

CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

125031Orig1s181

Trade Name: NEULASTA

Generic or Proper Name: pegfilgrastim

Sponsor: Amgen

Approval Date: 09/23/2015

Indication: 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.

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

CENTER FOR DRUG EVALUATION AND RESEARCH

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APPROVAL LETTER



BLA 125031/S-170, 179 & 181

SUPPLEMENT APPROVAL

Amgen Inc.
Attention: Tai H. Yu, MS
Senior Manager, Global Regulatory Affairs
One Amgen Center Drive
Mail Stop: 17-2-A
Thousand Oaks, CA 91320-1799

Dear Tai Yu:

Please refer to your Supplemental Biologics License Applications (sBLAs), dated and received March 24, 2014 (S-170) and February 5, 2015 (S-179 & S-181), submitted under section 351(a) of the Public Health Service Act for Neulasta[®] (pegfilgrastim) prefilled syringe/on-body injector (6 mg per 0.6 mL).

We acknowledge receipt of your amendments dated August 28 and September 23, 2014; January 8, July 10, August 27 and September 4, 2015.

Supplement 170 provides for revisions to the US Package Insert (USPI) and the US Patient Package Insert (USPPI) to add information about leukocytosis and splenomegaly, and capillary leak syndrome.

Supplement 179 provides for addition of glomerulonephritis to the Warnings and Precautions and Adverse Reactions sections of the USPI.

Supplement 181 provides for the proprietary name "Neulasta OnPRO[™]" for the Neulasta Delivery Kit.

APPROVAL & LABELING

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

We note that your September 4, 2015, submission includes final printed labeling (FPL) for your package insert and patient package inserts. We have not reviewed this FPL. You are responsible for assuring that the wording in this printed labeling is identical to that of the approved content of labeling in the structured product labeling (SPL) format.

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 <http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm>, that is identical to the enclosed labeling (text for the package insert and text for the patient package insert) and include the labeling changes proposed in any pending “Changes Being Effected” (CBE) supplements. Information on submitting SPL files using eLIST may be found in the guidance for industry titled “SPL Standard for Content of Labeling Technical Qs and As” at <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM072392.pdf>.

The SPL will be accessible via publicly available labeling repositories.

Also within 14 days, amend all pending supplemental applications that includes labeling changes for this BLA, including pending “Changes Being Effected” (CBE) supplements, for which FDA has not yet issued an action letter, with the content of labeling [21 CFR 601.12(f)] in MS Word format that includes the changes approved in this supplemental application.

CARTON AND IMMEDIATE CONTAINER LABELS

Submit final printed carton and container labels that are identical to the enclosed carton and immediate container labels submitted on July 10, 2015, as soon as they are available, but no more than 30 days after they are printed. Please submit these labels electronically according to the guidance for industry titled “Providing Regulatory Submissions in Electronic Format – Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications (June 2008)”. Alternatively, you may submit 12 paper copies, with 6 of the copies individually mounted on heavy-weight paper or similar material. For administrative purposes, designate this submission “**Product Correspondence – Final Printed Carton and Container Labels for approved BLA 125031/S-170-179-181.**” Approval of this submission by FDA is not required before the labeling is used.

Marketing the product with final printed labeling (FPL) that is not identical to the approved labeling text may render the product misbranded and an unapproved new drug.

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, 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 applications, you are exempt from this requirement.

PROMOTIONAL MATERIALS

You may request advisory comments on proposed introductory advertising and promotional labeling. To do so, submit, in triplicate, a cover letter requesting advisory comments, the proposed materials in draft or mock-up form with annotated references, and the package insert(s) to:

OPDP Regulatory Project Manager
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion
5901-B Ammendale Road
Beltsville, MD 20705-1266

Alternatively, you may submit a request for advisory comments electronically in eCTD format. For more information about submitting promotional materials in eCTD format, see the draft Guidance for Industry (available at: <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM443702.pdf>).

As required under 21 CFR 601.12(f)(4), you must submit final promotional materials, and the package insert(s), at the time of initial dissemination or publication, accompanied by a Form FDA 2253. Form FDA 2253 is available at <http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM083570.pdf>. Information and Instructions for completing the form can be found at <http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM375154.pdf>. For more information about submission of promotional materials to the Office of Prescription Drug Promotion (OPDP), see <http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm>.

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 package labeling. Within 7 days of receipt of this letter, submit your statement of intent to comply with 21 CFR 601.12(a)(4) to the address above, by fax to 301-847-8444, or electronically in eCTD format. For more information about submitting promotional materials in eCTD format, see the draft Guidance for Industry (available at: <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM443702.pdf>).

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, call Tinya Sensie, Regulatory Project Manager, at (240) 402-4230.

Sincerely,

{See appended electronic signature page}

Ann T. Farrell, MD
Director
Division of Hematology Products
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

ENCLOSURE(S):
Content of Labeling
Carton and Container Labeling

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

ANN T FARRELL
09/23/2015

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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 (5.6, 5.7, 5.8) 09/2015
- Dosage and Administration (2.3, 2.4) 12/2014
- Warnings and Precautions (5.4) 12/2014

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)

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

DOSAGE AND ADMINISTRATION

- 6 mg administered subcutaneously once per chemotherapy cycle. (2)
- Do not administer between 14 days before and 24 hours after administration of cytotoxic chemotherapy. (2)

DOSAGE FORMS AND STRENGTHS

- Injection: 6 mg/0.6 mL solution in a single use prefilled syringe for manual use only. (3)
- Injection: 6 mg/0.6 mL solution in a single prefilled syringe co-packaged with the On-body Injector for Neulasta.

CONTRAINDICATIONS

Do not administer Neulasta to patients with a history of serious allergic reactions to 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: Have occurred. (5.5)
- Glomerulonephritis: Evaluate and consider dose-reduction or interruption of Neulasta if causality is likely. (5.6)

ADVERSE REACTIONS

Most common adverse reactions ($\geq 5\%$ difference in incidence) in placebo controlled clinical trials 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.

USE IN SPECIFIC POPULATIONS

- Pregnancy: Based on animal data, may cause fetal harm. (8.1)
- Nursing Mothers: Caution should be exercised when administered to a nursing woman. (8.3)

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

Revised: 09/2015

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FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

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)*].

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

2 DOSAGE AND ADMINISTRATION

2.1 Recommended Dosage

The recommended dosage of Neulasta is a single subcutaneous injection of 6 mg administered once per chemotherapy cycle in adults. Do not administer Neulasta between 14 days before and 24 hours after administration of cytotoxic chemotherapy.

