11/04/08

OFFICE OF CLINICAL PHARMACOLOGY REVIEW

BLA or STN	125031/105
Submission Date	05/16/2008
PDUFA Due Date	11/18/2008
Brand Name	Neulasta®
Generic Name	Pegfilgrastim
Primary Reviewer	Jun Yang, Ph.D.
Primary Review Team Leader	Hong Zhao, Ph.D.
OCP Division	DCP 5
OND Division	Division of Biologic Oncology Products (DBOP)
Sponsor	Amgen
Submission Type	Prior Approval Labeling Supplement (pediatric PMC study)
Formulation	Prefilled syringes for subcutaneous (SC) injection
Approved Adult Indication	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
Dosage in Adults	The recommended dosage of Neulasta® is a single subcutaneous injection of 6 mg administered once per chemotherapy cycle. Neulasta® should not be administered in the period between 14 days before and 24 hours after administration of cytotoxic chemotherapy

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1. EXECUTIVE SUMMARY

Pegfilgrastim (Neulasta®, Neupopeg®, Neulastim®) is a pegylated form of filgrastim and has a sustained duration of action relative to filgrastim. Pegfilgrastim was approved on January 31, 2002, 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. The approval of Pegfilgrastim included the following two Post Marketing Commitment (PMC) studies under the Pediatric Research Equity Act (PREA).

Postmarketing Commitment Number 3 (PMC#3)

> To submit results from an ongoing study to evaluate the pharmacokinetics (PK), safety and efficacy of Pegfilgrastim in pediatric patients. The protocol for study 990130 entitled "A Single Dose Per Cycle Filgrastim-SD/01 as an Adjunct to VadriaC/IE Chemotherapy in Pediatric Sarcoma Patients" was submitted to BB-IND 7110 on August 9, 1999 and the study was initiated in April 2000. Patient accrual will be completed by December 2004, the study completed (last patient exited) by September 2005, and the final clinical study report, with revised labeling if applicable, will be submitted to FDA by February 2006.
> Upon completion of the study and prior to finalization of the study report, you commit to discuss with the Agency the appropriateness of an expanded access approval of an indication for pediatric use.

Postmarketing Commitment Number 4 (PMC#4)

> To develop a pediatric dosage form based upon the data obtained from the pediatric study 990130 described in item 3. Formulation development will be completed by March 2006, six-month stability studies will be completed by September 2006, and a supplement with revised labeling will be submitted to FDA by November 2006.

The use of dose-intensive chemotherapy is a standard approach for the treatment of pediatric sarcoma. Filgrastim is approved for clinical use in the United States (US) and other countries to decrease the incidence of infection, as manifested by febrile neutropenia, in adult and pediatric patients with nonmyeloid malignancies. The pediatric study 990130 was designed to determine whether a single dose of Pegfilgrastim per chemotherapy cycle was as effective and safe as daily filgrastim in pediatric subjects with sarcoma who were receiving myelosuppressive chemotherapy and to establish the appropriate pegfilgrastim dose for the reduction of severe neutropenia in pediatric subjects. The clinical hypothesis of this study was that a single dose of pegfilgrastim per chemotherapy cycle in pediatric subjects with sarcoma who were receiving VAdriaC/IE (vincristine, doxorubicin, cyclophosphamide, etoposide, and ifosfamide) chemotherapy would result in a duration of severe neutropenia, ANC recovery profile, and safety profile similar to that observed with daily administration of filgrastim.

On September 20, 2004, the Agency informed the Sponsor that submission of the pediatric study report and the above-mentioned supplement could be deferred until April 15, 2007 and January 15, 2008, respectively. Issues surrounding the Sponsor's difficulty accruing participants into Study 990130 in support of PMC 3 was discussed at the

October 10, 2005, Oncology Drugs Advisory Committee- Pediatric Subcommittee meeting. In the March 21, 2007 preliminary meeting comments, the Agency concurred with the Sponsor's proposal to close Study 990130 at that time with a total of 44 subjects. The Agency also concurred that an expanded access study is not warranted for pegfilgrastim. Further, the Agency acknowledged the Sponsor's proposed revised timeline to submit the final clinical study report for Study 990130, closed with a total of 44 subjects, by August 31, 2007.

