reported an incidence of neutropenic infections between 27–47%. Therefore, the prophylactic CSF is recommended in patients with lymphoma aged 65 and older treated with chemotherapy (CHOP or more aggressive regimens) to reduce the incidence of FN and infections.

Pediatric Population

Similar to recommendations for adults, the use of CSF in pediatric patients is for the primary prophylaxis of FN, and the secondary prophylaxis should be limited to high-risk patients. However, the use of CSF in children with ALL should be considered carefully since the prognosis in children with ALL is excellent, but there is a potential of recurrence of myeloid leukemia or myelodysplastic syndrome due to CSF therapy.

Radiation Injury

Current ASCO recommendations for the management of patients exposed to lethal doses of total body radiotherapy or accidental total body radiation include the administration of CSF or pegylated G-CSF. Total body radiation leads to probable or certain death from bone marrow failure at doses of 3–10 Grays (Gy) without supportive care, CSFs, and/or a bone marrow transplant. No prospective randomized trials have been conducted to determine the benefit of hematopoietic growth factors in humans exposed to accidental or intentional radiation injury. This recommendation is based on observation of cases in the Radiation Emergency Assistance Center Training Site in the Radiation Accident Registry Center.

Patients weighing 45 kg or more should receive pegfilgrastim 6 mg once per chemotherapy cycle. Pegfilgrastim is not recommended for patients weighing less than 45 kg. Pegfilgrastim should be administered at least 24 hours after completion of chemotherapy cycle administration, and at least 14 days before the next chemotherapy cycle begins.

Coding/Billing Information

Note: This list of codes may not be all-inclusive.

Covered when medically necessary:

HCPCS Codes	Description
J1440	Injection, filgrastim (G-CSF), 300 mcg
J1441	Injection, filgrastim (G-CSF), 480 mcg
J2505	Injection, pegfilgrastim, 6 mg

ICD-9-CM Diagnosis Codes	Description
140.0-209.75	Malignant neoplasms
238.72-238.75	Myelodysplastic syndromes
260-269	Nutritional deficiencies
284.9	Aplastic anemia, unspecified
288.00	Neutropenia, unspecified
288.01	Congenital neutropenia
288.02	Cyclic neutropenia
288.03	Drug-induced neutropenia
288.04	Neutropenia due to infection
288.09	Other neutropenia

References

1. Amgen, Inc. Neulasta (pegfilgrastim) product information. Thousand Oaks, CA: Amgen Inc. November 2008.

2. Amgen, Inc. Neupogen® (filgrastim) product information. Thousand Oaks, CA: Amgen Inc. September 2007.
3. Crawford J, Garst J, Lee M, et al. A phase II multicycle trial of pegfilgrastim compared to filgrastim after myelosuppressive chemotherapy. {Abstract}. Proceedings of International Association for the Study of Lung Cancer, 9th world conference, Sep 2000.
4. Green M, Koelbl H, Baselga J, et al. A randomized, double-blind, phase 3 study evaluating fixed dose, breast cancer. {Abstract 90}. Proceedings of American Society of Clinical Oncology, 37th annual meeting, May 2001.
5. Holmes F, Jones S, O'shaughnessy J, et al. A single dose of pegfilgrastim is as effective as daily filgrastim to reduce the duration of severe, chemotherapy-induced neutropenia. {Abstract 191} Proceedings of American Society of Clinical Oncology, 36th annual meeting, May 2000.
6. Holmes F, Jones S, O'shaughnessy J, et al. Once-per-cycle pegylated filgrastim (SD/01) is as effective and safe as daily filgrastim in reducing chemotherapy-induced neutropenia over multiple cycles of therapy. {Abstract 355}. Proceedings of San Antonio Breast Cancer Symposium, 23rd annual meeting, Dec 2000.
7. Holmes F, O'Shaughnessy J, Vukelja S, et al. Blinded, randomized, multicenter study to evaluate single administration pegfilgrastim once per cycle versus daily filgrastim as an adjunct to chemotherapy in patients with high-risk stage II or stage III/IV breast cancer. *J Clin Oncol* 2002; 20:727-31.
8. Jansen J, Thompson J, Dugan M, et al. Peripheral blood progenitor cell transplantation. *Ther Apher* 2002;6:5-14.
9. Johnston E, Crawford J, Blackwell S, et al. Randomized, dose-escalation study of SD/01 compared with daily filgrastim in patients receiving chemotherapy. *J Clin Oncol* 2000;18:2522-2528.
10. Malcolm M. Colony-stimulating factors. In: Rich RR, Fleisher TA, Shearer WT, Kotzin BL, Schroeger HW, eds. *Clinical Immunology Principles and Practice* 2nd Edition. London. Mosby International Limited, 2001:114.
11. AHFS 2009 Drug Information. Bethesda, MD: American Society of Health-Systems Pharmacists, Inc; 2009.
12. Molineux G, Kinstler O, Briddell B, et al. A new form of filgrastim with sustained duration in vivo and enhanced ability to mobilize PBPC in both mice and humans. *Exp Hematol* 1999;27:1724-1734.
13. Smith TJ, Khatcheressian J, Lyman GH, et al. 2006 update of recommendations for the use of white blood cell growth factors: An evidence-based clinical practice guideline. *Clin Oncol*. 2006;24(19):3187-3205. Available at: <http://www.jco.org/cgi/reprint/JCO.2006.06.4451v2.pdf>. Accessed February, 2006.
14. Vose J, Crump M, Lazarus H, et al. Single dose pegfilgrastim is as effective as daily filgrastim following ESHAP chemotherapy for subjects with Non-Hodgkin's Lymphoma or Hodgkin's Disease: results of a randomized, open-label study. {Abstract 3322}. *Blood* 2001;98:799a.
15. Welte K, Gahrilove J, Bronchud M, Platzer E, Morstyn G. Filgrastim (r-metHuG-CSF): the first 10 years. *Blood* 1996;88:1907-29.
16. Yang B, Lum P, Renwick J et al. Pharmacokinetic rationale for a fixed-dose regimen of a sustained duration Hematology, 2000.

Policy History

Pre-Merger Organizations	Last Review Date	Policy Number	Title
CIGNA HealthCare Great-West Healthcare	4/15/2008	4033	Granulocyte Colony Stimulating Factor Therapy

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