2.2 Administration

Neulasta is administered subcutaneously via a single prefilled syringe for manual use or for use with the On-body Injector for Neulasta which is co-packaged with a single prefilled syringe.

For manual use or On-body Injector for Neulasta use, visually inspect parenteral drug products (prefilled syringe) 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.

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

A healthcare provider must fill the On-body Injector with Neulasta using the prefilled syringe and then apply the On-body Injector 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 On-body Injector for Neulasta. Approximately 27 hours after the On-body Injector 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 On-body Injector for Neulasta on the same day as the administration of cytotoxic chemotherapy, as long as the On-body Injector 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 On-body Injector for Neulasta. The prefilled syringe contains additional solution to compensate for liquid loss during delivery through the On-body Injector 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 use prefilled syringe for manual use is used with the On-body Injector for Neulasta, the patient may receive less than the recommended dose.

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

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

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

Refer to the Healthcare Provider Instructions for Use for the On-body Injector for Neulasta for full administration information.

2.4 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 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 On-body Injector for Neulasta for completed delivery. Ensure patients understand how to identify signs of malfunction of On-body Injector for Neulasta. *[see Warnings and Precautions (5.3) and Patient Counseling Information (17)].*

3 DOSAGE FORMS AND STRENGTHS

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

4 CONTRAINDICATIONS

Do not administer Neulasta to patients with a history of serious allergic reactions to pegfilgrastim or filgrastim.

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 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 sickle cell crises can occur in patients with sickle cell disorders receiving Neulasta. Severe and sometimes fatal sickle cell crises can occur in patients with sickle cell disorders receiving filgrastim, the parent compound of pegfilgrastim.

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 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.

5.9 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.

6 ADVERSE REACTIONS

The following serious 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)]*
- Capillary Leak Syndrome *[See Warnings and Precautions (5.8)]*

- Potential for Tumor Growth Stimulatory Effects on Malignant Cells [See Warnings and Precautions (5.9)]

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 1 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 ≥ 5% of patients and with a between-group difference of ≥ 5% higher in the pegfilgrastim arm in placebo controlled clinical trials are bone pain and pain in extremity.

Table 1. Adverse Reactions With ≥ 5% Higher Incidence in Neulasta Patients Compared to Placebo in Study 3

System Organ Class Preferred Term	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 x 10⁹/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. 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.

The detection of antibody formation is highly dependent on the sensitivity and specificity of the assay, and the observed incidence of 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 Neulasta with the incidence of antibodies to other products may be misleading.

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. Decisions to include these reactions in labeling are typically based on one or more of the following factors: (1) seriousness of the reaction, (2) reported frequency of the reaction, or (3) strength of causal relationship to Neulasta.

Gastro-intestinal disorders: Splenic rupture and splenomegaly (enlarged spleen) [see *Warnings and Precautions* (5.1)]

Blood and lymphatic system disorder: Sick cell crisis [see *Warnings and Precautions* (5.5)], Leukocytosis [see *Warnings and Precautions* (5.7)]

Hypersensitivity reactions: Allergic reactions/hypersensitivity, including anaphylaxis, skin rash, and urticaria, generalized erythema and flushing [see *Warnings and Precautions* (5.3)]

Respiratory, thoracic, and mediastinal disorder: ARDS [see *Warnings and Precautions* (5.2)]

Renal and urinary disorder: Glomerulonephritis [see *Warnings and Precautions* (5.6)]

Vascular disorder: Capillary leak syndrome [see *Warnings and Precautions* (5.8)]

General disorders and administration site conditions: Injection site reactions

Skin and subcutaneous tissue disorders: Sweet's syndrome, Cutaneous vasculitis

7 DRUG INTERACTIONS

No formal drug interaction studies between Neulasta and other drugs have been performed. Increased hematopoietic activity of the bone marrow in response to growth factor therapy may result in transiently positive bone-imaging changes. Consider these findings when interpreting bone-imaging results.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category C

There are no adequate and well-controlled studies in pregnant women. Pegfilgrastim was embryotoxic and increased pregnancy loss in pregnant rabbits that received cumulative doses approximately 4 times the recommended human dose (based on body surface area). Signs of maternal toxicity occurred at these doses. Neulasta should be used during pregnancy only if the potential benefit to the mother justifies the potential risk to the fetus.

In animal reproduction studies, when pregnant rabbits received pegfilgrastim at cumulative doses approximately 4 times the recommended human dose (based on body surface area), increased embryoletality and spontaneous abortions occurred. Signs of maternal toxicity (reductions in body weight gain/food consumption) and decreased

fetal weights occurred at maternal doses approximately equivalent to the recommended human dose (based on body surface area). There were no structural anomalies observed in rabbit offspring at any dose tested. 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) [see *Nonclinical Toxicology* (13.3)].

8.3 Nursing Mothers

It is not known whether pegfilgrastim is secreted in human milk. Other recombinant G-CSF products are poorly secreted in breast milk and G-CSF is not orally absorbed by neonates. Caution should be exercised when administered to a nursing woman.

8.4 Pediatric Use

Safety and effectiveness of Neulasta in pediatric patients have not been established. The adverse reaction profile and pharmacokinetics of pegfilgrastim were studied in 37 pediatric patients with sarcoma. The mean ($\pm$ standard deviation [SD]) systemic exposure ($AUC_{0-\infty}$) of pegfilgrastim after subcutaneous administration at 100 mcg/kg was 22.0 ($\pm$ 13.1) mcg·hr/mL in the 6 to 11 years age group (n = 10), 29.3 ($\pm$ 23.2) mcg·hr/mL in the 12 to 21 years age group (n = 13), and 47.9 ($\pm$ 22.5) mcg·hr/mL in the youngest age group (0 to 5 years, n = 11). The terminal elimination half-lives of the corresponding age groups were 20.2 ($\pm$ 11.3) hours, 21.2 ($\pm$ 16.0) hours, and 30.1 ($\pm$ 38.2) hours, respectively. The most common adverse reaction was bone pain.

8.5 Geriatric Use

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

8.6 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. Therefore, pegfilgrastim dose adjustment in patients with renal dysfunction is not necessary [Clinical Pharmacology (12.3)].

