

CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

125031Orig1s203

Trade Name: Neulasta for injection

Generic or Proper Name: pegfilgrastim, 6 mg/06mL solution

Sponsor: Amgen, Inc.

Approval Date: February 2, 2021

Indication: This supplement provides for:

Addition of “Thrombocytopenia: Monitor platelet counts. (5.8)” to Highlights, Warnings and Precautions subsection to reflect the new Warning added in the Full Prescribing Information.

Addition of “Myelodysplastic Syndrome and Acute Myeloid Leukemia: Monitor patients with breast and lung cancer using Neulasta in conjunction with chemotherapy and/or radiotherapy for signs and symptoms of MDS/AML. (5.11)” to Highlights Warnings and Precautions subsection to reflect the new Warning added in the Full Prescribing Information.

“Fatal sickle cell crises” wording in the Warnings and Precautions section of Highlights is being updated for clarity in alignment with the Warnings and Precautions in section 5.5.

Acute Myeloid Leukemia/Myelodysplastic Syndrome wording in section 17 Patient Counseling Information is being corrected since information applicable only to Neupogen (filgrastim) was inadvertently included in the S-202 final approved label.

CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number:
125031Orig1s203

CONTENTS

Reviews / Information Included in this NDA Review.

Approval Letter	X
Other Action Letters	
Labeling	X
REMS	
Summary Review	
Office Director Memo	
Clinical Review	
Product Quality Review	
Environmental Assessment	
Non-Clinical Review	
Statistical Review	
Product Quality Review	
Other Reviews	X

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

125031Orig1s203

APPROVAL LETTER



BLA 125031/S-203

SUPPLEMENT APPROVAL

Amgen, INC.
Attention: Jose Alberto Huerta Salazar
Senior Manager, Regulatory Affairs
One Amgen Center Drive
Mail Stop: 27-2-D
Thousand Oaks, CA 91320-1799

Dear Mr. Salazar:

Please refer to your supplemental biologics license application (sBLA), dated and received February 1, 2021, submitted under section 351(a) of the Public Health Service Act for Neulasta (pegfilgrastim) 6 mg/0.6 mL Solution for Injection.

This “Changes Being Effectuated” supplemental biologics application provides for:

- Addition of “Thrombocytopenia: Monitor platelet counts. (5.8)” to Highlights, Warnings and Precautions subsection to reflect the new Warning added in the Full Prescribing Information.
- Addition of “Myelodysplastic Syndrome and Acute Myeloid Leukemia: Monitor patients with breast and lung cancer using Neulasta in conjunction with chemotherapy and/or radiotherapy for signs and symptoms of MDS/AML. (5.11)” to Highlights Warnings and Precautions subsection to reflect the new Warning added in the Full Prescribing Information.
- “Fatal sickle cell crises” wording in the Warnings and Precautions section of Highlights is being updated for clarity in alignment with the Warnings and Precautions in section 5.5.
- Acute Myeloid Leukemia/Myelodysplastic Syndrome wording in section 17 Patient Counseling Information is being corrected since information applicable only to Neupogen (filgrastim) was inadvertently included in the S-202 final approved label.

APPROVAL & LABELING

We have completed our review of this application. It is approved, effective on the date of this letter, for use as recommended in the enclosed agreed-upon labeling.

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, submit, via the FDA automated drug registration and listing system (eLIST), the content of labeling [21 CFR 601.14(b)] in structured product labeling (SPL) format, as described at FDA.gov,¹ that is identical to the enclosed labeling (text for the Prescribing Information) and include the labeling changes proposed in any pending “Changes Being Effectuated” (CBE) supplements.

Information on submitting SPL files using eLIST may be found in the guidance for industry *SPL Standard for Content of Labeling Technical Qs and As*.²

The SPL will be accessible via publicly available labeling repositories.

Also within 14 days, amend all pending supplemental applications that include labeling changes for this BLA, including pending “Changes Being Effectuated” (CBE) supplements, for which FDA has not yet issued an action letter, with the content of labeling [21 CFR 601.12(f)] in Microsoft Word format that includes the changes approved in this supplemental application, as well as annual reportable changes. To facilitate review of your submission(s), provide a highlighted or marked-up copy that shows all changes, as well as a clean Microsoft Word version. The marked-up copy should provide appropriate annotations, including supplement number(s) and annual report date(s).

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients (which includes new salts and new fixed combinations), new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

Because none of these criteria apply to your application, you are exempt from this requirement.

PROMOTIONAL MATERIALS

You may request advisory comments on proposed introductory advertising and promotional labeling. For information about submitting promotional materials, see the final guidance for industry *Providing Regulatory Submissions in Electronic and Non-*

¹ <http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm>

² We update guidances periodically. For the most recent version of a guidance, check the FDA Guidance Documents Database <https://www.fda.gov/RegulatoryInformation/Guidances/default.htm>.

*Electronic Format—Promotional Labeling and Advertising Materials for Human Prescription Drugs.*³

As required under 21 CFR 601.12(f)(4), you must submit final promotional materials, and the Prescribing Information, at the time of initial dissemination or publication, accompanied by a Form FDA 2253. Form FDA 2253 is available at FDA.gov.⁴ Information and Instructions for completing the form can be found at FDA.gov.⁵

All promotional materials for your drug product that include representations about your drug product must be promptly revised to make it consistent with the labeling changes approved in this supplement, including any new safety information [21 CFR 601.12(a)(4)]. The revisions to your promotional materials should include prominent disclosure of the important new safety information that appears in the revised labeling. Within 7 days of receipt of this letter, submit your statement of intent to comply with 21 CFR 601.12(a)(4).

REPORTING REQUIREMENTS

We remind you that you must comply with reporting requirements for an approved BLA (in 21 CFR 600.80 and in 21 CFR 600.81).

If you have any questions, contact Courtney Hamilton, Regulatory Project Manager at 301-796-6849 or at Courtney.Hamilton@fda.hhs.gov.

Sincerely,

{See appended electronic signature page}

Ann T. Farrell, MD
Director
Division of Nonmalignant Hematology
Office of Cardiology, Hematology,
Endocrinology, and Nephrology
Center for Drug Evaluation and Research

ENCLOSURE(S):

- Content of Labeling
 - Prescribing Information

³ For the most recent version of a guidance, check the FDA guidance web page at <https://www.fda.gov/media/128163/download>.

⁴ <http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM083570.pdf>

⁵ <http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM375154.pdf>

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

ANN T FARRELL
02/02/2021 02:30:09 PM

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

125031Orig1s203

LABELING

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use NEULASTA safely and effectively. See [full prescribing information for NEULASTA](#).