As part of Postmarketing Study Commitment Number 3, the Sponsor submitted the final study report for Study 990130 on August 24, 2007 (STN 125031/0, Sequence Number 0059.) In the above-mentioned March 21, 2007 preliminary meeting comments, the Agency stated that the results from Study 990130 are likely to support a labeling supplement for modifications to the PRECAUTIONS: Pediatric Use section of the US package insert (USPI); however, the study is not considered adequate enough in design to support inclusion in the CLINICAL STUDIES section of the USPI.

1.1. Recommendation

1. The application is acceptable from a Clinical Pharmacology perspective provided that the Sponsor and the Agency come to an agreement on labeling under pediatric use section.

1.2. Phase 4 Study Commitments

There is no additional phase 4 commitment request from a clinical pharmacology perspective.

1.3. Summary of Clinical Pharmacology Findings

A total of 44 subjects (38 in the pegfilgrastim group, 6 in the filgrastim group) were enrolled in the study. Pegfilgrastim (10 mg/mL) was provided for subcutaneous (SC) administration at a dose of 100 mcg/kg in 1.0-mL vials. Subjects could receive up to 4 chemotherapy cycles, with each cycle expected to be 21 days.

Pharmacokinetic (PK) data were available for 36 subjects who received pegfilgrastim and 6 subjects who received filgrastim. The neutrophil-mediated clearance mechanism previously observed in adults was evident in this pediatric study. After subcutaneous administration of pegfilgrastim to pediatric subjects, the maximum pegfilgrastim concentration was achieved at approximately 24 hrs post-dose and was sustained until the ANC nadir occurred. As ANC started to recover, the pegfilgrastim concentration declined rapidly, consistent with a neutrophil-mediated clearance mechanism. The PK profile was similar in the two older age groups; the youngest age group appeared to have higher median exposure ($AUC_{0\text{-}inf}$). This may relate to the fact that subjects in the youngest age group had neutropenia that was more severe, of longer duration, and with a deeper ANC nadir. Compared with the serum pegfilgrastim concentration profile, the serum concentration of filgrastim declined rapidly after the first dose. However, the PK

parameters of filgrastim were not estimated due to insufficient concentration data and limited number of subjects studied in each age group.

Differences were observed between treatment groups and across the age strata; however, such differences should be interpreted with caution because of the small number of subjects in the filgrastim treatment group (n = 6) and within the age strata (0 to 5 years: 12 pegfilgrastim, 1 filgrastim; 6 to 11 years: 10 pegfilgrastim, 2 filgrastim; 12 to 21 years: 16 pegfilgrastim, 3 filgrastim).

Immunogenicity

Ten of 41 subjects (8 in the pegfilgrastim group, 2 in the filgrastim group) tested positive for pre-existing antibodies against filgrastim or pegfilgrastim; 5 of these subjects (4 in the pegfilgrastim group, 1 in the filgrastim group) were also positive for neutralizing antibodies to pegfilgrastim in the baseline samples. No neutralizing antibody to filgrastim was detected in the baseline samples. Subsequent samples from subjects with pre-existing antibodies were less reactive than the baseline sample. One subject (4 years old) developed transient post-dose antibodies against filgrastim at a single time point after receiving pegfilgrastim. No consistent effects of the antibodies were noted in the clinical or PK profiles for these subjects.

Date: 11/4/08

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2. QUESTION-BASED REVIEW

2.1. General Attributes

2.1.1. What are the properties of the drug substance and the formulation of the drug product?

Pegfilgrastim is a pegylated form of filgrastim. Pegfilgrastim has a sustained duration of action relative to filgrastim.

2.1.2. What is the proposed mechanism of action and therapeutic indication?

Neutrophil-mediated clearance is the primary route of elimination of pegfilgrastim, and because pegfilgrastim directly stimulates the production of neutrophils, it effectively regulates its own clearance. Pegfilgrastim is approved in the US to decrease the risk of infection, as manifested by febrile neutropenia, in patients with nonmyeloid malignancies receiving myelosuppressive chemotherapy.

