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## Pegfilgrastim

(Neulasta<sup>®</sup>, Amgen)

### Summary

**Indications:** Pegfilgrastim (Neulasta<sup>®</sup>, Amgen) is the pegylated version of filgrastim (Neupogen<sup>®</sup>, Amgen). It is FDA approved for reducing the incidence of febrile neutropenia in patients with non-myeloid cancers receiving myelosuppressive chemotherapy. There are currently no published studies supporting its use in other situations such as stem cell mobilization and severe chronic neutropenia.

**Monitoring Parameters:** Medullary bone pain was the most common adverse effect observed in clinical trials. Other reported effects that include 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. However, underlying malignancy or chemotherapy may have caused these effects. The incidence of leukocytosis was rare, and pegfilgrastim was associated with transient elevations in lactate dehydrogenase, alkaline phosphatase, and uric acid. Patients undergoing pegfilgrastim therapy should receive complete blood counts at baseline and at regular intervals to assure hematologic response.

**Dose:** The labeled dose of pegfilgrastim is 6 mg (contents of one pre-filled syringe) injected subcutaneously once per chemotherapy cycle, either greater than 14 days before or 24 hours after chemotherapy.

**Pediatrics:** Published studies involving pegfilgrastim have not enrolled patients less than 18 years old, and the safety and efficacy is not established in this patient population. The manufacturer recommends that the fixed dose of 6 mg subcutaneously should not be used in pediatric patients, including adolescents weighing less than 45 kilograms.

**Geriatrics:** In clinical trials, the safety and effectiveness of pegfilgrastim between geriatric and younger patients were comparable.

**Pregnancy:** Category C. At doses of 4 times the recommended human dose, pegfilgrastim induced teratogenic effects in rabbits. Higher doses increased the number of abortions and decreased the number of live rabbit fetuses. Therefore, pegfilgrastim should only be used during pregnancy if the benefits outweigh the risks.

**Breast Feeding:** It has not been determined if pegfilgrastim is excreted into human milk. Therefore, use caution when

administering this drug to nursing mothers.

**Stability/Storage:** The pre-filled syringes of pegfilgrastim should not be shaken, should be stored at refrigerated temperature (2-8°C), and should be protected from light. The product may be left at room temperature for up to 48 hours before it must be discarded. In case of accidental freezing, pegfilgrastim can be thawed in the refrigerator, but should be discarded if frozen a second time.

**Cost:** Pegfilgrastim is supplied in 0.6 mL single dose syringes containing 6 mg of pegfilgrastim. The average wholesale price (AWP) for one syringe is \$2,950.

### Introduction

Colony stimulating factors first became available in February 1991 when the US Food and Drug Administration (FDA) approved filgrastim (granulocyte colony stimulating factor, G-CSF, filgrastim, Neupogen<sup>®</sup>, Amgen). In March 1991, sargramostim (granulocyte-macrophage colony stimulating factor, GM-CSF, Leukine<sup>®</sup>, Berlex) was approved. Filgrastim was originally indicated for reducing the incidence of febrile neutropenia in patients receiving myelosuppressive chemotherapy for non-myeloid malignancies, and sargramostim was originally indicated for accelerating engraftment in patients undergoing autologous bone marrow transplantation. Since then, colony stimulating factors have been used to treat a wide variety of conditions.<sup>2</sup> In an effort to streamline the use of these drugs, the American Society of Clinical Oncology has published guidelines on the appropriate use of colony stimulating factors based on the available evidence.<sup>3</sup>

The newest colony stimulating factor approved by the Food and Drug Administration is pegfilgrastim (Neulasta<sup>®</sup>, Amgen). Addition of a polyethylene glycol moiety to bioactive proteins appears to be a trend in the pharmaceutical industry. This technology was studied in the late 1970s and has recently been applied to many biopharmaceuticals. It is believed that pegylation of proteins increases half-life, reduces antigenicity, increases solubility, and reduces degradation by proteolysis without losing any biological activity.<sup>4</sup> This technology allows for dose optimization of the new product. Pegfilgrastim is given as a single injection twenty-four hours after chemo-

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therapy, whereas filgrastim is given once daily until a target absolute neutrophil count (ANC) is achieved. Pegfilgrastim is currently the only pegylated colony stimulating factor available in the United States.