NEULASTA® (pegfilgrastim) injection, for subcutaneous use
Initial U.S. Approval: 2002

RECENT MAJOR CHANGES

Warnings and Precautions, Thrombocytopenia (5.8) 01/2021
Warnings and Precautions, Myelodysplastic Syndrome (MDS) and Acute Myeloid Leukemia (AML) (5.11) 01/2021

INDICATIONS AND USAGE

- Neulasta is a leukocyte growth factor 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. (1.1)
 - Increase survival in patients acutely exposed to myelosuppressive doses of radiation (Hematopoietic Subsyndrome of Acute Radiation Syndrome). (1.2)

Limitations of Use

Neulasta is not indicated for the mobilization of peripheral blood progenitor cells for hematopoietic stem cell transplantation.

DOSAGE AND ADMINISTRATION

- Patients with cancer receiving myelosuppressive chemotherapy
 - 6 mg administered subcutaneously once per chemotherapy cycle. (2.1)
 - Do not administer between 14 days before and 24 hours after administration of cytotoxic chemotherapy. (2.1)
 - Use weight based dosing for pediatric patients weighing less than 45 kg; refer to Table 1. (2.3)
- Patients acutely exposed to myelosuppressive doses of radiation
 - Two doses, 6 mg each, administered subcutaneously one week apart. Administer the first dose as soon as possible after suspected or confirmed exposure to myelosuppressive doses of radiation, and a second dose one week after. (2.2)
 - Use weight based dosing for pediatric patients weighing less than 45 kg; refer to Table 1. (2.3)

DOSAGE FORMS AND STRENGTHS

- Injection: 6 mg/0.6 mL solution in a single-dose prefilled syringe for manual use only. (3)

- Injection: 6 mg/0.6 mL solution in a single-dose prefilled syringe co-packaged with the on-body injector for Neulasta. (3)

CONTRAINDICATIONS

Patients with a history of serious allergic reactions to human granulocyte colony-stimulating factors such as pegfilgrastim or filgrastim. (4)

WARNINGS AND PRECAUTIONS

- Fatal splenic rupture: Evaluate patients who report left upper abdominal or shoulder pain for an enlarged spleen or splenic rupture. (5.1)
- Acute respiratory distress syndrome (ARDS): Evaluate patients who develop fever, lung infiltrates, or respiratory distress. Discontinue Neulasta in patients with ARDS. (5.2)
- Serious allergic reactions, including anaphylaxis: Permanently discontinue Neulasta in patients with serious allergic reactions. (5.3)
- The on-body injector for Neulasta uses acrylic adhesive. For patients who have reactions to acrylic adhesives, use of this product may result in a significant reaction. (5.4)
- Fatal sickle cell crises: Discontinue Neulasta if sickle cell crisis occurs. (5.5)
- Glomerulonephritis: Evaluate and consider dose-reduction or interruption of Neulasta if causality is likely. (5.6)
- Thrombocytopenia: Monitor platelet counts. (5.8)
- Myelodysplastic Syndrome (MDS) and Acute Myeloid Leukemia (AML): Monitor patients with breast and lung cancer using Neulasta in conjunction with chemotherapy and/or radiotherapy for signs and symptoms of MDS/AML. (5.11)
- Potential device failures: Instruct patients to notify their healthcare provider if they suspect the on-body injector may not have performed as intended. (5.12)

ADVERSE REACTIONS

Most common adverse reactions (≥ 5% difference in incidence compared to placebo) are bone pain and pain in extremity. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Amgen Inc. at 1-800-77-AMGEN (1-800-772-6436) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling

Revised: 02/2021

FULL PRESCRIBING INFORMATION: CONTENTS*

1 INDICATIONS AND USAGE

- 1.1 Patients with Cancer Receiving Myelosuppressive Chemotherapy
- 1.2 Patients with Hematopoietic Subsyndrome of Acute Radiation Syndrome

2 DOSAGE AND ADMINISTRATION

- 2.1 Patients with Cancer Receiving Myelosuppressive Chemotherapy
- 2.2 Patients with Hematopoietic Subsyndrome of Acute Radiation Syndrome
- 2.3 Administration
- 2.4 Special Healthcare Provider Instructions for the On-body Injector for Neulasta
- 2.5 Advice to Give to Patients Regarding Administration via the On-body Injector for Neulasta

3 DOSAGE FORMS AND STRENGTHS

4 CONTRAINDICATIONS

5 WARNINGS AND PRECAUTIONS

- 5.1 Splenic Rupture
- 5.2 Acute Respiratory Distress Syndrome
- 5.3 Serious Allergic Reactions
- 5.4 Allergies to Acrylics
- 5.5 Use in Patients with Sickle Cell Disorders
- 5.6 Glomerulonephritis
- 5.7 Leukocytosis
- 5.8 Thrombocytopenia
- 5.9 Capillary Leak Syndrome
- 5.10 Potential for Tumor Growth Stimulatory Effects on Malignant Cells

5.11 Myelodysplastic Syndrome (MDS) and Acute Myeloid Leukemia (AML) in Patients with Breast and Lung Cancer

5.12 Potential Device Failures

5.13 Aortitis

5.14 Nuclear Imaging

6 ADVERSE REACTIONS

6.1 Clinical Trials Experience

6.2 Immunogenicity

6.3 Postmarketing Experience

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

8.2 Lactation

8.4 Pediatric Use

8.5 Geriatric Use

10 OVERDOSAGE

11 DESCRIPTION

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

12.2 Pharmacodynamics

12.3 Pharmacokinetics

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

14 CLINICAL STUDIES

14.1 Patients with Cancer Receiving Myelosuppressive Chemotherapy

14.2 Patients with Hematopoietic Subsyndrome of Acute Radiation Syndrome

16 HOW SUPPLIED/STORAGE AND HANDLING

17 PATIENT COUNSELING INFORMATION

*Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

1.1 Patients with Cancer Receiving Myelosuppressive Chemotherapy

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 [*see Clinical Studies (14.1)*].

Limitations of Use

Neulasta is not indicated for the mobilization of peripheral blood progenitor cells for hematopoietic stem cell transplantation.

1.2 Patients with Hematopoietic Subsyndrome of Acute Radiation Syndrome

Neulasta is indicated to increase survival in patients acutely exposed to myelosuppressive doses of radiation [*see Dosage and Administration (2.2) and Clinical Studies (14.2)*].

2 DOSAGE AND ADMINISTRATION

2.1 Patients with Cancer Receiving Myelosuppressive Chemotherapy

The recommended dosage of Neulasta is a single subcutaneous injection of 6 mg administered once per chemotherapy cycle. For dosing in pediatric patients weighing less than 45 kg, refer to Table 1. Do not administer Neulasta between 14 days before and 24 hours after administration of cytotoxic chemotherapy.