2.2. General Clinical Pharmacology

2.2.1. What are the design features of the clinical pharmacology and clinical studies used to support dosing or claims?

This was a multicenter, randomized, open-label study evaluating the efficacy, safety, and pharmacokinetics of a single dose of pegfilgrastim 100 μg/kg or daily doses of filgrastim 5 μg/kg administered after the completion of myelosuppressive chemotherapy in pediatric subjects with sarcoma. The primary objective was to assess the absolute neutrophil count (ANC) profile after myelosuppressive chemotherapy followed by single-dose administration of pegfilgrastim or daily filgrastim in pediatric subjects with sarcoma. Secondary objectives were to assess the pharmacokinetic and safety profiles of single-dose pegfilgrastim and daily filgrastim in this setting.

The study was divided into 2 parts. In part 1 of the study, 3 subjects were enrolled to receive 100 μg/kg pegfilgrastim to evaluate the safety of this dose in pediatric subjects. After establishing an acceptable safety profile in these 3 subjects, 18 additional subjects were randomized into each of 3 age groups (0 to 5, 6 to 11, and 12 to 21 years) to achieve a 6:1 ratio of pegfilgrastim:filgrastim. The 3 subjects initially assessed for safety were included in the pegfilgrastim group in this randomization, for a total of 21 subjects in the first cohort. Subjects randomized to receive pegfilgrastim received a single dose of 100 μg/kg approximately 24 hours after completion of chemotherapy. Subjects randomized to receive filgrastim were administered 5 μg/kg/day beginning approximately 24 hours after completion of chemotherapy and continuing either until a post-nadir ANC of $\geq 10 \times 10^{9}$/L was obtained or until 24 hours before the next chemotherapy cycle, whichever occurred first. Subjects could receive a maximum of 4 chemotherapy cycles on study.

After completion of each enrollment into each age stratum, safety and efficacy data were evaluated by the Safety Monitoring Committee to determine whether the dose should be escalated, de-escalated, or remain the same within the age stratum. For the pegfilgrastim cohorts, dose escalation was to be considered for an age stratum if ≥ 2 of the 6 subjects

randomized to pegfilgrastim failed to achieve ANC recovery (defined as ANC $\geq 0.5 \times 10^9$/L for 2 consecutive measurements by day 21 of the chemotherapy cycle) in cycle 1. If $\leq$ 1 subject who received pegfilgrastim in a given age stratum of 7 subjects did not obtain ANC recovery to $\geq 0.5 \times 10^9$/L, and the evaluated dose was well tolerated, 1 additional cohort of 7 subjects within the same age stratum was to be enrolled at the same dose, for a total of 21 additional subjects. Thus, a minimum of 42 subjects (12 pegfilgrastim and 2 filgrastim in each of the 3 age strata) were required to complete study enrollment. An age stratum was closed to accrual after 2 successive cohorts randomized to receive pegfilgrastim (within the age stratum) achieved ANC recovery at the same dose level.

Schedule of Assessments for PK and PD

In Cycles 1 and 3, PK samples were taken before day 1 and at 1, 2, 4, 24, and 48 hours after the single injection of pegfilgrastim or first injection of filgrastim within the cycle; Additional samples were drawn on Days 4, 5, 6. The complete blood count with differential was drawn concurrently.

Complete blood count (CBC) included white blood cells with 5-part differential, platelets, red blood cells, hemoglobin, and hematocrit. For Cycles 1 and 3, CBC was done at Screening and on Day 1. Additional CBCs were done daily starting with cycle day 4 until 2 consecutive ANCs of $> 0.5 \times 10^9$/L were recorded; thereafter, CBCs were done once weekly. For Cycles 2 and 4, CBCs were done daily starting with cycle day 4 until 2 consecutive ANCs of > 0.5 x 109/L were recorded; thereafter, CBCs were done once weekly and approximately 1 and 3 months after day 21 of the last on-study chemotherapy cycle.

