

Bon Secours Richmond
Pharmacy & Therapeutics Committees
Pegfilgrastim (Neulasta™)
September 2002

Recommendations: (MEC Approved)

- Pegfilgrastim (Neulasta™) is not suggested for addition to the formulary. It lacks adequate additional benefit for the hospitalized individual as compared to filgrastim (Neupogen®) and is much more expensive.
- An automatic substitution with filgrastim (Neupogen®) 5mcg/kg/day, rounded to the closest vial size (300 mcg or 480 mcg) is recommended when pegfilgrastim (Neulasta™) is ordered.

Findings:

- Pegfilgrastim (Neulasta™) and filgrastim (Neupogen®) are colony stimulating factors which have the same mechanism of action. They are FDA approved to decrease the incidence of infection, as manifested by febrile neutropenia, in patients with non-myeloid malignancies receiving myelosuppressive anti-cancer chemotherapy associated with a significant incidence of febrile neutropenia.
- *Pegfilgrastim consist of a filgrastim structure with a polyethylene glycol molecule attached. The pegylation allows for an extended half-life (15 to 80 hours vs. 2 to 7 hours) and longer duration of action. Pegfilgrastim is produced by covalently binding a 20-kilodalton-monomethoxypolyethylene glycol molecule to the N-terminal methionyl residue of filgrastim.*
- *Clinical studies show pegfilgrastim (Neulasta™) is equally effective at reducing and improving the incidences of neutropenia as filgrastim (Neupogen®) with similar adverse events primarily being bone pain.*
- Some examinations were done using pegfilgrastim 100mcg/kg/chemotherapy cycle compared to filgrastim 5mcg/kg/day while others evaluated pegfilgrastim 6mg/chemo cycle to filgrastim 5mcg/kg/day. Both doses yielded equivalent results. The package insert suggests a fixed-dose regimen of 6mg/cycle is adequate and should be used over the 100mcg/kg/cycle schedule.
- Pegfilgrastim displays nonlinear kinetics with decreased clearance with increases in dose.
- There is a large variability in pharmacokinetics of pegfilgrastim in cancer patients with a half-life of 15-80 hours after SC injection.
- *The 6 mg dose should not be used in patients weighing less than 45 kg.*
- *Pegfilgrastim may only be given SC.*
- Pegfilgrastim has reduced renal clearance and prolonged persistence in vivo as compared to filgrastim. No adjustment is necessary for renal dysfunction.
- As neutrophil-mediated clearance is the predominant elimination mechanism, alteration of the pharmacokinetics of pegfilgrastim is not expected in hepatic insufficiency, and dose adjustments do not appear necessary.
- *Elimination of pegfilgrastim is almost entirely via a saturable neutrophil receptor-mediated clearance (self-regulation); serum clearance decreases with increasing doses, and it is directly related to the number of neutrophils. Serum concentrations of the drug remain elevated during chemotherapy-related neutropenia, and fall rapidly at the onset of neutrophil recovery.*
- Pegfilgrastim distribution is limited to the plasma compartment
- *Pegfilgrastim should not be administered in the period between 14 days before and 24 hours after administration of cytotoxic chemotherapy.*
- Pegfilgrastim should be stored refrigerated at 2° to 8°C; syringes should be kept in their carton to protect from light until time of use. Shaking should be avoided. Before injection, pegfilgrastim may be allowed to reach room temperature for a maximum of 48 hours but should be protected from light.
- Pegfilgrastim left at room temperature for more than 48 hours should be discarded. Freezing should be avoided; however, if accidentally frozen, pegfilgrastim should be allowed to thaw in the refrigerator before administration. If frozen a second time, pegfilgrastim should be discarded.