2.2 Patients with Hematopoietic Subsyndrome of Acute Radiation Syndrome

The recommended dose of Neulasta is two doses, 6 mg each, administered subcutaneously one week apart. For dosing in pediatric patients weighing less than 45 kg, refer to Table 1. Administer the first dose as soon as possible after suspected or confirmed exposure to radiation levels greater than 2 gray (Gy). Administer the second dose one week after the first dose.

Obtain a baseline complete blood count (CBC). Do not delay administration of Neulasta if a CBC is not readily available. Estimate a patient's absorbed radiation dose (i.e., level of radiation exposure) based on information from public health authorities, biodosimetry if available, or clinical findings such as time to onset of vomiting or lymphocyte depletion kinetics.

2.3 Administration

Neulasta is administered subcutaneously via a single-dose prefilled syringe for manual use or for use with the on-body injector (OBI) for Neulasta, which is co-packaged with a single-dose prefilled syringe. Use of the OBI for Neulasta is not recommended for patients with Hematopoietic Subsyndrome of Acute Radiation Syndrome. Use of the OBI for Neulasta has not been studied in pediatric patients.

Prior to use, remove the carton from the refrigerator and allow the Neulasta prefilled syringe to reach room temperature for a minimum of 30 minutes. Discard any prefilled syringe left at room temperature for greater than 48 hours.

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit. Do not administer Neulasta if discoloration or particulates are observed.

The needle cap on the prefilled syringes contains dry natural rubber (derived from latex); persons with latex allergies should not administer these products.

Pediatric Patients weighing less than 45 kg

The Neulasta prefilled syringe is not designed to allow for direct administration of doses less than 0.6 mL (6 mg). The syringe does not bear graduation marks, which are necessary to accurately measure doses of Neulasta less than 0.6 mL (6 mg) for direct administration to patients. Thus, the direct administration to patients requiring dosing of less than 0.6 mL (6 mg) is not recommended due to the potential for dosing errors. Refer to Table 1.

Table 1. Dosing of Neulasta for pediatric patients weighing less than 45 kg

Body Weight	Neulasta Dose	Volume to Administer
Less than 10 kg*	See below*	See below*
10 - 20 kg	1.5 mg	0.15 mL
21 - 30 kg	2.5 mg	0.25 mL
31 - 44 kg	4 mg	0.4 mL

*For pediatric patients weighing less than 10 kg, administer 0.1 mg/kg (0.01 mL/kg) of Neulasta.

2.4 Special Healthcare Provider Instructions for the On-body Injector for Neulasta

A healthcare provider must fill the on-body injector (OBI) with Neulasta using the prefilled syringe and then apply the OBI for Neulasta to the patient's skin (abdomen or back of arm). The back of the arm may only be used if there is a caregiver available to monitor the status of the OBI for Neulasta. Approximately 27 hours after the OBI for Neulasta is applied to the patient's skin, Neulasta will be delivered over approximately 45 minutes. A healthcare provider may initiate administration with the OBI for Neulasta on the same day as the administration of cytotoxic chemotherapy, as long as the OBI for Neulasta delivers Neulasta no less than 24 hours after administration of cytotoxic chemotherapy.

The prefilled syringe co-packaged in Neulasta Onpro® kit must only be used with the OBI for Neulasta. The prefilled syringe contains additional solution to compensate for liquid loss during delivery through the OBI for Neulasta. If the prefilled syringe co-packaged in Neulasta Onpro kit is used for manual subcutaneous injection, the patient will receive an overdose. If the single-dose prefilled syringe for manual use is used with the OBI for Neulasta, the patient may receive less than the recommended dose.

Do not use the OBI for Neulasta to deliver any other drug product except the Neulasta prefilled syringe co-packaged with the OBI for Neulasta.

The OBI for Neulasta should be applied to intact, non-irritated skin on the arm or abdomen.

A missed dose could occur due to an OBI for Neulasta failure or leakage. If the patient misses a dose, a new dose should be administered by single-dose prefilled syringe for manual use, as soon as possible after detection.

Refer to the Healthcare Provider Instructions for Use for the OBI for Neulasta for full administration information.

2.5 Advice to Give to Patients Regarding Administration via the On-body Injector for Neulasta

Advise patients to avoid activities such as traveling, driving, or operating heavy machinery during hours 26-29 following application of the on-body injector (OBI) for Neulasta (this includes the 45-minute delivery period plus an hour post-delivery). Patients should have a caregiver nearby for the first use.

Refer the patient to the dose delivery information written on the Patient Instructions for Use. Provide training to patients to ensure they understand when the dose delivery of Neulasta will begin and how to monitor the OBI for Neulasta for completed delivery. Ensure patients understand how to identify signs of malfunction of OBI for Neulasta [see *Warnings and Precautions (5.12) and Patient Counseling Information (17)*]. Instruct patients using the OBI to notify their healthcare professional immediately in order to determine the need for a replacement dose of Neulasta if they suspect that the device may not have performed as intended [see *Warnings and Precautions (5.12)*].

3 DOSAGE FORMS AND STRENGTHS

Neulasta is a clear, colorless, preservative-free solution available as:

- Injection: 6 mg/0.6 mL in a single-dose prefilled syringe for manual use only.
- Injection: 6 mg/0.6 mL in a single-dose prefilled syringe co-packaged with the on-body injector (OBI) for Neulasta (Neulasta Onpro kit).

4 CONTRAINDICATIONS

Neulasta is contraindicated in patients with a history of serious allergic reactions to pegfilgrastim or filgrastim. Reactions have included anaphylaxis [see *Warnings and Precautions (5.3)*].

5 WARNINGS AND PRECAUTIONS

5.1 Splenic Rupture

Splenic rupture, including fatal cases, can occur following the administration of Neulasta. Evaluate for an enlarged spleen or splenic rupture in patients who report left upper abdominal or shoulder pain after receiving Neulasta.

5.2 Acute Respiratory Distress Syndrome

Acute respiratory distress syndrome (ARDS) can occur in patients receiving Neulasta. Evaluate patients who develop fever and lung infiltrates or respiratory distress after receiving Neulasta, for ARDS. Discontinue Neulasta in patients with ARDS.

5.3 Serious Allergic Reactions

Serious allergic reactions, including anaphylaxis, can occur in patients receiving Neulasta. The majority of reported events occurred upon initial exposure. Allergic reactions, including anaphylaxis, can recur within days after the discontinuation of initial anti-allergic treatment. Permanently discontinue Neulasta in patients with serious allergic reactions. Do not administer Neulasta to patients with a history of serious allergic reactions to pegfilgrastim or filgrastim.

5.4 Allergies to Acrylics

The on-body injector (OBI) for Neulasta uses acrylic adhesive. For patients who have reactions to acrylic adhesives, use of this product may result in a significant reaction.

5.5 Use in Patients with Sickle Cell Disorders

Severe and sometimes fatal sickle cell crises can occur in patients with sickle cell disorders receiving pegfilgrastim products. Discontinue Neulasta if sickle cell crisis occurs.