Unfortunately, this advance in colony stimulating factor technology further increases the acquisition cost associated with these products. Current debate still exists whether traditional colony stimulating factors are cost effective.<sup>3</sup> It is expected that pegylated colony stimulating factors will be scrutinized for cost-efficiency just as traditional colony stimulating factors were in the mid-1990s. This monograph reviews the current available literature regarding pegfilgrastim and discusses its role in treating neutropenia.

### Pharmacology/pharmacokinetics

Pegfilgrastim is a pegylated form of filgrastim and involves covalently bonding a 20-kilodalton polyethylene glycol moiety to the N-terminal methionine residue of filgrastim. This new entity acts via the same mechanism as filgrastim by binding to receptors on hematopoietic cells and stimulating proliferation, differentiation, commitment, and end cell functional activation.<sup>1</sup>

The half-life of pegfilgrastim ranges from 15 to 80 hours.<sup>1</sup> It displays nonlinear pharmacokinetics in cancer patients as the clearance decreases when the dose is increased. Studies show that pegfilgrastim levels are affected mostly through neutrophil receptor mediated clearance.<sup>1,5</sup> Therefore, serum concentrations decrease when neutrophil counts increase with little influence through renal clearance.<sup>5</sup> This unique pharmacokinetic profile allows the drug to be given as a single, fixed dose. Mathematical pharmacokinetic models predicted that a single dose of 6 mg would provide sufficient drug exposure to a wide range of patient body weights.<sup>5</sup>

### Clinical trials

#### Phase III Clinical Trials

A randomized, double blind, placebo controlled trial by Green et al evaluated 157 patients.<sup>6</sup> The investigators compared the duration of chemotherapy induced neutropenia (defined as  $ANC < 0.5 \times 10^9/L$ ) between a single 6 mg dose of pegfilgrastim and filgrastim 5 mcg/kg/day in patients receiving treatment for stage II to IV breast cancer. The total dose of chemotherapy administered was similar between each group. No significant differences were detected between groups in the mean duration of severe neutropenia in the first cycle (1.8 days with pegfilgrastim vs 1.6 days with filgrastim), the incidence of severe neutropenia in the first cycle (82% with pegfilgrastim and 84% with filgrastim), or the incidence of febrile neutropenia over all cycles (13% for pegfilgrastim and 20% for filgrastim). The incidence, severity, and duration of adverse events (including bone pain) were also similar.

Data from another randomized, blinded, multicenter trial

performed by Holmes et al suggest pegfilgrastim is as safe and effective as filgrastim in reducing neutropenia in patients receiving four cycles of chemotherapy.<sup>7</sup> The 310 patients receiving docetaxel 75 mg/m<sup>2</sup> and doxorubicin 60 mg/m<sup>2</sup> for breast cancer were randomized to receive either pegfilgrastim or filgrastim after chemotherapy. Patients enrolled in the study must have been greater than 18 years old and diagnosed with stage II-IV breast cancer. The patients were either chemotherapy naïve or have received no more than one course of chemotherapy for metastatic disease 4 weeks prior to randomization. These patients also had an Eastern Cooperative Oncology Group performance status of at least 2, ANC of at least 1,500/mL, platelets of at least 100,000/mL and good hepatic and cardiac function.

A single dose of pegfilgrastim at 100 mcg/kg (actual body weight) or 5 mcg/kg daily of filgrastim per chemotherapy cycle was initiated on day 2 of the cycle, approximately 24 hours after chemotherapy. Those receiving filgrastim continued to receive the drug until the ANC reached 10,000/mL or until 14 doses were given. Chemotherapy was repeated every 3 weeks for four cycles unless ANC was less than 1,000/mL and platelets were less than 100,000/mL. Primary efficacy was measured as duration of grade 4 neutropenia ( $ANC < 500/mL$ ) in the first cycle. Secondary endpoints were duration of grade 4 neutropenia in cycles two through four, depth of ANC nadir in each cycle, incidence of febrile neutropenia, and time to ANC recovery in all cycles. Incidence of adverse effects, changes in laboratory values, and presence of antibodies were used to assess safety in this study.

