Criteria For Non-formulary Use of Pegfilgrastim (Neulasta™)

VHA Pharmacy Benefits Management Strategic Healthcare Group and
the Medical Advisory Panel

These criteria were based on the best clinical evidence currently available. The recommendations in this document are dynamic, and will be revised as new clinical information becomes available. These guidelines are intended to assist practitioners in providing consistent, high quality, cost effective drug therapy. They are not intended to interfere with clinical judgment; the clinician must ultimately decide the course of therapy based on individual patient situations.

1. Pegfilgrastim was approved in January of 2002 to decrease the incidence of infection that manifests as febrile neutropenia in patients with non-myeloid malignancies receiving myelosuppressive chemotherapy that is associated with a significant incidence of febrile neutropenia**.**

Criteria for VA Use

Patients with non-myeloid malignancies receiving myelosuppressive chemotherapy likely to cause neutropenic fever, as outlined in the ASCO guidelines for the use of hematopoietic colony-stimulating factors and endorsed by the IDSA*, who are unable to self inject and require a home-health nurse or other practitioner to administer growth factor injections and who have limited accessibility to medical care.

AND

Use is restricted to chemotherapy cycles that are at least 21 days in length or longer. Pegfilgrastim should **NOT** be administered in the period 14 days before and 24 hours after administration of myelosuppressive chemotherapy.

AND

Patients should not have allergies to *E. coli*-derived proteins, pegfilgrastim, filgrastim, or any component of the drug product.

*ASCO guideline summary (http://www.asco.org/asco/ascoMainConstructor/1,47468,_12|002130,00.asp see 2000 update)

1. Primary Prophylactic CSF Administration: Reserved for patients expected to experience febrile neutropenia at least as often or greater than control groups in clinical trials (expected incidence of ≥40%). For the majority of untreated patients receiving most standard chemotherapy regimens, primary prophylaxis is not recommended. Patients who are at high risk for febrile neutropenia (pre-existing neutropenia due to disease, extensive prior chemotherapy, irradiation to large masses of bone marrow like the pelvis, a history of recurrent febrile neutropenia with earlier chemotherapy of similar or less intensity, poor performance status and more advanced cancer, decreased immune function, open wounds, or active tissue infection) should be evaluated individually for prophylactic treatment with CSF.

2. Secondary Prophylactic CSF Administration (administration of CSF in subsequent cycles after the development of febrile neutropenia): In the absence of clinical data supporting maintenance of dose intensity (e.g., potentially curable tumors), physicians should consider dose reduction after febrile neutropenia or prolonged neutropenia in previous cycles rather than the use of G-CSF.

3. Established Neutropenia
   Afebrile: CSF should not be routinely used in patients with neutropenia who are afebrile.

   Febrile: CSF should not be routinely used in the adjunct therapy of uncomplicated febrile neutropenia (<10 days duration, no evidence of pneumonia, cellulitis, abscess, sinusitis, hypotension, multiorgan dysfunction, invasive fungal infection, or uncontrolled malignancy). Although benefit has not been confirmed, G-CSF may be considered for use in high-risk patients. High-risk factors include the presence of profound neutropenia, i.e. ANC< 100/µl, multiorgan dysfunction, hypotension, pneumonia, and invasive fungal infection. In addition, age >65 years old and post-treatment lymphopenia may also be considered as high risk factors).

4. CSF to increase Dose Intensity: No justification for the use of CSF to increase dose-intensity outside of a clinical trial.

5. While the use of pegfilgrastim has not been studied in peripheral blood stem cell transplantation, myelodysplastic syndrome, acute myelogenous leukemia, or acute lymphoblastic leukemia the use of G-CSF has been studied and is a reasonable alternative. Those patients who cannot self inject should be evaluated on a case-by-case basis.