5.6 Glomerulonephritis

Glomerulonephritis has occurred in patients receiving Neulasta. The diagnoses were based upon azotemia, hematuria (microscopic and macroscopic), proteinuria, and renal biopsy. Generally, events of glomerulonephritis resolved after dose-reduction or discontinuation of Neulasta. If glomerulonephritis is suspected, evaluate for cause. If causality is likely, consider dose-reduction or interruption of Neulasta.

5.7 Leukocytosis

White blood cell (WBC) counts of $100 \times 10^9/L$ or greater have been observed in patients receiving pegfilgrastim. Monitoring of complete blood count (CBC) during pegfilgrastim therapy is recommended.

5.8 Thrombocytopenia

Thrombocytopenia has been reported in patients receiving pegfilgrastim. Monitor platelet counts.

5.9 Capillary Leak Syndrome

Capillary leak syndrome has been reported after G-CSF administration, including Neulasta, and is characterized by hypotension, hypoalbuminemia, edema and hemoconcentration. Episodes vary in frequency, severity and may be life-threatening if treatment is delayed. Patients who develop symptoms of capillary leak syndrome should be closely monitored and receive standard symptomatic treatment, which may include a need for intensive care.

5.10 Potential for Tumor Growth Stimulatory Effects on Malignant Cells

The granulocyte colony-stimulating factor (G-CSF) receptor through which pegfilgrastim and filgrastim act has been found on tumor cell lines. The possibility that pegfilgrastim acts as a growth factor for any tumor type, including myeloid malignancies and myelodysplasia, diseases for which pegfilgrastim is not approved, cannot be excluded.

5.11 Myelodysplastic Syndrome (MDS) and Acute Myeloid Leukemia (AML) in Patients with Breast and Lung Cancer

MDS and AML have been associated with the use of Neulasta in conjunction with chemotherapy and/or radiotherapy in patients with breast and lung cancer. Monitor patients for signs and symptoms of MDS/AML in these settings.

5.12 Potential Device Failures

Missed or partial doses have been reported in patients receiving Neulasta via the on-body injector (OBI) due to the device not performing as intended. In the event of a missed or partial dose, patients may be at increased risk of events such as neutropenia, febrile neutropenia and/or infection than if the dose had been correctly delivered. Instruct patients using the OBI to notify their healthcare professional immediately in order to determine the need for a replacement dose of Neulasta if they suspect that the device may not have performed as intended.

5.13 Aortitis

Aortitis has been reported in patients receiving Neulasta. It may occur as early as the first week after start of therapy. Manifestations may include generalized signs and symptoms such as fever, abdominal pain, malaise, back pain, and increased inflammatory markers (e.g., c-reactive protein and white blood cell count). Consider aortitis in patients who develop these signs and symptoms without known etiology. Discontinue Neulasta if aortitis is suspected.

5.14 Nuclear Imaging

Increased hematopoietic activity of the bone marrow in response to growth factor therapy has been associated with transient positive bone imaging changes. This should be considered when interpreting bone imaging results.

6 ADVERSE REACTIONS

The following clinically significant adverse reactions are discussed in greater detail in other sections of the labeling:

- Splenic Rupture [see Warnings and Precautions (5.1)]
- Acute Respiratory Distress Syndrome [see Warnings and Precautions (5.2)]
- Serious Allergic Reactions [see Warnings and Precautions (5.3)]
- Allergies to Acrylics [see Warnings and Precautions (5.4)]
- Use in Patients with Sickle Cell Disorders [see Warnings and Precautions (5.5)]
- Glomerulonephritis [see Warnings and Precautions (5.6)]
- Leukocytosis [see Warnings and Precautions (5.7)]
- Thrombocytopenia [see Warnings and Precautions (5.8)]
- Capillary Leak Syndrome [see Warnings and Precautions (5.9)]
- Potential for Tumor Growth Stimulatory Effects on Malignant Cells [see Warnings and Precautions (5.10)]
- Myelodysplastic syndrome [see Warnings and Precautions (5.11)]
- Acute myeloid leukemia [see Warnings and Precautions (5.11)]
- Aortitis [see Warnings and Precautions (5.13)]

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared with rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice.

Neulasta clinical trials safety data are based upon 932 patients receiving Neulasta in seven randomized clinical trials. The population was 21 to 88 years of age and 92% female. The ethnicity was 75% Caucasian, 18% Hispanic, 5% Black, and 1% Asian. Patients with breast (n = 823), lung and thoracic tumors (n = 53) and lymphoma (n = 56) received Neulasta after nonmyeloablative cytotoxic chemotherapy. Most patients received a single 100 mcg/kg (n = 259) or a single 6 mg (n = 546) dose per chemotherapy cycle over 4 cycles.

The following adverse reaction data in Table 2 are from a randomized, double-blind, placebo-controlled study in patients with metastatic or non-metastatic breast cancer receiving docetaxel 100 mg/m² every 21 days (Study 3). A total of 928 patients were randomized to receive either 6 mg Neulasta (n = 467) or placebo (n = 461). The patients were 21 to 88 years of age and 99% female. The ethnicity was 66% Caucasian, 31% Hispanic, 2% Black, and < 1% Asian, Native American, or other.

The most common adverse reactions occurring in $\geq 5\%$ of patients and with a between-group difference of $\geq 5\%$ higher in the pegfilgrastim arm in placebo-controlled clinical trials are bone pain and pain in extremity.

Table 2. Adverse Reactions with $\geq 5\%$ Higher Incidence in Neulasta Patients Compared to Placebo in Study 3

Body System Adverse Reaction	Placebo (N = 461)	Neulasta 6 mg SC on Day 2 (N = 467)
Musculoskeletal and connective tissue disorders		
Bone pain	26%	31%
Pain in extremity	4%	9%

Leukocytosis

In clinical studies, leukocytosis (WBC counts $> 100 \times 10^9/L$) was observed in less than 1% of 932 patients with non-myeloid malignancies receiving Neulasta. No complications attributable to leukocytosis were reported in clinical studies.

6.2 Immunogenicity

As with all therapeutic proteins, there is a potential for immunogenicity. The detection of antibody formation is highly dependent on the sensitivity and specificity of the assay. Additionally, the observed incidence of antibody (including neutralizing antibody) positivity in an assay may be influenced by several factors, including assay methodology, sample handling, timing of sample collection, concomitant medications, and underlying disease. For these reasons, comparison of the incidence of antibodies to pegfilgrastim in the studies described below with the incidence of antibodies in other studies or to other products may be misleading.