10 OVERDOSAGE

The maximum amount of Neulasta that can be safely administered in single or multiple doses has not been determined. Single subcutaneous doses of 300 mcg/kg have been administered to 8 healthy volunteers and 3 patients with non-small cell lung cancer without serious adverse effects. These patients experienced a mean maximum absolute neutrophil count (ANC) of $55 \times 10^9/L$, with a corresponding mean maximum WBC of $67 \times 10^9/L$. The absolute maximum ANC observed was $96 \times 10^9/L$ with a corresponding absolute maximum WBC observed of $120 \times 10^9/L$. The duration of leukocytosis ranged from 6 to 13 days. The effectiveness of leukapheresis in the management of symptomatic individuals with Neulasta-induced leukocytosis has not been studied.

11 DESCRIPTION

Neulasta (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 comes in two presentations:

- Neulasta for manual subcutaneous injection is supplied in 0.6 mL prefilled syringes.
- On-body Injector 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 On-body Injector for Neulasta.

The delivered 0.6 mL dose from either the prefilled syringe for manual subcutaneous injection or the On-body Injector 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.

12.3 Pharmacokinetics

The pharmacokinetics of pegfilgrastim were studied in 379 patients with cancer. The pharmacokinetics of pegfilgrastim were 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 for Neulasta.

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)]. The pharmacokinetics of pegfilgrastim were studied in pediatric patients with sarcoma [see *Use in Specific Populations* (8.4)]. Renal dysfunction had no effect on the pharmacokinetics of pegfilgrastim. [see *Use in Specific Populations* (8.6)]. The pharmacokinetic profile in patients with hepatic insufficiency has not been assessed.

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).

13.3 Reproductive and Developmental Toxicology

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), 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).

14 CLINICAL STUDIES

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 ≥ 38.2°C and ANC ≤ 0.5 x 10⁹/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.

16 HOW SUPPLIED/STORAGE AND HANDLING

16.1 Neulasta single use prefilled syringe for manual use

Neulasta is supplied in a prefilled single use 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 6mg/0.6 mL prefilled syringe (NDC 55513-190-01).

Store refrigerated between 36° to 46°F (2° 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.

16.2 Neulasta Onpro™ kit

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

The single use prefilled syringe contains 0.64 mL of solution that delivers 6 mg/0.6 mL of pegfilgrastim when used with the On-body Injector for Neulasta. The prefilled syringe is 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).

Store Neulasta Onpro kit in the refrigerator at 36°F to 46°F (2°C to 8°C) until ready for use. Because the On-body Injector 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 On-body Injector for Neulasta if its packaging has been previously opened.

17 PATIENT COUNSELING INFORMATION

Advise patients of the following risks for Neulasta:

- Splenic rupture and splenomegaly
- Acute Respiratory Distress Syndrome
- Serious allergic reactions
- Sickle cell crisis
- Glomerulonephritis
- Capillary Leak Syndrome

Have patients immediately contact their healthcare provider and report:

- Left upper quadrant or shoulder pain
- Shortness of breath
- Signs or symptoms of sickle cell crisis
- Signs or symptoms of infection
- Flushing, dizziness, or rash
- Swelling of the face or ankles
- Dark colored urine or blood in the urine
- Decrease in urine production
- Swelling or puffiness, which may be associated with passing water less frequently, difficulty breathing, abdominal swelling and feeling of fullness, and a general feeling of tiredness

Advise patients on the use of the On-body Injector 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 On-body Injector 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 On-body Injector for Neulasta.**
- **If the On-body Injector for Neulasta is placed on the back of the arm, remind the patient that a caregiver must be available to monitor the On-body Injector for Neulasta.**
- If a patient calls the healthcare provider regarding any On-body Injector 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 On-body Injector for Neulasta is flashing red (see the Patient Instructions for Use).
 - to inform their healthcare provider if the adhesive on the On-body Injector 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 On-body Injector for Neulasta dry for approximately the last 3 hours prior to the dose delivery start to better enable potential leak detection.
 - that the On-body Injector for Neulasta should only be exposed to temperatures between 41°F and 104°F (5°C-40°C)
 - to keep the On-body Injector 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 On-body Injector 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 On-body Injector for Neulasta removal, place the used On-body Injector for Neulasta in a sharps disposal container to avoid accidental needle stick and call their healthcare provider immediately.
 - to remove the On-body Injector for Neulasta after the green light shines continuously and to place the used On-body Injector for Neulasta in a sharps disposal container (see the Patient Instructions for Use).
- Advise the patient:
 - **do not** reapply the On-body Injector for Neulasta if the On-body Injector for Neulasta comes off before full dose is delivered and instead call their healthcare provider immediately.
 - avoid bumping the On-body Injector for Neulasta or knocking the On-body Injector for Neulasta off the body.
 - **do not** expose the On-body Injector for Neulasta to medical imaging studies, e.g. X-ray scan, MRI, CT scan, ultrasound and oxygen rich environments such as hyperbaric chambers to avoid On-body Injector 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 On-body Injector for Neulasta dislodged during the pat down process.

- sleeping on the On-body Injector for Neulasta or applying pressure on the On-body Injector for Neulasta as this may affect On-body Injector for Neulasta performance.
- getting body lotions, creams, oils and cleaning agents near the On-body Injector for Neulasta as these products may loosen the adhesive.
- using hot tubs, whirlpools, or saunas and avoid exposing the On-body Injector for Neulasta to direct sunlight as these may affect the drug.
- peeling off or disturbing the On-body Injector 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
US License No. 1080

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

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www.neulasta.com

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

09/2015

V1X

Neulasta®

Pegfilgrastim

Information for Patients and Caregivers

This patient package insert provides information and instructions for people who will be receiving Neulasta or their caregivers. This patient package insert does not tell you everything about Neulasta. You should discuss any questions you have about treatment with Neulasta with your doctor.

What is Neulasta?

Neulasta is a man-made form of granulocyte colony-stimulating factor (G-CSF), which is made using the bacteria *Escherichia coli*. G-CSF is a substance produced by the body. It stimulates the growth of neutrophils (**nu**-tro-fils), a type of white blood cell important in the body's fight against infection.

Who should not take Neulasta?

Do not take Neulasta if you have had:

- A serious allergic reaction to Neulasta® (pegfilgrastim) or to Neupogen® (filgrastim).

What important information do I need to know about receiving Neulasta?

Occasionally, pain and redness may occur at the injection site. If there is a lump, swelling, or bruising at the injection site that does not go away, talk to the doctor.