2. Dosage

Pegfilgrastim is approved for use as a single 6mg subcutaneous injection given once per cycle. It should not be administered in the period 14 days before and 24 hours after chemotherapy administration. In clinical trials, pegfilgrastim was administered on day 2 of the chemotherapy cycle, 24 hours after administration of chemotherapy. Use in patients weighing less than 45 kg has not been studied.

3. Safety

Warnings:

Splenic Rupture: Rare cases have been reported with the parent compound, filgrastim, and some were fatal. Pegfilgrastim has not been studied in PBPC mobilization and should not be used for this indication.

Adult Respiratory Distress Syndrome (ARDS): ARDS has been reported in neutropenic adults with sepsis receiving filgrastim. If patients develop fever, lung infiltrates or respiratory distress while on pegfilgrastim, they should be evaluated for ARDS and pegfilgrastim should be discontinued.

Sickle Cell Disease: Severe sickle cell crisis has been reported in sickle cell patients receiving filgrastim; one was fatal. Pegfilgrastim should be used with caution in this population.

The use of pegfilgrastim has not been studied in patients receiving radiation therapy.

The use of pegfilgrastim with chemotherapy drugs that cause delayed myelosuppression has not been studied.
Adverse Effects:

The most common adverse reactions reported in clinical trials were most likely attributed to the underlying disease or chemotherapy and included: nausea, fatigue, alopecia, diarrhea, vomiting, constipation, fever, anorexia, skeletal pain, headache, taste perversion, dyspepsia, myalgia, insomnia, abdominal pain, arthralgia, generalized weakness, peripheral edema, dizziness, granulocytopenia, stomatitis, mucositis, and neutropenic fever. The most common adverse event attributed to pegfilgrastim was bone pain reported in 26%. In addition, reversible elevations in LDH, alkaline phosphatase, and uric acid were observed but did not require intervention.

4. Summary of Clinical Trials

Published Trials

- In a dose-finding study in lung cancer patients, pegfilgrastim produced dose dependent increases in the absolute neutrophil count (ANC). A dose of pegfilgrastim of 100 mcg/kg produced maximum ANC results similar to the standard filgrastim 5 mcg/kg/day.
- In two randomized trials, pegfilgrastim was compared to filgrastim in women with breast cancer receiving chemotherapy (doxorubicin and docetaxel). One study was a dose-finding study comparing pegfilgrastim 30, 60, and 100mcg/kg, and one used a fixed dose of 100mcg/kg.

	Pegfilgrastim 100mcg/kg (N=46) (dose-finding study)	Filgrastim 5mg/kg (N=25)		Pegfilgrastim 100mcg/kg (N=149)	Filgrastim 5mcg/kg (N=147)
Duration of gr IV neutropenia, Cycle 1	1.3 days	1.6 days		1.7 days	1.8 days
Duration of gr IV neutropenia, Cycle 2 Cycle 3 Cycle 4	 <3 <3 <3	 <3 <3 <3		 0.9 (p=0.001) 0.9 (p<0.001) 1.2 (p<0.025)	 1.1 1.2 1.3
Febrile neutropenia incidence Cycle 1 Cycles 1-4	 7% 11%	 4% 12%		 7% 9% (p=0.029)	 12% 18%
Time to ANC recovery Cycle 1	9.5 days	9.4 days		9.3 days	9.7 days

References

Johnston E, Crawford J, Blackwell S, Bjurstrom T, Lockbaum P, Roskos L, et al. Randomized, dose-escalation study of SD/01 compared with daily filgrastim in patients receiving chemotherapy. J Clin Oncol 2000;18:2522-2528.

Holmes FA, O'Shaughnessy JA, Vukelja S, Jones SE, Shogan J, Savin M, 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;20:727-731.

Holmes FA, Jones Se, O'Shaughnbessy J, Vukelja S, George T, Savin M, et al. Comparable efficacy and safety profiles of once-per-cycle pegfilgrastim and daily injection filgrastim in chemotherapy-induced neutropenia: a multicenter dose-finding study in women with breast cancer. Ann Oncol 2002;13:903-909.

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