Binding antibodies to pegfilgrastim were detected using a BIAcore assay. The approximate limit of detection for this assay is 500 ng/mL. Pre-existing binding antibodies were detected in approximately 6% (51/849) of patients with metastatic breast cancer. Four of 521 pegfilgrastim-treated subjects who were negative at baseline developed binding antibodies to pegfilgrastim following treatment. None of these 4 patients had evidence of neutralizing antibodies detected using a cell-based bioassay.

6.3 Postmarketing Experience

The following adverse reactions have been identified during post approval use of Neulasta. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

- Splenic rupture and splenomegaly (enlarged spleen) [see Warnings and Precautions (5.1)]
- Acute respiratory distress syndrome (ARDS) [see Warnings and Precautions (5.2)]
- Allergic reactions/hypersensitivity, including anaphylaxis, skin rash, urticaria, generalized erythema, and flushing [see Warnings and Precautions (5.3)]
- Sick cell crisis [see Warnings and Precautions (5.5)]
- Glomerulonephritis [see Warnings and Precautions (5.6)]
- Leukocytosis [see Warnings and Precautions (5.7)]
- Thrombocytopenia [see Warnings and Precautions (5.8)]
- Capillary Leak Syndrome [see Warnings and Precautions (5.9)]

- Injection site reactions
- Sweet's syndrome (acute febrile neutrophilic dermatosis), cutaneous vasculitis
- Application site reactions (including events such as application site hemorrhage, application site pain, application site discomfort, application site bruise, and application site erythema) have been reported with the use of the on-body injector for Neulasta.
- Contact dermatitis and local skin reactions such as rash, pruritus, and urticaria have been reported with the use of the on-body injector for Neulasta, possibly indicating a hypersensitivity reaction to the adhesive.
- Myelodysplastic syndrome (MDS) and acute myeloid leukemia (AML) in patients with breast and lung cancer receiving chemotherapy and/or radiotherapy [see *Warnings and Precautions (5.11)*]
- Aortitis [see *Warnings and Precautions (5.13)*]
- Alveolar hemorrhage

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Although available data with Neulasta use in pregnant women are insufficient to establish whether there is a drug associated risk of major birth defects, miscarriage, or adverse maternal or fetal outcomes, there are available data from published studies in pregnant women exposed to filgrastim products. These studies have not established an association of filgrastim product use during pregnancy with major birth defects, miscarriage, or adverse maternal or fetal outcomes.

In animal studies, no evidence of reproductive/developmental toxicity occurred in the offspring of pregnant rats that received cumulative doses of pegfilgrastim approximately 10 times the recommended human dose (based on body surface area). In pregnant rabbits, increased embryoletality and spontaneous abortions occurred at 4 times the maximum recommended human dose simultaneously with signs of maternal toxicity (*see Data*).

The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. In the U.S. general population, the estimated background risks of major birth defects and miscarriage in clinically recognized pregnancies is 2-4% and 15-20%, respectively.

Data

Animal Data

Pregnant rabbits were dosed with pegfilgrastim subcutaneously every other day during the period of organogenesis. At cumulative doses ranging from the approximate human dose to approximately 4 times the recommended human dose (based on body surface area), the treated rabbits exhibited decreased maternal food consumption, maternal weight loss, as well as reduced fetal body weights and delayed ossification of the fetal skull; however, no structural anomalies were observed in the offspring from either study. Increased incidences of post-implantation losses and spontaneous abortions (more than half the pregnancies) were observed at cumulative doses approximately 4 times the recommended human dose, which were not seen when pregnant rabbits were exposed to the recommended human dose.

Three studies were conducted in pregnant rats dosed with pegfilgrastim at cumulative doses up to approximately 10 times the recommended human dose at the following stages of gestation: during the period of organogenesis, from mating through the first half of pregnancy, and from the first trimester through delivery and lactation. No evidence of fetal loss or structural malformations was observed in any study. Cumulative doses equivalent to approximately 3 and 10 times the recommended human dose resulted in transient evidence of wavy ribs in fetuses of treated mothers (detected at the end of gestation but no longer present in pups evaluated at the end of lactation).

8.2 Lactation

Risk Summary

There are no data on the presence of pegfilgrastim in human milk, the effects on the breastfed child, or the effects on milk production. Other filgrastim products are secreted poorly into breast milk, and filgrastim products are not absorbed orally by neonates. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for Neulasta and any potential adverse effects on the breastfed child from Neulasta or from the underlying maternal condition.

8.4 Pediatric Use

The safety and effectiveness of Neulasta have been established in pediatric patients. No overall differences in safety were identified between adult and pediatric patients based on postmarketing surveillance and review of the scientific literature.

Use of Neulasta in pediatric patients for chemotherapy-induced neutropenia is based on adequate and well-controlled studies in adults with additional pharmacokinetic and safety data in pediatric patients with sarcoma [see *Clinical Pharmacology (12.3) and Clinical Studies (14.1)*].

The use of Neulasta to increase survival in pediatric patients acutely exposed to myelosuppressive doses of radiation is based on efficacy studies conducted in animals and clinical data supporting the use of Neulasta in patients with cancer receiving myelosuppressive chemotherapy. Efficacy studies of Neulasta could not be conducted in humans with acute radiation syndrome for ethical and feasibility reasons. Results from population modeling and simulation indicate that two doses of Neulasta (Table 1), administered one week apart provide pediatric patients with exposures comparable to that in adults receiving two 6 mg doses one week apart [see *Dosage and Administration (2.3), Clinical Pharmacology (12.3) and Clinical Studies (14.2)*].

8.5 Geriatric Use

Of the 932 patients with cancer who received Neulasta in clinical studies, 139 (15%) were aged 65 and over, and 18 (2%) were aged 75 and over. No overall differences in safety or effectiveness were observed between patients aged 65 and older and younger patients.

10 OVERDOSAGE

Overdosage of Neulasta may result in leukocytosis and bone pain. Events of edema, dyspnea, and pleural effusion have been reported in a single patient who administered Neulasta on 8 consecutive days in error. In the event of overdose, the patient should be monitored for adverse reactions [see *Adverse Reactions (6)*].

11 DESCRIPTION

Pegfilgrastim is a covalent conjugate of recombinant methionyl human G-CSF (filgrastim) and monomethoxypolyethylene glycol. Filgrastim is a water-soluble 175 amino acid protein with a molecular weight of approximately 19 kilodaltons (kD). Filgrastim is obtained from the bacterial fermentation of a strain of *E coli* transformed with a genetically engineered plasmid containing the human G-CSF gene. To produce pegfilgrastim, a 20 kD monomethoxypolyethylene glycol molecule is covalently bound to the N-terminal methionyl residue of filgrastim. The average molecular weight of pegfilgrastim is approximately 39 kD.

Neulasta is provided in two presentations:

- Neulasta for manual subcutaneous injection is supplied in 0.6 mL prefilled syringes. The prefilled syringe does not bear graduation marks and is designed to deliver the entire contents of the syringe (6 mg/0.6 mL).

