



To: 125031 File

From: Jeff Summers, MD, Medical Review Officer for Division of Biologic Oncology Products *J Summers*

Through: Joseph Gootenberg, Deputy Division Director of Biologic Oncology Products *JG* 11/4/08

Date: November 2, 2008

Re: PeRC Pediatric Assessment for Neulasta (pegfilgrastim) for PMC 3-4 (125031.0)  
STN 125031\105 Submitted 16-MAY-08, received 19-MAY-08, GSR sequence number 0081, PDUFA due date 18-NOV-08

### Executive Summary

Study 990130 was intended to assess the ANC, PK and safety profile of pegfilgrastim in pediatric patients. The Sponsor encountered substantive challenges in conducting this study mostly secondary to slow patient accrual and low interest on the part of investigators. Only eighteen of 50 eligible sites agreed to participate in the study and only 10 of the 18 accrued patients.

Study 990130 provides descriptive PK data for pegfilgrastim. There was a tendency toward a higher median exposure of pegfilgrastim in the youngest age group and this 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 the neutrophil-mediated clearance mechanism for pegfilgrastim. The greater severity of neutropenia in the youngest patients was most likely secondary to an increased intensity of myelosuppressive chemotherapy based on weight and BSA compared to the older age groups. See the Clinical Pharmacology review by Dr. Jun Yang for a complete description of the PK data obtained from study 990130.

Unfortunately, the small numbers of subjects in this study, particularly on the filgrastim control arm, preclude the ability to draw any definitive conclusions regarding efficacy of pegfilgrastim in decreasing the incidence of infection based on either the number of episodes of febrile neutropenia or the duration of severe neutropenia observed in the two arms of this study. There were no new safety signals identified in this pediatric study. Bone pain was the most common treatment emergent adverse event occurring in 11% of subjects on the pegfigrastim arm and 17% of subjects on the filgrastim arm.

The Division of Biologic Oncology Products has decided to consider PMC number 3 fulfilled and will release Amgen from PMC number 4. The Chairman for the Children's Oncology Group (COG) was contacted regarding their members interest in pursuing an additional study that could provide sufficient data to support a pediatric indication. The COG stated that this study would not be of high priority. FDA contacted the pediatric

group of EMEA through the FDA pediatric liaison Dr. Temeck. The EMEA does not have a PIP for pegfilgrastim and therefore stated that there would be no interest in discussing a pediatric study to support the efficacy of pegfilgrastim in the prevention of febrile neutropenia. Since the sponsor has pursued due diligence in attempting to conduct the agreed upon PMCs, and the lack of interest in the pediatric oncology community does not avail itself to support the conduct of additional studies, the DBOP will request that Amgen revise the Neulasta label to include PK data obtained from study 990130, and we will consider PMC #3 fulfilled and PMC #4 released. This study was discussed with the Pediatric Review Committee on 29-OCT-08 who agreed with the plan as stated above.

## **Brief Review of FSR to fulfill PMC number 3 (125031\0)**

**Application #:** STN 125031\105

**Drug Name:** Neulasta (pegfilgrastim)

**Approved Indications:** Neulasta is indicated 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.

**Date Submitted:** 16-MAY-08

**Date Received:** 19-MAY-08

**GSR Sequence number:** 0081

**Submission eCTD link:** [\\cbsap58\M\eCTD\\_Submissions\STN125031\125031.enx](\\cbsap58\M\eCTD_Submissions\STN125031\125031.enx)

**PDUFA DUE DATE:** 18-NOV-08

### **PREA Commitment**

*Pediatric deferred required studies as agreed to under the January 31, 2002 original Neulasta approval.*

#### **PMC number 3 (125103.0)**

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 study to make Pegfilgrastim available to children between study closure and approval of an indication for pediatric use.

#### **PMC number 4 (125103.0)**

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

**Indication(s) to be studied:** 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.

**Drug information:**

- **Route of administration:** Subcutaneous
- **Formulation:** Preservative-free solution containing 6 mg (0.6 mL) of pegfilgrastim (10 mg/mL) in a single-dose syringe with a 27-gauge, 1/2-inch needle with an UltraSafe Needle Guard
- **Dosage:** 6 mg
- **Regimen:** 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.

**Types of studies/ Study Design:** Study 990130: Multicenter, randomized (6:1), open label study in which pediatric subjects with sarcoma received either a single dose of pegfilgrastim 100 µg/kg administered subcutaneously or daily doses of filgrastim 5 µg/kg administered subcutaneously after the completion of VAdriaC/IE chemotherapy.

**Age group and population in which study will be performed:** The study was to consist of up to 4 cohorts with each cohort containing 21 subjects with 3 age strata in each cohort and 7 subjects per age stratum. A total of 44 subjects were enrolled in the study. 13 subjects in the 0- to 5-year age group, 12 subjects in the 6- to 11-year age group, and 19 subjects in the 12- to 21-year age group.

**Number of patients to be studied or power of study to be achieved:** 42-84 subjects. The study was designed to provide descriptive statistics regarding the duration of severe neutropenia, depth of the ANC nadir, time to ANC recovery, and proportion of subjects who had an ANC < 0.5 x 10<sup>9</sup>/L day 21 of cycle 1 and cycle 3.