Neulasta should only be injected on the day the doctor has determined and should not be injected until approximately 24 hours after receiving chemotherapy.

The needle cover on the single-use prefilled syringe contains dry natural rubber (latex), which should not be handled by persons sensitive to this substance.

What should I tell my healthcare provider before taking Neulasta?

If you have a sickle cell disorder, make sure that your doctor knows about it before you start using Neulasta. If you have a sickle cell crisis after getting Neulasta, tell your doctor right away.

If you have a problem with your kidneys, make sure that your doctor knows about it before you start using Neulasta as you may need more frequent urine tests.

If you have any questions, talk to your doctor.

What are possible serious side effects of Neulasta?

- **Spleen Rupture.** Your spleen may become enlarged and can rupture while taking Neulasta. A ruptured spleen can cause death. The spleen is located in the upper left section of your stomach area. Call your doctor right away if you have pain in the left upper stomach area or left shoulder tip area. This pain could mean your spleen is enlarged or ruptured.
- **A serious lung problem called Acute Respiratory Distress Syndrome (ARDS).** Call your doctor or seek emergency care right away if you have shortness of breath, trouble breathing, or a fast rate of breathing.
- **Serious Allergic Reactions.** Neulasta can cause serious allergic reactions. These reactions can cause shortness of breath, wheezing, dizziness, swelling around the mouth or eyes, fast pulse, sweating, and hives. If you start to have any of these symptoms, call your doctor or seek emergency care right away.

If you have an allergic reaction during the injection of Neulasta, stop the injection. Call your doctor right away.

- **Sickle Cell Crises.** You may have a serious sickle cell crisis if you have a sickle cell disorder and take Neulasta. Serious and sometimes fatal sickle cell crises can occur in patients with sickle cell disorders receiving filgrastim, a medicine similar to Neulasta (pegfilgrastim). Call your doctor right away if you have symptoms of sickle cell crisis such as pain or difficulty breathing.
- **Kidney injury (glomerulonephritis).** Kidney injury has been seen in patients who received Neulasta. Call your doctor right away if you experience puffiness in your face or ankles, blood in your urine or brown colored urine or you notice you urinate less than usual.
- **Increased white blood cell count (leukocytosis).** Your doctor will check your blood during treatment with Neulasta.
- **Capillary Leak Syndrome.** Neulasta can cause fluid to leak from blood vessels into your body's tissues. This condition is called "Capillary Leak Syndrome" (CLS). CLS can quickly cause you to have symptoms that may become life-threatening. Get emergency medical help right away if you develop any of the following symptoms:
 - swelling or puffiness and are urinating less often
 - trouble breathing
 - swelling of your stomach-area (abdomen) and feeling of fullness
 - dizziness or feeling faint
 - a general feeling of tiredness

What are the most common side effects of Neulasta?

The most common side effect you may experience is aching in the bones and muscles. If this happens, it can usually be relieved with a non-aspirin pain reliever, such as acetaminophen.

What about pregnancy or breastfeeding?

Neulasta has not been studied in pregnant women, and its effects on unborn babies are not known. If you take Neulasta while you are pregnant, it is possible that small amounts of it may get into your baby's blood. It is not known if Neulasta can get into human breast milk. If you are pregnant, plan to become pregnant, think you may be pregnant, or are breastfeeding, you should tell your doctor before using Neulasta. If you become pregnant during Neulasta treatment, you are encouraged to enroll in Amgen's Pregnancy Surveillance Program. You should call 1-800-77-AMGEN (1-800-772-6436) to enroll.

HOW TO PREPARE AND GIVE A NEULASTA INJECTION

Neulasta is provided in a prefilled syringe. **Neulasta should be stored in its carton to protect from light until use.** If you are giving someone else Neulasta injections, it is important that you know how to inject Neulasta. Before getting your Neulasta injection, always check to see that:

- The name Neulasta appears on the carton and prefilled syringe label.
- The expiration date on the prefilled syringe has not passed. **You should not use a prefilled syringe after the date on the label.**
- The Neulasta liquid should always be clear and colorless. Do not use Neulasta if the contents of the prefilled syringe appear discolored or cloudy, or if the prefilled syringe appears to contain lumps, flakes, or particles.

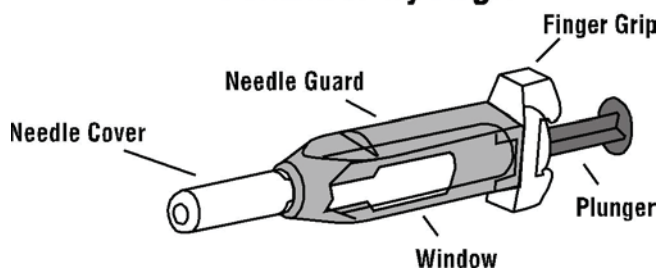
IMPORTANT: TO HELP AVOID POSSIBLE INFECTION, YOU SHOULD FOLLOW THESE INSTRUCTIONS.

Setting up for an injection

Note: The needle cover on the single-use prefilled syringe contains dry natural rubber (latex), which should not be handled by persons sensitive to this substance.

1. Find a clean, flat working surface, such as a table.
2. Remove the carton containing the prefilled syringe of Neulasta from the refrigerator. Allow Neulasta to reach room temperature (this takes about 30 minutes). Remove the syringe from the carton before injection. Each prefilled syringe should be used only once. **DO NOT SHAKE THE PREFILLED SYRINGE.** Shaking may damage Neulasta. If the prefilled syringe has been shaken vigorously, the solution may appear foamy and it should not be used.
3. Assemble the supplies you will need for an injection:
 - Neulasta prefilled syringe with transparent (clear) plastic blue needle guard attached