- On-body injector (OBI) for Neulasta is supplied with a prefilled syringe containing 0.64 mL of Neulasta in solution that delivers 0.6 mL of Neulasta in solution when used with the OBI for Neulasta. The syringe does not bear graduation marks and is only to be used with the OBI for Neulasta.

The delivered 0.6 mL dose from either the prefilled syringe for manual subcutaneous injection or the OBI for Neulasta contains 6 mg pegfilgrastim (based on protein weight) in a sterile, clear, colorless, preservative-free solution (pH 4.0) containing acetate (0.35 mg), polysorbate 20 (0.02 mg), sodium (0.02 mg), and sorbitol (30 mg) in Water for Injection, USP.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Pegfilgrastim is a colony-stimulating factor that acts on hematopoietic cells by binding to specific cell surface receptors, thereby stimulating proliferation, differentiation, commitment, and end cell functional activation.

12.2 Pharmacodynamics

Animal data and clinical data in humans suggest a correlation between pegfilgrastim exposure and the duration of severe neutropenia as a predictor of efficacy. Selection of the dosing regimen of Neulasta is based on reducing the duration of severe neutropenia.

12.3 Pharmacokinetics

The pharmacokinetics of pegfilgrastim was studied in 379 patients with cancer. The pharmacokinetics of pegfilgrastim was nonlinear, and clearance decreased with increases in dose. Neutrophil receptor binding is an important component of the clearance of pegfilgrastim, and serum clearance is directly related to the number of neutrophils. In addition to numbers of neutrophils, body weight appeared to be a factor. Patients with higher body weights experienced higher systemic exposure to pegfilgrastim after receiving a dose normalized for body weight. A large variability in the pharmacokinetics of pegfilgrastim was observed. The half-life of Neulasta ranged from 15 to 80 hours after subcutaneous injection. In healthy volunteers, the pharmacokinetics of pegfilgrastim were comparable when delivered subcutaneously via a manual prefilled syringe versus via the on-body injector (OBI) for Neulasta.

Specific Populations

No gender-related differences were observed in the pharmacokinetics of pegfilgrastim, and no differences were observed in the pharmacokinetics of geriatric patients (≥ 65 years of age) compared with younger patients (< 65 years of age) [see *Use in Specific Populations (8.5)*].

Renal Impairment

In a study of 30 subjects with varying degrees of renal dysfunction, including end stage renal disease, renal dysfunction had no effect on the pharmacokinetics of pegfilgrastim.

Pediatric Patients with Cancer Receiving Myelosuppressive Chemotherapy

The pharmacokinetics and safety of pegfilgrastim were studied in 37 pediatric patients with sarcoma in Study 4 [see *Clinical Studies (14.1)*]. The mean (\pm standard deviation [SD]) systemic exposure (AUC_{0-inf}) of Neulasta after subcutaneous administration at 100 mcg/kg was 47.9 (± 22.5) mcg·hr/mL in the youngest age group (0 to 5 years, $n = 11$), 22.0 (± 13.1) mcg·hr/mL in the 6 to 11 years age group ($n = 10$), and 29.3 (± 23.2) mcg·hr/mL in the 12 to 21 years age group ($n = 13$). The terminal elimination half-lives of the corresponding age groups were 30.1 (± 38.2) hours, 20.2 (± 11.3) hours, and 21.2 (± 16.0) hours, respectively.

Patients Acutely Exposed to Myelosuppressive Doses of Radiation

The pharmacokinetics of pegfilgrastim is not available in patients acutely exposed to myelosuppressive doses of radiation. Based on limited pharmacokinetic data in irradiated non-human primates, the area under the concentration-time curve (AUC), reflecting the exposure to pegfilgrastim in non-human primates following a 300 mcg/kg dose of Neulasta, appears to be greater than in humans receiving a 6 mg dose. Results from population modeling and simulation indicate that two 6 mg doses of Neulasta administered one week apart in adults result in clinically relevant effects on duration of grade 3 and 4 neutropenia. In addition, weight based dosing in pediatric patients weighing less than 45 kg [see *Dosage and Administration, Section 2.3, Table 1*] provides exposures comparable to those in adults receiving two 6 mg doses one week apart.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

No carcinogenicity or mutagenesis studies have been performed with pegfilgrastim.

Pegfilgrastim did not affect reproductive performance or fertility in male or female rats at cumulative weekly doses approximately 6 to 9 times higher than the recommended human dose (based on body surface area).

14 CLINICAL STUDIES

14.1 Patients with Cancer Receiving Myelosuppressive Chemotherapy

Neulasta was evaluated in three randomized, double-blind, controlled studies. Studies 1 and 2 were active-controlled studies that employed 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 (ANC < 0.5 x 10⁹/L) with a mean duration of 5 to 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-treated patients in the mean days of severe neutropenia.

In Study 1, 157 patients were randomized to receive a single subcutaneous injection of Neulasta (6 mg) on day 2 of each chemotherapy cycle or daily subcutaneous filgrastim (5 mcg/kg/day) beginning on day 2 of each chemotherapy cycle. In Study 2, 310 patients were randomized to receive a single subcutaneous injection of Neulasta (100 mcg/kg) on day 2 or daily subcutaneous filgrastim (5 mcg/kg/day) beginning on day 2 of each chemotherapy cycle.

Both studies met the major efficacy outcome measure of demonstrating that the mean days of severe neutropenia of Neulasta-treated patients did not exceed that of filgrastim-treated patients by more than 1 day in cycle 1 of chemotherapy. The mean days of cycle 1 severe neutropenia in Study 1 were 1.8 days in the Neulasta arm compared to 1.6 days in the filgrastim arm [difference in means 0.2 (95% CI - 0.2, 0.6)] and in Study 2 were 1.7 days in the Neulasta arm compared to 1.6 days in the filgrastim arm [difference in means 0.1 (95% CI - 0.2, 0.4)].

A secondary endpoint in both studies was days of severe neutropenia in cycles 2 through 4 with results similar to those for cycle 1.

Study 3 was a randomized, double-blind, placebo-controlled study that employed docetaxel 100 mg/m² administered every 21 days for up to 4 cycles for the treatment of metastatic or non-metastatic breast cancer. In this study, 928 patients were randomized to receive a single subcutaneous injection of Neulasta (6 mg) or placebo on day 2 of each chemotherapy cycle. Study 3 met the major trial outcome measure of demonstrating that the incidence of

febrile neutropenia (defined as temperature $\geq 38.2^{\circ}\text{C}$ and ANC $\leq 0.5 \times 10^9/\text{L}$) was lower for Neulasta-treated patients as compared to placebo-treated patients (1% versus 17%, respectively, $p < 0.001$). The incidence of hospitalizations (1% versus 14%) and IV anti-infective use (2% versus 10%) for the treatment of febrile neutropenia was also lower in the Neulasta-treated patients compared to the placebo-treated patients.