Pharmacokinetics (PK) Results

Neutrophil-mediated clearance is the primary route of elimination of pegfilgrastim, and because pegfilgrastim directly stimulates the production of neutrophils, it effectively regulates its own clearance. The Sponsor characterized the general PK of pegfilgrastim in pediatric patients after SC administration at a dose of 100 mcg/kg. Standard PK parameters (noncompartmental analysis) were summarized in Table 1.

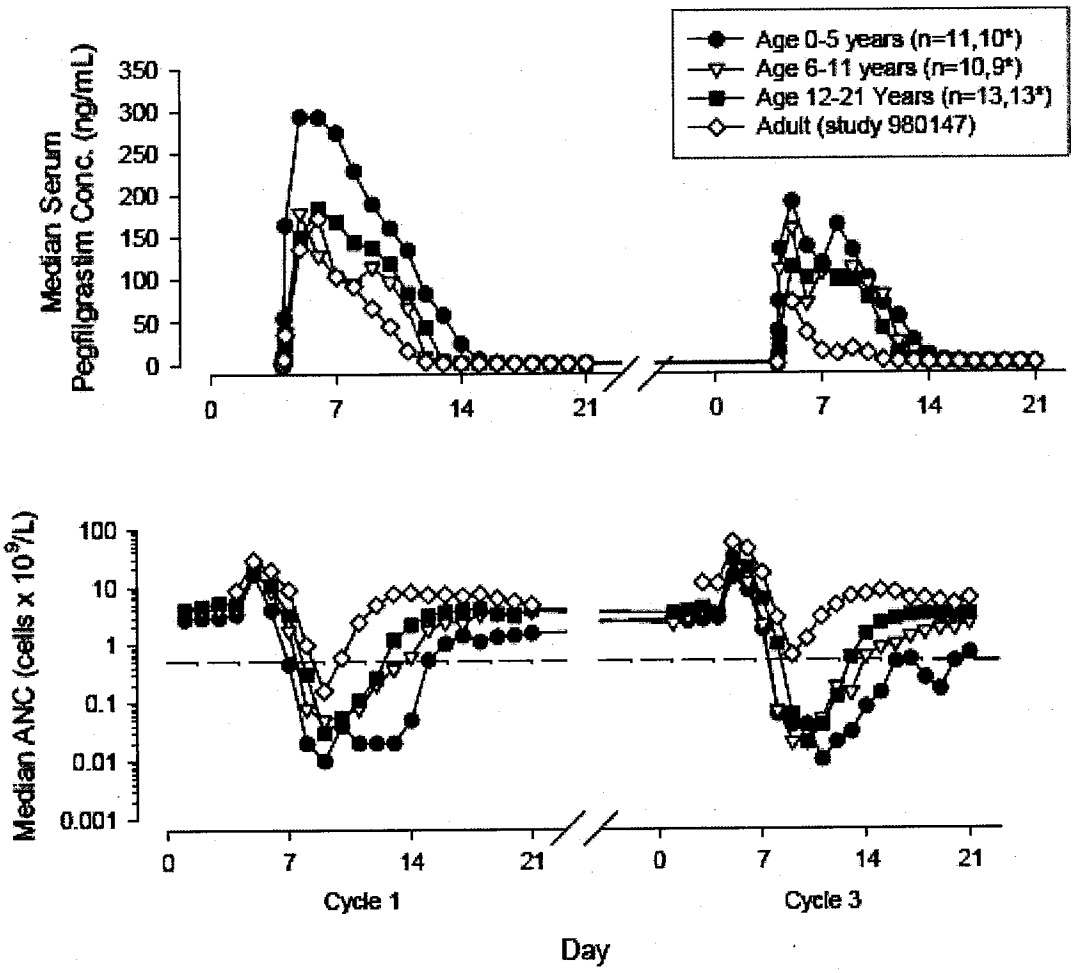
Table 1. Summary of Pegfilgrastim PK parameter values in Cycles 1 and 3.