Prefilled Syringe



- An alcohol swab and a cotton ball or gauze

Alcohol Swab



Cotton Ball



- Puncture-proof disposal container

4. Wash your hands with soap and warm water.

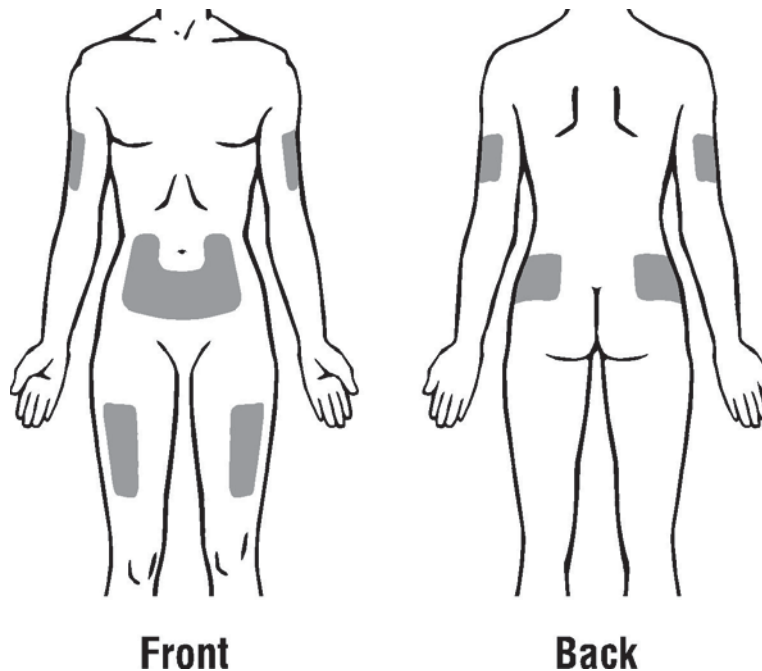


HOW TO PREPARE FOR INJECTION OF NEULASTA

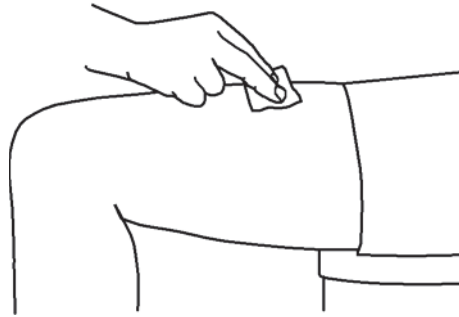
5. Remove the prefilled syringe from the package and the tray. Check to see that the plastic blue needle guard is covering the barrel of the glass syringe. **DO NOT** push the blue needle guard over the needle cover before injection. This may activate or lock the needle guard. If the blue needle guard is covering the needle that means it has been activated. **DO NOT** use that syringe. Dispose of that syringe in the puncture-proof disposal container. Use a new prefilled syringe. **Do not activate the needle guard prior to injection.**
6. Hold the syringe barrel through the needle guard windows with the needle pointing up. Holding the syringe with the needle pointing up helps to prevent medicine from leaking out of the needle. Carefully pull the needle cover straight off.
7. Check the syringe for air bubbles. If there are air bubbles, gently tap the syringe with your fingers until the air bubbles rise to the top of the syringe. Slowly push the plunger up to force the air bubbles out of the syringe.
8. Gently place the prefilled syringe with the window flat on your clean working surface so that the needle does not touch anything.

Selecting and preparing the injection site

9. Choose an injection site. Four recommended injection sites for Neulasta are:
 - The outer area of the upper arms
 - The abdomen, except for the two-inch area around the navel
 - The front of the middle thighs
 - The upper outer areas of the buttocks

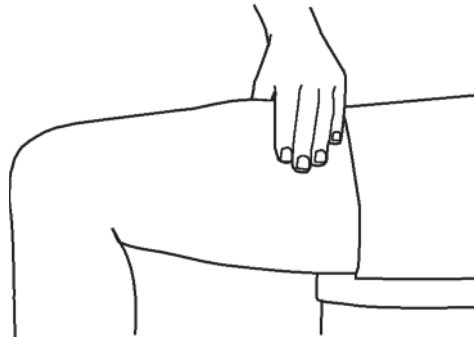


10. Clean the injection site with an alcohol swab.

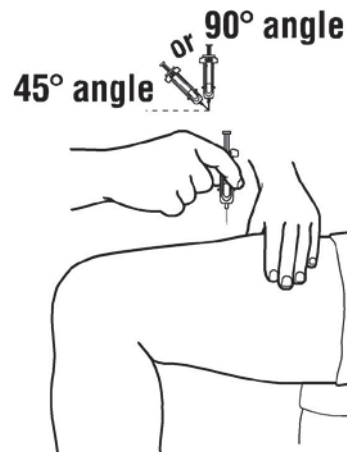


Injecting the dose of Neulasta

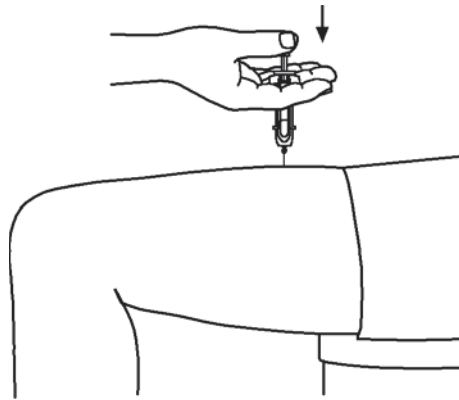
11. Pick up the prefilled syringe from your clean, flat working surface by grabbing the sides of the needle guard with your thumb and forefinger.
12. Hold the syringe in the hand you will use to inject Neulasta. Use the other hand to pinch a fold of skin at the cleaned injection site. Note: Hold the syringe barrel through the needle guard windows when giving the injection.



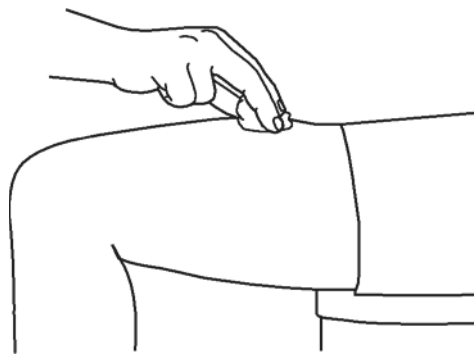
13. Holding the syringe like a pencil, use a quick “dart-like” motion to insert the needle either straight up and down (90 degree angle) or at a slight angle (45 degrees) into the skin.