Results analyzed using intent-to-treat analysis suggest that the safety and efficacy of one injection of pegfilgrastim were similar to that of daily injections of filgrastim. Duration of grade 4 neutropenia in the first cycle was similar in both groups (filgrastim = 1.8 days, pegfilgrastim = 1.7 days,  $p > 0.5$ ). The incidence of grade 4 neutropenia in the first cycle was 79% and 77% in the filgrastim and pegfilgrastim groups, respectively ( $p > 0.5$ ). The incidence of neutropenia in subsequent cycles was also statistically similar in both groups, but was numerically lower in the pegfilgrastim group. Duration of grade 4 neutropenia in cycles two through four also was lower in the pegfilgrastim group, with values of 0.9, 0.9, and 1.2 days versus 1.1, 1.4, and 1.5 days in the filgrastim group, respectively ( $p = 0.001$ ,  $<0.001$ ,  $<0.025$ , respectively). The ANC values during the nadir were slightly higher in the pegfilgrastim group, and rates of febrile neutropenia in all cycles favored the pegfilgrastim group (9% vs. 18%,  $p = 0.029$ ). The difference between the groups in time to ANC recovery was not statistically different. Based on these results, it can be concluded that a single 100 mcg/kg injection of pegfilgrastim was equivalent to 5 mcg/kg/day filgrastim for 11 days in reducing the duration of grade 4 neutropenia.

**Table 1. Summary of phase III clinical trials involving pegfilgrastim<sup>6,7</sup>**

	Green et al	Holmes et al
Number of patients	157	310
Patient population	Stage II-IV breast cancer	Stage II-IV breast cancer
Chemotherapy regimen	Doxorubicin 60 mg/m <sup>2</sup> Docetaxol 75 mg/m <sup>2</sup> 4 cycles	Doxorubicin 60 mg/m <sup>2</sup> Docetaxol 75 mg/m <sup>2</sup> Every 3 weeks for 4 cycles
Dose pegfilgrastim	6 mg SQ x 1 dose	100 mcg/kg SQ x 1 dose
Dose filgrastim	5 mcg/kg/day until ANC $\geq$ 10,000/mL (max of 14 days)	5 mcg/kg/day until ANC $\geq$ 10,000/mL (max of 14 days)
Duration of neutropenia in cycle 1 (pegfilgrastim vs. filgrastim)	1.8 days vs. 1.6 days	1.7 days vs. 1.8 days
Incidence febrile neutropenia (pegfilgrastim vs. filgrastim)	13% vs. 20%	9% vs. 18% (p=0.029)

Safety parameters were similar in both treatment groups. The most common reported adverse event was skeletal pain (25% in pegfilgrastim group vs 26% in filgrastim group). Six patients in the pegfilgrastim group withdrew due to adverse events (pleural effusion, cardiac failure, dehydration, gastrointestinal disorder, hypovolemia, nausea, vomiting, abdominal pain), and four patients withdrew from the filgrastim treatment arm (due to fever, granulocytopenia, disease progression, syncope). Transient increases in liver function tests (lactic dehydrogenase, AST, ALT) were observed in both the filgrastim and pegfilgrastim treatment groups and were not clinically significant. Anemia of grade 3 and higher, and thrombocytopenia of grade 4 and higher were similar between the pegfilgrastim and filgrastim groups (7% and 10%, respectively for anemia, and < 5% for thrombocytopenia).