PK parameters: Mean (SD)		0-5 Yrs	6-11 Yrs	12-21 Yrs
1st Cycle	# of subject	11	10	13
	$t_{1/2}$ (h)	30.1 (38.2)	20.2 (11.3)	21.2 (16.0)
	$AUC_{0\text{-inf}}$ (µg·h/mL)	47.9 (22.5)	22.0 (13.1)	29.3 (23.2)
3rd Cycle	# of subject	10	9	13
	$t_{1/2}$ (h)	30.8 (19.9)	23.1 (13.5)	19.3 (10.2)
	$AUC_{0\text{-inf}}$ (µg·h/mL)	36.3 (30.4)	21.2 (14.5)	22.3 (14.3)

The maximum pegfilgrastim concentration was achieved approximately 24 hrs post dose and was sustained until the ANC nadir occurred (Figure 1). As the ANC began to recover, the pegfilgrastim concentration declined rapidly. There is a tendency toward a higher median exposure ($AUC_{0\text{-inf}}$) in the youngest age group (0~5 yrs). During cycle 3,

median exposures were lower than those in cycle 1 for each age group, potentially as a result of the expansion of neutrophils and neutrophils precursor mass with time.

Figure 1. Median Pegfilgrastim Concentration-time and ANC-time Profiles After SC Administration of 100 μg/kg Pegfilgrastim to Pediatric Subjects in the Protocol-specified Age Groups (*n= Cycle 1, Cycle 3)



Summary of Efficacy Results

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✓ Trade Secret / Confidential (b4)

_____ Draft Labeling (b4)

_____ Draft Labeling (b5)

_____ Deliberative Process (b5)

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2.3. Intrinsic Factors

The relationship between exposure and demographic variables, age, gender and body weight was also examined.

Age:

The tendency toward a higher median exposure in the youngest age group (Figures 2 and 3) may relate to the fact that these subjects had more severe neutropenia with a deeper ANC nadir and a longer duration of neutropenia, consistent with a neutrophil-mediated clearance mechanism.

Figure 2. Relationship Between Pegfilgrastim $AUC_{0\text{-}inf}$ and Age Group After SC Injection of Pegfilgrastim 100 µg/kg (Protocol-specified Age Groups).

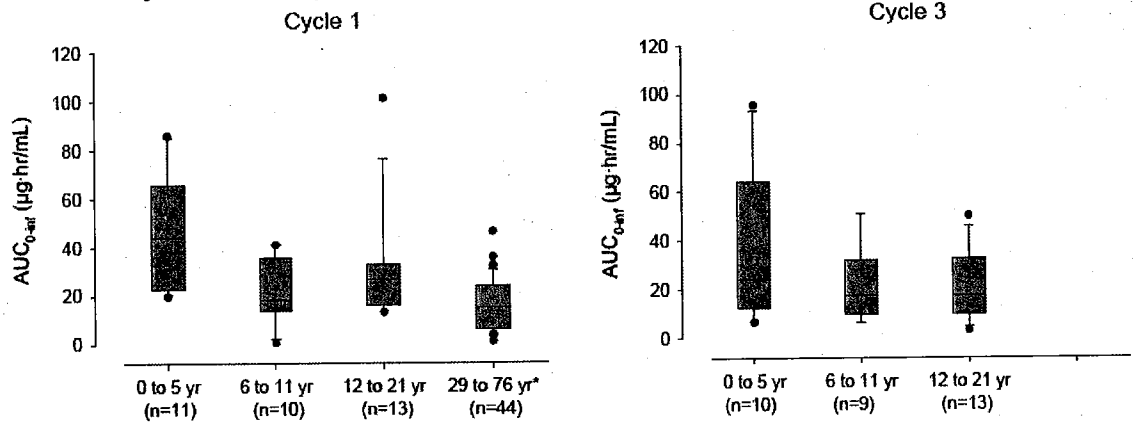
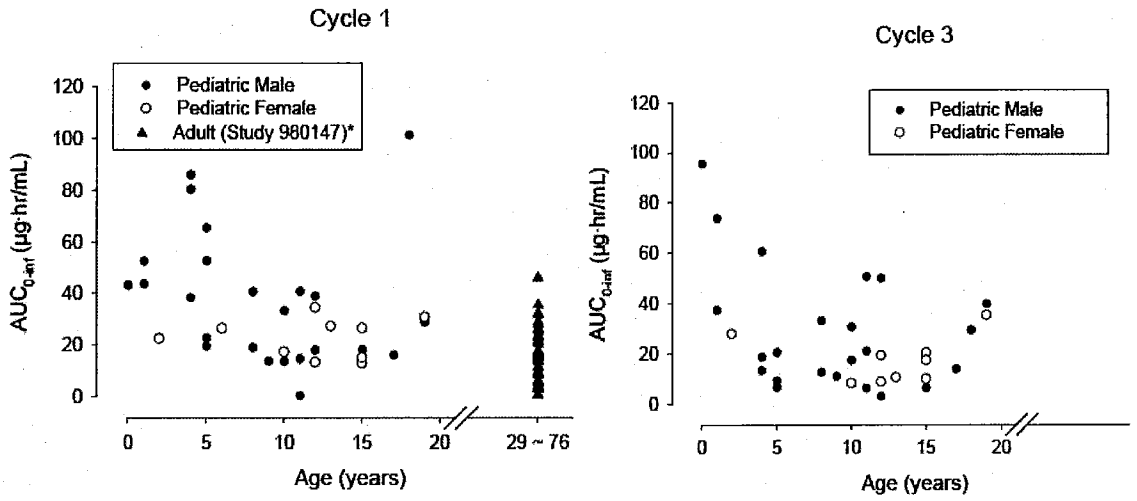