14. Inject the prescribed dose subcutaneously as directed by your doctor, nurse, or pharmacist.



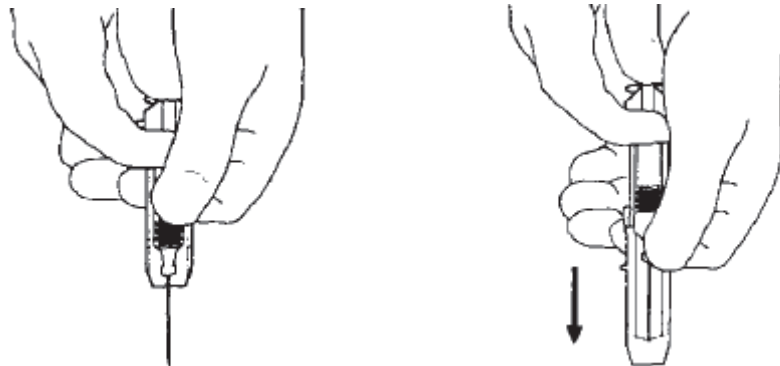
15. When the syringe is empty, pull the needle out of the skin and place a cotton ball or gauze over the injection site and press for several seconds.



16. Use a prefilled syringe with the needle guard only once.

Activating the Needle Guard after the injection has been given

17. After injecting Neulasta from the prefilled syringe, do not recap the needle. Keep your hands behind the needle at all times. While holding the clear plastic finger grip of the syringe with one hand, grasp the blue needle guard with your free hand and slide the blue needle guard over the needle until the needle is completely covered and the needle guard clicks into place. **NOTE: If an audible click is not heard, the needle guard may not be completely activated.**



18. Place the prefilled syringe with the activated needle guard into a puncture-proof container for proper disposal as described below.

Disposal of prefilled syringes and needle guards

You should always follow the instructions given by your doctor, nurse, or pharmacist on how to properly dispose of containers with used syringes and needle guards. There may be special state and local laws for disposal of used needles and syringes.

- Do not throw the container in the household trash. Do not recycle.
- DO NOT put the needle cover (the cap) back on the needle.
- Place all used needle covers and syringes in a hard plastic container with a screw-on cap or in a metal container with a plastic lid such as a coffee can labeled “used syringes.” If a metal container is used, cut a small hole in the plastic lid and tape the lid to the metal container. If a hard plastic container is used, always screw the cap on tightly after each use.
- Do not use glass or clear plastic containers.
- When the container is full, tape around the cap or lid to make sure the cap or lid does not come off.
- **Always** keep the container out of the reach of children.

How should Neulasta be stored?

Neulasta should be stored in the refrigerator at 2° to 8°C (36° to 46°F), but not in the freezer. Neulasta should be protected from light, so you should keep it in its carton until you are ready to use it. Avoid shaking Neulasta. If Neulasta is accidentally frozen, allow it to thaw in the refrigerator before injecting. However, if it is frozen a second time, do not use. Neulasta can be left out at room temperature for up to 48 hours. Do not leave Neulasta in direct sunlight. For all questions about storage, contact your doctor, nurse, or pharmacist.

What are the ingredients in Neulasta?

Each syringe contains pegfilgrastim in a sterile, clear, colorless, preservative-free solution containing acetate, sorbitol, polysorbate 20, and sodium.



Neulasta® (pegfilgrastim)

Manufactured by:

Amgen Inc.
One Amgen Center Drive
Thousand Oaks, California 91320-1799

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

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www.neulasta.com

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

Revised: 09/2015

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Patient Information
Neulasta® (nu-las-tah)
(pegfilgrastim)
injection
On-body Injector for Neulasta

Read this Patient Information before you receive Neulasta and each time you receive Neulasta with the On-body Injector for Neulasta. There may be new information. This information does not take the place of talking with your healthcare provider about your medical condition or your treatment.

What is the most important information I need to know about receiving Neulasta with the On-body Injector for Neulasta?

- **See the Instructions for Use for the On-body Injector for Neulasta for detailed information about the On-body Injector for Neulasta and important information about your dose delivery that has been written by your healthcare provider.**
 - o Know the time that delivery of your dose of Neulasta is expected to start.
 - o Avoid traveling, driving, or operating heavy machinery during hour 26 through hour 29 after the On-body Injector for Neulasta is applied. Avoid activities and places that may interfere with monitoring during the **45-minute** period that Neulasta is expected to be delivered by the On-body Injector for Neulasta, and for 1 hour after delivery.
- A caregiver should be with you the first time that you receive Neulasta with the On-body Injector for Neulasta.
- **If you have an allergic reaction during the delivery of Neulasta, remove the On-body Injector for Neulasta by grabbing the edge of the adhesive pad and peeling off the On-body Injector for Neulasta. Get emergency medical help right away.**
- **You should only receive a dose of Neulasta on the day your healthcare provider tells you.**
- **You should not receive your dose of Neulasta any sooner than 24 hours after you finish receiving your chemotherapy.** The On-body Injector for Neulasta is programmed to deliver your dose about 27 hours after your healthcare provider places the On-body Injector for Neulasta on your skin.
- **Do not** expose the On-body Injector for Neulasta to the following because the On-body Injector for Neulasta may be damaged and you could be injured:
 - MRI
 - X-ray
 - CT-Scan
 - Ultrasound
 - Oxygen rich environments, such as hyperbaric chambers

- Avoid airport X-ray scans. Request a manual pat down instead. Use care during a manual pat down to help prevent the On-body Injector for Neulasta from being accidentally removed.
- **Keep the On-body Injector for Neulasta at least 4 inches away from electrical equipment such as cell phones, cordless telephones, microwaves and other common appliances.** If the On-body Injector for Neulasta is too close to electrical equipment, it may not work correctly and can lead to a missed or incomplete dose of Neulasta.
- **Call your healthcare provider right away if the:**
 - On-body Injector for Neulasta comes off before or during a dose delivery. **Do not re-apply it.**
 - On-body Injector for Neulasta is leaking.
 - adhesive on your On-body Injector for Neulasta becomes noticeably wet (saturated) with fluid, or there is dripping. This may mean that Neulasta is leaking out of your On-body Injector for Neulasta. If this happens you may only receive some of your dose of Neulasta, or you may not receive a dose at all.
 - On-body Injector for Neulasta status light is flashing red.

What is Neulasta?

Neulasta is a prescription medicine used to help reduce the chance of infection due to a low white blood cell count, in people with certain types of cancer (non-myeloid), who receive anti-cancer medicines (chemotherapy) that can cause fever and low blood cell count.

It is not known if Neulasta is safe and effective in children.

Who should not take Neulasta?

Do not take Neulasta if you have had a serious allergic reaction to pegfilgrastim (Neulasta[®]) or to filgrastim (Neupogen[®]).

What should I tell my healthcare provider before receiving Neulasta?