While data from both clinical trials suggest some marginal benefit of pegfilgrastim over filgrastim in reducing the incidence and duration of febrile neutropenia, these studies were not designed to measure pegfilgrastim superiority, but rather non-inferiority. Therefore, pegfilgrastim can only be considered as not inferior to filgrastim until additional evidence suggests otherwise. Table 1 displays results from both phase III trials.

### **Dose-Defining Studies**

Prior to the approval of a fixed pegfilgrastim dose regimen, phase II dose finding studies evaluated pegfilgrastim at a variety of dose ranges (mostly based on weight). Holmes et al studied pegfilgrastim at doses of 10, 60, and 100 mcg/kg as a single dose and compared these doses to filgrastim 5 mcg/kg/day.<sup>9</sup> Duration of grade 4 neutropenia during the first cycle was the main efficacy endpoint. Other endpoints included duration of grade 4 neutropenia in cycles two through four, time to ANC recovery, and rates of febrile neutropenia. Pegfilgrastim at a dose of 100 mcg/kg produced an efficacy profile similar to that of daily filgrastim with a mean grade 4 neutropenia duration of

1.3 days for pegfilgrastim 100 mcg/kg and 1.6 days for filgrastim.

Another, randomized, open-label phase II trial compared the safety and efficacy of a single dose of pegfilgrastim of 100 mcg/kg to daily filgrastim at 5 mcg/kg/day in 60 patients.<sup>10</sup> Similarly to other studies, the primary efficacy endpoint was duration of grade 4 neutropenia after the first cycle. The results showed a similar profile; the duration of grade 4 neutropenia was 2.8 days with pegfilgrastim and 2.4 days with filgrastim.<sup>10</sup> The incidence of grade 4 neutropenia during the first cycle was also measured, with similar results between groups (69% in the pegfilgrastim group vs 68% in the filgrastim group). Adverse events were similar in both treatment arms, with bone pain and fatigue being the most common.

A retrospective analysis of data compiled from the two phase II trials comparing filgrastim to pegfilgrastim (6 mg and 100 mcg/kg) in breast cancer patients was performed.<sup>8</sup> Outcomes analyzed were duration of severe neutropenia, febrile neutropenia, grade 4 neutropenia, intravenous antibiotic use, and hospitalizations stratified into two groups: greater than and less than 65 years old. Parameters were not different between pegfilgrastim and filgrastim except for the incidence of febrile neutropenia. Patients treated with pegfilgrastim were observed to have a decreased incidence of febrile neutropenia. However, no statistical analysis was reported to test for significance. Table 2 reports the data from this analysis.

The pharmacokinetic profiles of pegfilgrastim in earlier studies prompted the manufacturers to develop the drug as a single, fixed dose. Lighter patients exposed to the drug achieved lower concentrations of pegfilgrastim in the blood.<sup>5</sup> A mathematical pharmacokinetic model determined that a single, fixed dose of pegfilgrastim might result in more consistent drug levels for a wide range of patient weights due to its neutrophil-mediated clearance. This hypothesis was tested in a pharmacokinetic trial which exposed 29 patients to a 6 mg

**Table 2. Summary of endpoints of two phase II clinical trials (adapted from Shogan et al)<sup>8</sup>**

	< 65 years		> 65 years	
	Pegfilgrastim	Filgrastim	Pegfilgrastim	Filgrastim
Duration of severe neutropenia	1.8%	1.6%	1.7%	2.1%
Febrile neutropenia	10%	18%	15%	22%
Grade 4 neutropenia	86%	85%	89%	97%
IV antibiotic use	19%	20%	26%	34%
Hospitalizations	18%	23%	22%	25%

dose of pegfilgrastim.<sup>11</sup> The range of body weights did not affect the duration of grade 4 neutropenia. Patients with weights lower than the median (78 kg) experienced a mean duration of 0.9 days, while those heavier than 78 kg had a mean duration of 1.1 days.