Figure 3. Relationship Between Pegfilgrastim $AUC_{0\text{-}inf}$, and Age as well as $AUC_{0\text{-}inf}$ and Gender After SC Injection of Pegfilgrastim 100 µg/kg.



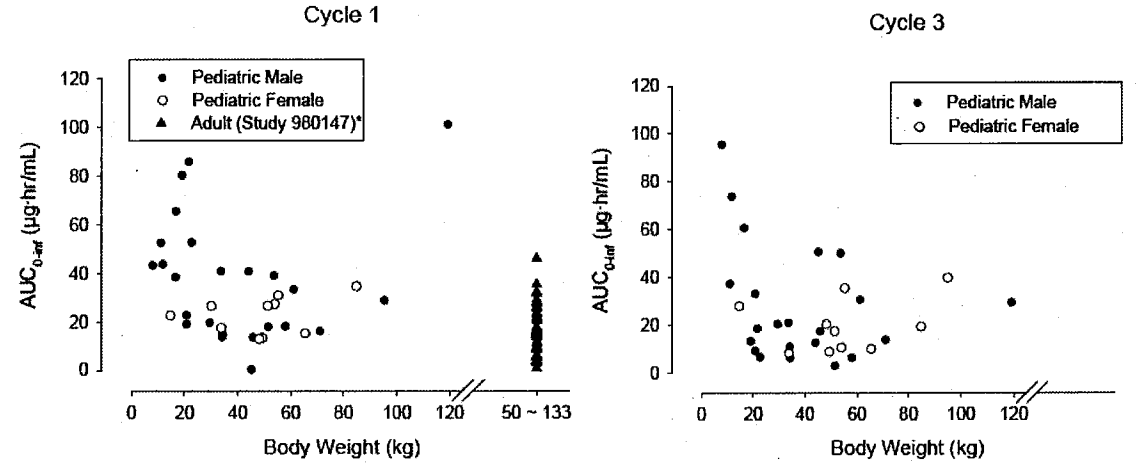
Gender:

The relationship between exposure and gender was also examined (Figure 3). There was no apparent difference between male and female pediatric subjects in exposure.

Body weight:

With respect to body weight, pegfilgrastim exposure appeared to be higher for subjects who weighed less (Figure 4). However, this difference may be related to the age difference.