Study 4 was a multicenter, randomized, open-label study to evaluate the efficacy, safety, and pharmacokinetics [see *Clinical Pharmacology (12.3)*] of Neulasta in pediatric and young adult patients with sarcoma. Patients with sarcoma receiving chemotherapy age 0 to 21 years were eligible. Patients were randomized to receive subcutaneous Neulasta as a single-dose of 100 mcg/kg ($n = 37$) or subcutaneous filgrastim at a dose 5 mcg/kg/day ($n = 6$) following myelosuppressive chemotherapy. Recovery of neutrophil counts was similar in the Neulasta and filgrastim groups. The most common adverse reaction reported was bone pain.

14.2 Patients with Hematopoietic Subsyndrome of Acute Radiation Syndrome

Efficacy studies of Neulasta could not be conducted in humans with acute radiation syndrome for ethical and feasibility reasons. Approval of this indication was based on efficacy studies conducted in animals and data supporting Neulasta's effect on severe neutropenia in patients with cancer receiving myelosuppressive chemotherapy [see *Dosage and Administration (2.1)*].

The recommended dose of Neulasta is two doses, 6 mg each, administered one week apart for humans exposed to myelosuppressive doses of radiation. For pediatric patients weighing less than 45 kg, dosing of Neulasta is weight based and is provided in Table 1 [see *Dosage and Administration (2.3)*]. This dosing regimen is based on population modeling and simulation analyses. The exposure associated with this dosing regimen is expected to provide sufficient pharmacodynamic activity to treat humans exposed to myelosuppressive doses of radiation [see *Clinical Pharmacology (12.3)*]. The safety of Neulasta at a dose of 6 mg has been assessed on the basis of clinical experience in patients with cancer receiving myelosuppressive chemotherapy.

The efficacy of Neulasta for the acute radiation syndrome setting was studied in a randomized, placebo-controlled non-human primate model of radiation injury. Rhesus macaques were randomized to either a control ($n = 23$) or treated ($n = 23$) cohort. On study day 0, animals ($n = 6$ to 8 per irradiation day) were exposed to total body irradiation (TBI) of 7.50 ± 0.15 Gy delivered at 0.8 ± 0.03 Gy/min, representing a dose that would be lethal in 50% of animals by 60 days of follow-up (LD50/60). Animals were administered subcutaneous injections of a blinded treatment (control article [5% dextrose in water] or pegfilgrastim [300-319 mcg/kg/day]) on study day 1 and on study day 8. The primary endpoint was survival. Animals received medical management consisting of intravenous fluids, antibiotics, blood transfusions, and other support as required.

Pegfilgrastim significantly (at 0.0014 level of significance) increased 60-day survival in irradiated non-human primates: 91% survival (21/23) in the pegfilgrastim group compared to 48% survival (11/23) in the control group.

16 HOW SUPPLIED/STORAGE AND HANDLING

Neulasta single-dose prefilled syringe for manual use

Neulasta injection is a clear, colorless solution supplied in a prefilled single-dose syringe for manual use containing 6 mg pegfilgrastim, supplied with a 27-gauge, 1/2-inch needle with an UltraSafe® Needle Guard.

The needle cap of the prefilled syringe contains dry natural rubber (a derivative of latex).

Neulasta is provided in a dispensing pack containing one sterile 6 mg/0.6 mL prefilled syringe (NDC 55513-190-01).

Neulasta prefilled syringe does not bear graduation marks and is intended only to deliver the entire contents of the syringe (6 mg/0.6 mL) for direct administration. Use of the prefilled syringe is not recommended for direct

administration for pediatric patients weighing less than 45 kg who require doses that are less than the full contents of the syringe.

Store refrigerated between 36°F to 46°F (2°C to 8°C) in the carton to protect from light. Do not shake. Discard syringes stored at room temperature for more than 48 hours. Avoid freezing; if frozen, thaw in the refrigerator before administration. Discard syringe if frozen more than once.

Neulasta Onpro® kit

Neulasta Onpro kit is provided in a carton containing one sterile prefilled syringe and one sterile on-body injector (OBI) for Neulasta (NDC 55513-192-01).

The Neulasta injection single-dose prefilled syringe contains 0.64 mL of a clear, colorless solution that delivers 6 mg/0.6 mL of pegfilgrastim when used with the OBI for Neulasta. The prefilled syringe is supplied with a 27-gauge, 1/2-inch needle. The syringe does not bear graduation marks and is only to be used with the OBI for Neulasta.

The needle cap of the prefilled syringe contains dry natural rubber (a derivative of latex).

Store Neulasta Onpro kit in the refrigerator at 36°F to 46°F (2°C to 8°C) until 30 minutes prior to use. Because the OBI for Neulasta is at room temperature during the period of use, Neulasta Onpro kit should not be held at room temperature longer than 12 hours prior to use. Discard Neulasta Onpro kit if stored at room temperature for more than 12 hours.

Do not use the OBI for Neulasta if its packaging has been previously opened.

17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Patient Information and Instructions for Use).

Advise patients of the following risks and potential risks with Neulasta:

- Splenic rupture and splenomegaly
- Acute Respiratory Distress Syndrome
- Serious allergic reactions
- Sickle cell crisis
- Glomerulonephritis
- Increased risk of Myelodysplastic Syndrome and/or Acute Myeloid Leukemia in patients with breast and lung cancer who receive Neulasta in conjunction with chemotherapy and/or radiation therapy
- Capillary Leak Syndrome
- Aortitis

Advise patients acutely exposed to myelosuppressive doses of radiation (Hematopoietic Subsyndrome of Acute Radiation Syndrome) that efficacy studies of Neulasta for this indication could not be conducted in humans for ethical and feasibility reasons and that, therefore, approval of this use was based on efficacy studies conducted in animals [*see Clinical Studies (14.2)*].

Instruct patients who self-administer Neulasta using the single-dose prefilled syringe of the:

- Importance of following the Instructions for Use.
- Dangers of reusing syringes.

- Importance of following local requirements for proper disposal of used syringes.