### **Dose-Response Studies**

Earlier work performed by Johnston et al assessed preliminary usefulness of pegylated filgrastim in clinical applications.<sup>12</sup> The purpose was to study the pharmacokinetics, safety, and preliminary efficacy of pegfilgrastim compared to filgrastim in 13 patients with non-small cell lung cancer. Doses of pegfilgrastim were either 10, 100, or 300 mcg/kg 2 weeks before and 24 hours after chemotherapy. Even though the ANC of both groups increased, patients receiving pegfilgrastim experienced a greater dose dependent duration of effect than those receiving 5 days of filgrastim. Safety profiles of both drugs were similar, with bone pain being most common. Higher doses of pegfilgrastim did not seem to increase the frequency and severity of bone pain.

Other early preclinical trials studied the ability of pegfilgrastim to mobilize neutrophils.<sup>13</sup> Thirty-two healthy volunteers were injected with 30, 60, 100, and 300 mcg/kg of pegfilgrastim. Blood was drawn at baseline, then at least daily for a total of 18 days. Dose related elevations of ANC were observed. Adverse events in this study were bone pain, headache, and transient elevations in serum enzymes and uric acid.

### **Other Data from Abstracts**

Pegfilgrastim is marketed based on its advantage of once-per-cycle dosing. Traditional colony stimulating factors (specifically filgrastim) must be administered once a day for up to 14 injections per chemotherapy cycle. Pegfilgrastim may be a more favorable option for outpatients who are unable to self-

administer these daily injections. Not surprisingly, one study (to date only published in abstract) suggests that 9 out of 10 patients receiving filgrastim therapy at one of three US oncology clinics would prefer an agent that provides equal efficacy with one injection per cycle.<sup>14</sup> Sixty percent of those patients reported dissatisfaction associated with traveling to clinic for their daily injections.

### **Adverse effects**

Overall, the adverse effects of pegfilgrastim were similar to those of filgrastim and were well tolerated. Common adverse events include nausea, fatigue, alopecia, diarrhea, vomiting, constipation, fever, anorexia, skeletal pain, headache, taste disturbances, dyspepsia, myalgia, insomnia, abdominal pain, arthralgia, generalized weakness, peripheral edema, dizziness, granulocytopenia, stomatitis, mucositis, and neutropenic fever.<sup>1</sup> Pegfilgrastim is a protein-derivative, and there is a potential for allergic reactions which includes anaphylaxis, skin rash, and urticaria.

The most common adverse effects related to pegfilgrastim use were medullary bone pain (26%). In clinical trials, the incidence of bone pain with pegfilgrastim use was similar to the incidence of those receiving filgrastim. Bone pain in clinical trials was bothersome enough that 12% of subjects used non-narcotic analgesics. Less than 6% of subjects required narcotic medications to control bone pain. No patients dropped out of any study due to bone pain. A retrospective analysis was performed on both phase III trials of pegfilgrastim and compared the profile of bone pain between filgrastim and pegfilgrastim.<sup>16</sup> There were no statistically significant differences between treatment arms. Table 3 compares the incidence of bone pain in both phase III clinical trials.

Other adverse effects observed that were transient and did

**Table 3. Comparison of bone pain in phase III clinical trials (adapted from Glaspy et al)<sup>16</sup>**

	Holmes et al		Green et al	
	Filgrastim 5 mcg/kg/day	Pegfilgrastim 100 mcg/kg	Filgrastim 5 mcg/kg/day	Pegfilgrastim 6 mg
Incidence of bone pain	34%	29%	42%	37%
Mean duration of bone pain	1.3 days	1.5 days	1.6 days	1.2 days

**Table 4. Economic impact of various doses of filgrastim (based on AWP)**

	Filgrastim 300 mcg/day (\$227.63/syr)	Filgrastim 480 mcg/day (\$362.63/syr)	Pegfilgrastim 6 mg dose (\$2950.00/syr)
1 dose	\$227.63	\$362.63	\$2950.00 (given at a maximum of every 14 days)
3 doses	\$682.89	\$1087.89	
5 doses	\$1138.15	\$1813.15	
7 doses	\$1593.41	\$2538.41	
8 doses	\$1821.04	\$2901.04	
9 doses	\$2048.67	\$3263.67	
12 doses	\$2731.56	\$4351.56	
14 doses	\$3186.82	\$5076.82	

not require therapeutic intervention were elevations in lactate dehydrogenase, alkaline phosphatase, and uric acid. The incidence of leukocytosis was rare (<1%) and did not produce any consequences.<sup>1</sup>