Figure 4. Relationship Between Pegfilgrastim $AUC_{0\text{-}inf}$ and Body Weight After SC Injection of Pegfilgrastim 100 µg/kg.



2.4. Extrinsic Factors

2.4.1. What extrinsic factors influence dose-exposure and/or -response and what is the impact of any differences in exposure on response?

There is no adequate information to assess the effect of extrinsic factors.

2.4.2. What is the incidence of immunogenicity? What is the impact of immunogenicity on PK, efficacy and safety?

Samples from 41 of 44 subjects (36 pegfilgrastim, 5 filgrastim) were available for antibody testing. One subject (4 years old) developed transient post-dose antibodies against filgrastim at a single time point after receiving pegfilgrastim. This sample was negative for neutralizing activity, and subsequent samples were negative for binding activity. No clear effect of the transient postdose antibodies to filgrastim was observed in the PK and PD or safety profiles for this subject.

Ten of 41 subjects (8 in the pegfilgrastim group, 2 in the filgrastim group) tested positive at baseline for pre-existing binding antibodies to pegfilgrastim or filgrastim. All 10 subjects became antibody-negative after initiation of treatment with pegfilgrastim or filgrastim. Two of the subjects with pre-existing antibodies had baseline samples that were reactive with both pegfilgrastim and filgrastim, 2 subjects had samples reactive only with filgrastim, and the remaining 6 subjects had samples that were reactive only with pegfilgrastim. Five subjects were also positive for neutralizing antibodies in the baseline samples. Of note, all 5 of these subjects had binding and neutralizing antibodies that were specific for pegfilgrastim but not filgrastim, indicating a possibility of reactivity with the polyethylene glycol moiety. Post-dose samples from the 10 subjects with pre-existing antibodies were less reactive than the baseline samples, likely as a result of the immunosuppressive effect of the aggressive chemotherapy regimen, and thus no post-dose samples from these subjects tested positive for antibodies. The preexisting antibodies did not appear to correlate with any clinical sequelae.

2.5. General Biopharmaceutics

No updates.

2.6. Analytical

Pegfilgrastim and filgrastim concentrations in human serum were analyzed by a conventional enzyme-linked immunosorbent assay (ELISA) that uses a solid phase "sandwich' or capture methodology. The assay dose not distinguish pegfilgrastim from filgrastim and endogenous G-CSF.

Two validated assays were used to test for anti-antibodies. With the first assay, all serum samples were screened for binding reactivity to pegfilgrastim and filgrastim using a (b) (4) biosensor immunoassay (b) (4) . Additional testing in the biosensor immunoassay was performed on all samples reacting to filgrastim or pegfilgrastim to confirm the presence of a human antibody and if necessary, to determine the specificity of

the antibody response. The second assay, a cell-based bioassay for neutralizing or inhibiting effects on the activity of pegfilgrastim and filgrastim, was used to analyze samples classified as positive for binding antibodies to pegfilgrastim or filgrastim. Samples that were positive in both the biosensor immunoassay and the bioassay were defined as positive for binding and neutralizing anti-product antibodies.

3. DETAILED LABELING RECOMMENDATIONS

Sponsor Proposed Labeling

(b) (4)

The 6 mg fixed dose single-use syringe formulation should not be used in infants, children, and smaller adolescents weighing less than 45 kg.

Clinical Pharmacology Suggested Labeling

Pediatric Use

The safety and pharmacokinetics of Neulasta® were studied in 37 pediatric patients with sarcoma. The mean (±Standard Deviation) systemic exposure ($AUC_{0\text{-}inf}$) of Neulasta® after subcutaneous administration at 100 mcg/kg was 22.0±13.1 mcg·hr/mL in the 6-11 years age group (n=10), 29.3±23.2 mcg.hr/mL in the 12-21 years age group (n=13) and 47.9±22.5 mcg.hr/mLin the youngest age group (0-5 years, n=11).The elimination half-life (b) (4) hours. The most common adverse reaction was bone pain.

The 6 mg fixed dose single-use syringe formulation should not be used in infants, children, and smaller adolescents weighing less than 45 kg.