Before you receive Neulasta, tell your healthcare provider if you:

- have sickle cell trait or sickle cell disease
- have had severe skin reactions to acrylic adhesives
- are allergic to latex
- have problems with your kidneys
- have any other medical problems
- are pregnant or plan to become pregnant. It is not known if Neulasta may harm your unborn baby.

Pregnancy Registry: There is a pregnancy registry for women who become pregnant during treatment with Neulasta. The purpose of this registry is to collect information

about the health of you and your baby. You are encouraged to enroll in this registry. Your healthcare provider may enroll you, or you may enroll by calling 1-800-AMGEN (1-800-772-6436).

- are breastfeeding or plan to breastfeed. It is not known if Neulasta passes into your breast milk.

Tell your healthcare provider about all the medicines you take, including prescription and over-the-counter medicines, vitamins, and herbal supplements.

How will I receive Neulasta?

See the Instructions for Use for detailed information about how you will receive a dose of Neulasta with the On-body Injector for Neulasta, and how to remove and dispose of the On-body Injector for Neulasta.

- **See the section “What is the most important information I need to know about receiving Neulasta with the On-body Injector for Neulasta?”**
- Neulasta is given as an injection under the skin (subcutaneous). Your healthcare provider will use a prefilled syringe with Neulasta to fill the On-body Injector prior to applying it. The prefilled syringe with Neulasta and the On-body Injector are provided to your healthcare provider as part of Neulasta Onpro™ kit. The On-body Injector for Neulasta will be applied to the stomach area (abdomen) or back of your arm by your healthcare provider. If the On-body Injector for Neulasta was placed on the back of your arm, a caregiver must be available to monitor the On-body Injector for Neulasta.
- Your healthcare provider should place the On-body Injector for Neulasta on an area of your skin that does not have swelling, redness, cuts, wounds, or abrasions. Tell your healthcare provider about any skin reactions that happen in the On-body Injector for Neulasta application area after it has been applied.
- The On-body Injector for Neulasta is programmed to deliver your dose about 27 hours after your healthcare provider places the On-body Injector for Neulasta on your skin.
- The dose of Neulasta will be delivered over about 45 minutes. During dose delivery and for 1 hour after delivery, it is best to stay in a place where you or a caregiver can monitor the On-body Injector for Neulasta to make sure you receive your full dose of Neulasta and watch for symptoms of an allergic reaction.
- Keep the On-body Injector for Neulasta dry for about the last 3 hours before the dose delivery is expected to start. This will help you to better detect possible leaking from the On-body Injector for Neulasta.
- Only expose the On-body Injector for Neulasta to temperatures between 41°F to 104°F (5°C to 40°C).

What should I avoid while the On-body Injector for Neulasta is in place?

While the On-body Injector for Neulasta is in place you should avoid:

- traveling, driving or operating heavy machinery during hour 26 through hour 29 after the On-body Injector for Neulasta is applied.

- sleeping on the On-body Injector for Neulasta or applying pressure on the On-body Injector for Neulasta. The On-body Injector for Neulasta may not work properly.
- bumping the On-body Injector for Neulasta or knocking it off your body.
- getting body lotion, creams, oils, and skin cleansing products near the On-body Injector for Neulasta. These products may loosen the adhesive that holds the On-body Injector for Neulasta onto your body.
- using hot tubs, whirlpools, or saunas, and direct sunlight. These may affect Neulasta.
- peeling off or disturbing the On-body Injector for Neulasta adhesive before you receive your full dose of Neulasta.

What are possible side effects of Neulasta?

Neulasta can cause serious side effects, including:

- **Spleen rupture.** Your spleen may become enlarged or may rupture during treatment with Neulasta. A ruptured spleen can cause death. Call your healthcare provider right away if you have pain in your left upper stomach area or left shoulder area. This pain could mean your spleen is enlarged or ruptured.
- **A serious lung problem called Acute Respiratory Distress Syndrome (ARDS).** Call your healthcare provider or get emergency medical help right away if you get any of these symptoms of ARDS: fever, shortness of breath, trouble breathing, or a fast rate of breathing.
- **Serious allergic reactions.** Get emergency medical help right away if you get any of these symptoms of a serious allergic reaction with Neulasta: shortness of breath, wheezing, dizziness, swelling around the mouth or eyes, fast pulse, sweating, and hives.

If you have an allergic reaction during the delivery of Neulasta, remove the On-body Injector for Neulasta by grabbing the edge of the adhesive pad and peeling off the On-body Injector for Neulasta. Get emergency medical help right away.

- **Sickle cell crises.** Severe sickle cell crises, and sometimes death, can happen in people with sickle cell trait or disease who receive filgrastim, a medicine similar to Neulasta (pegfilgrastim).
- **Kidney injury (glomerulonephritis).** Kidney injury has been seen in patients who received Neulasta. You should notify your healthcare provider right away if you experience puffiness in your face or ankles, blood in your urine or brown colored urine or you notice you urinate less than usual.
- **Increased white blood cell count (leukocytosis).** Your doctor will check your blood during treatment with Neulasta.

- **Capillary Leak Syndrome.** Neulasta can cause fluid to leak from blood vessels into your body's tissues. This condition is called "Capillary Leak Syndrome" (CLS). CLS can quickly cause you to have symptoms that may become life-threatening. Get emergency medical help right away if you develop any of the following symptoms:
 - o swelling or puffiness and are urinating less often
 - o trouble breathing
 - o swelling of your stomach-area (abdomen) and feeling of fullness
 - o dizziness or feeling faint
 - o a general feeling of tiredness

The most common side effect of Neulasta is pain in the bones and in your arms and legs.

Tell your healthcare provider if you have any side effect that bothers you or that does not go away.

These are not all the possible side effects of Neulasta. For more information, ask your healthcare provider or pharmacist.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

General information about the safe and effective use of Neulasta

Medicines are sometimes prescribed for purposes other than those listed in a Patient Information leaflet. If you would like more information about Neulasta, talk with your healthcare provider or pharmacist. You can ask your pharmacist for information about Neulasta that is written for health professionals.

For more information, go to www.neulasta.com or call 1-844-696-3852 (1-844-MYNEULASTA).

What are the ingredients in Neulasta?

Active ingredient: pegfilgrastim

Inactive ingredients: acetate, polysorbate 20, and sodium, sorbitol in Water for Injection.

This Patient Information has been approved by the U.S. Food and Drug Administration.