Cost Analysis				
Generic	Pegfilgrastim	Filgrastim	Filgrastim	Filgrastim
Brand	Neulasta	Neupogen	Neupogen	Neupogen
Dose	6mg/cycle- 1 dose	300 mcg/day for 5 days of treatment	480 mcg/day for 5 days	300 mcg/day for 14 days of treatment
Total Acquisition cost	\$2,266.54	\$759.67	\$1210.85	\$2,127.00

Package Insert Studies

- Neulasta was evaluated in two randomized, double-blind, active control studies, employing doxorubicin 60 mg/m² and docetaxel 75 mg/m² 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 (absolute neutrophil count [ANC] < 0.5 x 10⁹/L) with a mean duration of 5-7 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 (NEUPOGEN)-treated subjects in the mean days of severe neutropenia. In study 1, 157 subjects were randomized to receive a single SC dose of 6 mg of Neulasta on day 2 of each chemotherapy cycle or filgrastim at 5 mcg/kg/day SC beginning on day 2 of each cycle. In study 2, 310 subjects were randomized to receive a single SC injection of Neulasta at 100 mcg/kg on day 2 or filgrastim at 5 mcg/kg/day SC beginning on day 2 of each cycle of chemotherapy. Both studies met the primary objective of demonstrating that the mean days of severe neutropenia of Neulasta-treated patients did not exceed that of filgrastim-treated patients by more than one day in cycle 1 of chemotherapy. The rates of febrile neutropenia in the two studies were comparable for Neulasta and filgrastim (in the range of 10 to 20%). Other secondary endpoints included days of severe neutropenia in cycles 2-4, the depth of ANC nadir in cycles 1-4, and the time to ANC recovery after nadir. In both studies, the results for the secondary endpoints were similar between the two treatment groups.

Mean days of Severe Neutropenia in Cycle 1			
	Neulasta	Neupogen	Difference in Means (95% CI)
Study 1 n=157	6 mg	5 mcg/kg/day	0.2 (-0.2, 0.6) NS
Study 2 n=310	100 mcg/kg	5 mcg/kg/day	0.1 (-0.2, 0.4) NS

Other Studies:

- Holmes FA. A Single Dose of Pegfilgrastim Is as Effective as Daily Filgrastim to Reduce the Duration of Severe, Chemotherapy-Induced Neutropenia. American Society of Clinical Oncology. 2000; Abstract #191. 152 stage II (high risk)-IV breast cancer patients were treated with doxorubicin 60 mg/m² and docetaxel 75 mg/m² followed by sustained duration peg-Filgrastim (SD) or Filgrastim, repeated every 21 days for 4 cycles. Patients were randomized initially in a double blind comparison of SD (100 µg/kg) as a single injection per cycle of chemotherapy or filgrastim 5µg/kg given daily. Additional cohorts were randomized to receive open label pegfilgrastim (30, 60, or 100 µg/kg/cycle). The primary endpoint was duration of severe neutropenia (SN) (ANC < 0.5 x 10⁹/L) in cycle 1. Secondary endpoints were duration of SN in cycles 2-4, ANC profile, pharmacokinetics in cycle 1, time to ANC recovery and safety profile of SD post-chemotherapy in cycles 1-4. Pts median age was 50 years old. Most (80-90%) had not received prior chemotherapy or radiotherapy. Each cohort had comparable numbers of stage II, III, and IV pts. The percent of pts with either 0-2 or 3-5 days of SN in cycle 1 is shown below. Pts tx with 30 or 60 µg/kg of SD were at higher risk of inadequate neutrophil recovery. The pharmacokinetics of SD were nonlinear with a mean terminal half-life of up to 80 hours per group (versus 5 hours for Filgrastim). The safety profile of SD is similar to Filgrastim. No seroreactivity was noted in any pts tx on this study. SD 100 µg/kg administered once per cycle of chemotherapy requires fewer injections and results in the same duration of SN compared to Filgrastim.

Severe Neutropenia (Absolute Neutrophile Count < 0.5 x 10 ⁹ /L)				
	Pegfilgrastim			Filgrastim
Dose	30 mcg/kg	60 mcg/kg	100 mcg/kg	5 mcg/kg
Number of Patients	19	61	47	25
0-2 Days of Severe Neutropenia	37%	67%	89%	88%
3-5 days of Severe Neutropenia	63%	34%	11%	12%