Advise patients on the use of the on-body injector (OBI) for Neulasta:

- Review the Patient Information and Patient Instructions for Use with the patient and provide the instructions to the patient.
- Refer the patient to the dose delivery information written on the Patient Instructions for Use.
- Tell the patient when their dose delivery of Neulasta will begin and when their dose delivery should be completed.
- Advise the patient that serious allergic reactions can happen with Neulasta. Patients should have a caregiver nearby for the first use. Patients should plan to be in a place where they can appropriately monitor the OBI for Neulasta during the approximately 45 minute Neulasta delivery and for an hour after the delivery. Advise the patient to avoid traveling, driving, or operating heavy machinery during hours 26-29 following application of the OBI for Neulasta.
- If the OBI for Neulasta is placed on the back of the arm, remind the patient that a caregiver must be available to monitor the OBI for Neulasta.
- If a patient calls the healthcare provider regarding any OBI for Neulasta problems, the healthcare provider is advised to call Amgen at 1-800-772-6436.
- Advise the patient:
 - to call their healthcare provider immediately if the status light on the OBI for Neulasta is flashing red (*see the Patient Instructions for Use*).
 - to inform their healthcare provider if the adhesive on the OBI for Neulasta becomes saturated with fluid, or there is dripping, as this may be evidence of significant product leakage, resulting in inadequate or missed dose (*see the Patient Instructions for Use*).
 - to keep the OBI for Neulasta dry for approximately the last 3 hours prior to the dose delivery start to better enable potential leak detection.
 - that the OBI for Neulasta should only be exposed to temperatures between 41°F and 104°F (5°C-40°C).
 - to keep the OBI for Neulasta at least 4 inches away from electrical equipment such as cell phones, cordless telephones, microwaves, and other common appliances. Failure to keep the OBI for Neulasta at least this recommended distance may interfere with operation and can lead to a missed or incomplete dose of Neulasta.
 - that if the needle is exposed after OBI for Neulasta removal, place the used OBI for Neulasta in a sharps disposal container to avoid accidental needle stick and call their healthcare provider immediately.
 - to remove the OBI for Neulasta after the green light shines continuously and to place the used OBI for Neulasta in a sharps disposal container (*see the Patient Instructions for Use*).
- Advise the patient:
 - do not reapply the OBI for Neulasta if the OBI for Neulasta comes off before full dose is delivered and instead call their healthcare provider immediately, as they may need a replacement dose.
 - avoid bumping the OBI for Neulasta or knocking the OBI for Neulasta off the body.
 - do not use other materials to hold the on-body injector in place that could cover audio/visual indicators or compress the on-body injector against the patient's skin, as this could dislodge the cannula and lead to a missed dose or incomplete dose of Neulasta.
 - do not expose the OBI for Neulasta to medical imaging studies (e.g., X-ray scan, MRI, CT scan and ultrasound), radiation treatment, and oxygen rich environments such as hyperbaric chambers to avoid OBI for Neulasta damage and patient injury.

- Advise the patient to avoid:
 - airport X-ray scans and request a manual pat down instead; remind patients who elect to request a manual pat down to exercise care to avoid having the OBI for Neulasta dislodged during the pat down process.
 - sleeping on the OBI for Neulasta or applying pressure on the OBI for Neulasta as this may affect OBI for Neulasta performance.
 - getting body lotions, creams, oils, and cleaning agents near the OBI for Neulasta as these products may loosen the adhesive.
 - use of lotions, creams, or oils on their arms and abdomen prior to their next scheduled OBI for Neulasta dose (to help with device adherence to the skin).
 - using bath tubs, hot tubs, whirlpools, or saunas and avoid exposing the OBI for Neulasta to direct sunlight as these may affect the drug.
 - peeling off or disturbing the OBI for Neulasta adhesive before delivery of full dose is complete.



Neulasta® (pegfilgrastim)

Manufactured by:

Amgen Inc.
One Amgen Center Drive
Thousand Oaks, California 91320-1799
U.S. License No. 1080

Patent: <http://pat.amgen.com/onpro/>

© 2002-2021 Amgen Inc. All rights reserved.

www.neulasta.com

1-800-77-AMGEN (1-800-772-6436)

v27

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

125031Orig1s203

OTHER REVIEW(S)

Division of Nonmalignant Hematology Products Associate Director for Labeling Review of the Prescribing Information

Product Title	NEULASTA® (pegfilgrastim) injection, for subcutaneous use
Applicant	Amgen Inc.
Application/Supplement Number	sBLA 125031 S203
Is Proposed Labeling in Old Format? (Y/N)	N
Is Labeling Being Converted to PLR? (Y/N)	N
Is Labeling Being Converted to PLLR? (Y/N)	N
Approved Indication(s)	-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. -Increase survival in patients acutely exposed to myelosuppressive doses of radiation (Hematopoietic Subsyndrome of Acute Radiation Syndrome).
Date FDA Received Application	02/01/2021
Review Classification (Priority/Standard)	Standard; CBE
Action Goal Date	08/01/2021
Review Date	02/02/2021
Reviewer	Virginia Kwitkowski, MS, ACNP-BC

This Associate Director for Labeling (ADL) review provides recommendations on the content and format of the prescribing information (PI) to help ensure that PI:

- Is compliant with Physician Labeling Rule (PLR) and Pregnancy and Lactation Labeling Rule (PLLR) requirements¹
- Is consistent with labeling guidance recommendations³ and with CDER/OND best labeling practices and policies
- Conveys the essential scientific information needed for safe and effective use of the product
- Is clinically meaningful and scientifically accurate
- Is a useful communication tool for health care providers
- Is consistent with other PI with the same active moiety, drug class, or similar indication

Background: On 1/21/21, DNH issued a supplement request letter requesting that the Highlights section of labeling be updated with the newly added warnings for thrombocytopenia and MDS/AML that were approved on 01/05/2021. We also requested that they add the word “hemorrhage” to the last bullet in

¹ See [January 2006 Physician Labeling Rule](#); 21 CFR [201.56](#) and [201.57](#); and [December 2014 Pregnancy and Lactation Labeling Rule](#) (the PLLR amended the PLR regulations). For applications with labeling in non-PLR “old” format, see 21 CFR [201.56\(e\)](#) and [201.80](#).

³ See [PLR Requirements for PI](#) website for PLR labeling guidances.

section 6.3 that reads “Alveolar”. The labeling uploaded to Drugs@FDA with the action letter, the word “hemorrhage” was missing from the last bullet in section 6.3 that currently reads “Alveolar”.

This submission intends to remedy these labeling errors.

Reviewer Comments:

In addition to making the changes requested by DNH, the Applicant added the following revisions:

1. Added text “Discontinue Neulasta if sickle cell crisis occurs.” to the bullet in Highlights: Warnings and Precautions: Fatal Sickle Cell Crises. This addition is consistent with the full Warning in section 5.5.
2. In Section 17, removed “in patients with congenital neutropenia who receive Neulasta and”. This was removed because it only applies to Neupogen (filgrastim), which has an indication for congenital neutropenia.

The revised labeling submitted is acceptable without edit.

Regulatory Recommendation: This NDA is recommended for approval.

Attachments: Labeling submitted by the Applicant with tracked changes.

Sixteen (16) pages removed as (b)(4), draft labeling, immediately following this page.

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

VIRGINIA E KWITKOWSKI
02/02/2021 10:00:38 AM