#### **Pertinent Entry criteria**

- **Inclusion criteria:** Confirmed sarcoma diagnosis, ANC ≥ 1 x 10<sup>9</sup>/L and platelets ≥ 100 x 10<sup>9</sup>/L
- **Exclusion criteria:** Prior radiotherapy or chemotherapy, Hematologic malignancies or myelodysplasia, cytokine administration within 2 weeks of initiation of chemotherapy.

#### **Clinical endpoints**

- **Primary objective:** To assess ANC profile after myelosuppressive chemotherapy followed by a single dose of pegfilgrastim or daily filgrastim.
- **Secondary objectives:**
  1. To assess the pharmacokinetic profile of a single dose of pegfilgrastim in pediatric subjects
  2. To assess the safety profile of a single does of pegfilgrastim in pediatric subjects

**Timing of assessments:** CBC (cycle 1 and 3) baseline and then daily until 2 consecutive ANCs of ≥ 0.5 x 10<sup>9</sup>/L were recorded. Drug concentration measurements (cycle 1 and 3) predose and 1, 2, and 4 hours postdose and then daily from days 7-21.

**Statistical information (statistical analyses of the data to be performed):** The study was designed to provide descriptive statistics regarding the duration of severe neutropenia, depth of the ANC nadir, time to ANC recovery, and proportion of subjects who had an ANC < 0.5 x 10<sup>9</sup>/L day 21 of cycle 1 and cycle 3.

**Overall conclusions (Summary of Safety and Efficacy)**

The small numbers of subjects in this study, particularly on the filgrastim control arm, preclude the ability to draw any definitive conclusions regarding efficacy of pegfilgrastim in decreasing the incidence of infection based on either the number of episodes of febrile neutropenia or the duration of severe neutropenia observed in the two arms of this study. The following table briefly depicts the study results for cycle 1. See Tables 9-1 through 9-6 beginning on page 102 of the Amgen FSR for Study 990130 (19-JUL-07) for a complete summary of the efficacy results.

There were no new safety signals identified in this pediatric study. Bone pain was the most common treatment emergent adverse event occurring in 11% of subjects on the pegfigrastim arm and 17% of subjects on the filgrastim arm.

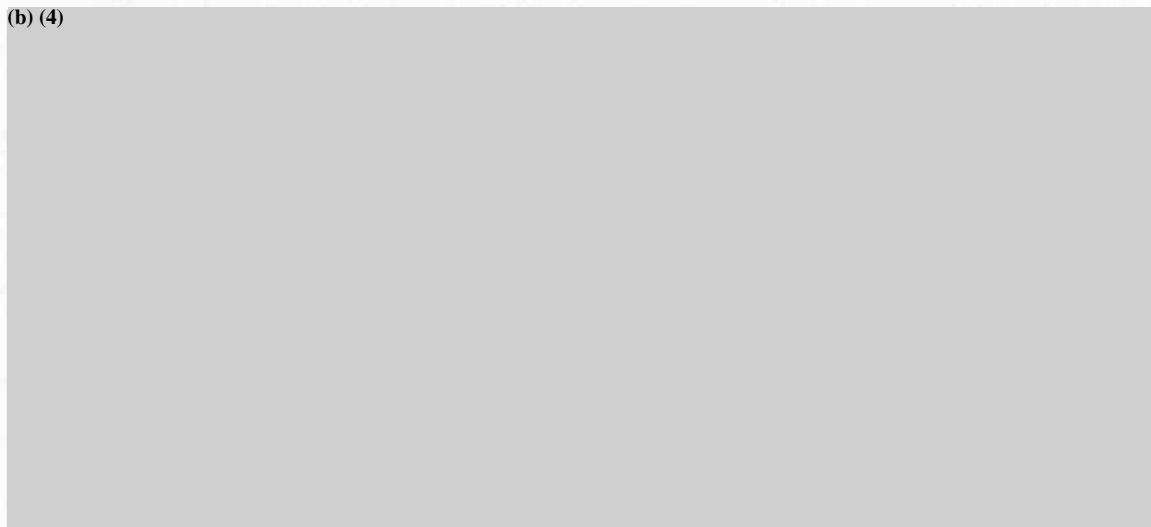
Age group	Duration of Severe Neutropenia						Time to ANC Recovery						Incidence of Febrile Neutropenia					
	0-1		6-11		12-21		0-1		6-11		12-21		0-1		6-11		12-21	
Drug	f	p	f	p	f	p	f	p	f	p	f	p	f	p	f	p	f	p
N	1	12	2	10	3	15	1	12	2	10	3	15	1	12	2	10	3	15
N (severe neutropenia ANC <500)	1	12	1	10	3	13												
Mean days	9.0	8.9	3.5	6.0	5.3	3.7												
Median days	9.0	8.0	3.5	6.0	6.0	4.0	16.0	15.0	15.0	14.0	14.0	13.0						
ANC < 500 T≥38.2°C													1 (100%)	10 (83%)	1 (50%)	8 (80%)	3 (100%)	7 (47%)

**Labelling**

*The Sponsor proposed the following Labelling Changes:*

**Pediatric Use**

(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.

# 2 Page(s) Withheld

       Trade Secret / Confidential (b4)

✓ Draft Labeling (b4)

       Draft Labeling (b5)

       Deliberative Process (b5)