### Cost, dose, how supplied

Pegfilgrastim is available as 6 mg/0.6 mL prefilled single use syringes containing a 27 gauge, ½ inch needle. The recommended labeled dose is 6 mg injected subcutaneously once per chemotherapy cycle.<sup>1</sup> It should be given at least 24 hours after or more than 14 days before chemotherapy. The AWP for one syringe is \$2,950. This compares to the AWP for filgrastim of \$227.63 for one 300 mcg syringe, and \$362.63 for one 480 mcg syringe.

Colony stimulating factors are expensive and have been scrutinized for economic optimization for the past 10 years. Economic evaluations have shown that filgrastim use after induction and consolidation in acute myelogenous leukemia can produce cost savings of 2.2 to 14.4% per patient.<sup>16</sup> This is attributed to a reduction in infections and length of hospital stay. Protocols have been developed to control the cost of colony stimulating factors and ensure efficient use of these drugs. A report published in 1999 showed that a pharmacy-based filgrastim protocol saved an institution \$22,416 within the first six months of implementing the protocol without sacrificing efficacy.<sup>17</sup> The protocol allowed pharmacists to monitor filgrastim therapy by ordering appropriate laboratory tests and discontinue filgrastim use according to established guidelines. There are currently no economic studies relating to pegfilgrastim, and it is uncertain if pharmacy-based pegfilgrastim protocols will save money. This is likely to be the subject of future study.

In phase III clinical trials, the duration and incidence of grade 4 neutropenia was similar when treated with filgrastim or pegfilgrastim. An economic analysis shown in Table 4 depicts that the cost of nine doses of filgrastim at 480 mcg/day is more expensive than one 6 mg dose of pegfilgrastim.

Therefore, in patients who require fewer than nine doses of filgrastim at 480 mcg/day to achieve neutropenic control, pegfilgrastim use may not be economically appropriate.

### Conclusions

Pegfilgrastim is the pegylated version of filgrastim. This modification increases the half-life, decreases degradation, and decreases antigenicity while retaining its activity. Studies suggest that the decreased duration of grade 4 neutropenia is similar between pegfilgrastim and standard filgrastim. In addition, the safety profile of both drugs is similar.

While improved simplicity of dosing and patient satisfaction are advantages of pegfilgrastim, the high acquisition costs of the drug has led to the restriction of the agent at the University of Wisconsin Hospital and Clinics (UWHC). The treatment algorithm approved by the UWHC Pharmacy and Therapeutics Committee for filgrastim and pegfilgrastim is outlined in Figure 1.

The UWHC guidelines recommend that colony stimulating factor-naïve patients, with an appropriate indication for use, should receive filgrastim first instead of pegfilgrastim. Appropriate indications for colony stimulating factor use include: myelosuppressive cancer chemotherapy, bone marrow transplant, antiretroviral-induced neutropenia, and peripheral blood progenitor cell collection. Patients who require nine doses or more of filgrastim 480 mcg/day to achieve adequate neutropenic control may be considered candidates for pegfilgrastim for the subsequent chemotherapy cycles. It is important to note that pegfilgrastim is only indicated for myelosuppressive cancer chemotherapy, and therefore is limited to this patient population at UWHC. Institutions considering similar restrictions are encouraged to evaluate both the acquisition cost and reimbursement patterns at their organizations. Reimbursement for medications administered in the outpatient setting, and particularly those in oncology, is currently in a state of substantial change. Therefore, the financial implications of changing prescribing patterns should be monitored closely. ■

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**Figure 1.**  
Flowchart of recommendations for CSF use in adult cancer patients receiving myelosuppressive chemotherapy