Neulasta® (pegfilgrastim)

Manufactured by:

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

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

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www.neulasta.com

1-844-MYNEULASTA (1-844-696-3852)

Issued: 09/2015

vX

{SIDE 1 Information}

Patient Instructions for Use

On-body Injector for Neulasta Description

The On-body Injector for Neulasta is intended for delivery of Neulasta. The On-body Injector is small, for one-time use, lightweight, battery-powered, and waterproof up to 8 feet for 1 hour. Your healthcare provider will use a prefilled syringe with Neulasta to fill the On-body Injector prior to applying it. The prefilled syringe with Neulasta and the On-body Injector are provided to your healthcare provider as part of Neulasta Onpro™ kit. The On-body Injector is applied directly to your skin using a self-adhesive backing. The On-body Injector informs you of its status with sounds and lights.

The On-body Injector contains electronic components as well as: a plastic housing, acrylic adhesive, batteries, a cannula introducer (needle) and a cannula. The On-body Injector is approximately: 2.4 in long, 1.6 in wide, 0.7 in height (62 mm long, 41 mm wide, 17 mm height).

Warnings

- **Before** you receive Neulasta, tell your healthcare provider if you:
 - o Have sickle cell trait or sickle cell disease
 - o Have problems with your kidneys
 - o Have any other medical problems
 - o Are pregnant or plan to become pregnant. It is not known if Neulasta may harm your unborn baby.
 - o Are breastfeeding or plan to breastfeed. It is not known if Neulasta passes into your breastmilk.
- **DO NOT** take Neulasta if you have had a serious allergic reaction to pegfilgrastim (Neulasta®) or to filgrastim (Neupogen®).
- Tell your healthcare provider if you are allergic to latex. A prefilled syringe is used to fill the On-body Injector by your healthcare provider prior to applying the On-body Injector. The prefilled syringe gray needle cap contains dry natural rubber, which is derived from latex. Latex may be transferred to your skin.
- Tell your healthcare provider if you have had severe skin reactions to acrylic adhesives.
- Avoid activities and places that may interfere with monitoring during the dosing of Neulasta administered by the On-body Injector. For example, **AVOID** traveling, driving, or operating heavy machinery during hours 26-29 following application of the On-body Injector for Neulasta (this includes the 45-minute dose delivery period plus an hour post-delivery). If you must travel by airplane **before** the approximately 45-minute dose delivery period with the On-body Injector, avoid airport X-ray scans. Request a manual pat down instead. Use care during a manual pat down to help prevent the On-body Injector from being accidentally removed. For more information go to <http://www.tsa.gov/traveler-information/travelers-disabilities-and-medical-conditions>
If you have an allergic reaction during the delivery of Neulasta, remove the On-body Injector by grabbing the edge of the adhesive pad and peeling off the On-body Injector. Get emergency medical help right away.
- Call your healthcare provider immediately if you have severe pain or skin discomfort around your On-body Injector.

- Call your healthcare provider right away if you have pain in your left upper stomach area or left shoulder area. This pain could mean your spleen is enlarged or ruptured.
- Call your healthcare provider or get emergency medical help right away if you get any of these symptoms of acute respiratory distress syndrome (ARDS): fever, shortness of breath, trouble breathing, or a fast rate of breathing.
- Call your healthcare provider right away if you experience any of these symptoms of kidney injury (glomerulonephritis): puffiness in your face or ankles, blood in your urine or brown colored urine or you notice you urinate less than usual.
- Keep children away from the used On-body Injector.
- You should only receive a dose of Neulasta on the day your healthcare provider tells you.
- You should not receive your dose of Neulasta any sooner than 24 hours after you finish receiving your chemotherapy. The On-body Injector for Neulasta is programmed to deliver your dose about 27 hours after your healthcare provider places the On-body Injector on your skin.
- It is not known if Neulasta is safe and effective in children.
- **DO NOT** expose the On-body Injector to the following because the On-body Injector may be damaged and you could be injured:
 - MRI
 - X-ray
 - CT-Scan
 - Ultrasound
 - Oxygen rich environments, such as hyperbaric chambers
- **DO NOT** use hot tubs, whirlpools, or saunas while wearing the On-body Injector. This may affect your medicine.
- **DO NOT** expose the On-body Injector to direct sunlight. If the On-body Injector is exposed to direct sunlight for more than 1 hour, it may affect your medicine. Wear the On-body Injector under clothing.
- **DO NOT** sleep on the On-body Injector or apply pressure during wear, especially during dose delivery. This may affect the On-body Injector performance.
- **DO NOT** peel off or disturb the On-body Injector's adhesive before your full dose is complete. This may result in a missed or incomplete dose of Neulasta.

Precautions

Environmental:

- Keep the On-body Injector dry for the last 3 hours prior to the dose delivery start.
- Only expose the On-body Injector to temperatures between 41°F and 104°F (5°C-40°C).
- Keep the On-body Injector at least 4 inches away from electrical equipment such as cell phones, cordless telephones, microwaves and other common appliances. Failure to keep the On-body Injector at least this recommended distance may interfere with operation and can lead to a missed or incomplete dose of Neulasta.

Activity Related:

- Avoid getting body lotions, creams, oils or cleaning agents near the On-body Injector as these products may loosen the adhesive.
- Be careful not to bump the On-body Injector or knock the On-body Injector off your body.

Biohazard:

Properly dispose of the On-body Injector:

- The On-body Injector contains batteries, electronics, and a needle. The On-body Injector should be placed in a sharps disposal container, with an appropriate sized opening, regardless of whether or not the needle is exposed. Follow instructions provided by your healthcare provider or by state or local laws.
- To participate in Amgen's voluntary disposal program, please call 1-844-MYNEULASTA (1-844-696-3852) or visit www.neulasta.com to enroll.
- For more information about safe sharps disposal, and for specific information about sharps disposal in the state that you live in, go to FDA's website at: <http://www.fda.gov/safesharpsdisposal>.

Risks

You can avoid most risks related to using the On-body Injector for Neulasta by following the Patient Instructions for Use. Immediately call your healthcare provider if any of the following occur:

- The adhesive becomes noticeably wet (saturated) with fluid, or you see dripping
- If the On-body Injector fill indicator is not at the empty position after On-body Injector removal (You should see a black line next to the EMPTY indicator.)
- The On-body Injector comes off from the skin before or during a dose delivery (**DO NOT re-apply it.**)
- Status light is flashing red
- Allergic reaction
- Persistent or worsening redness or tenderness at the application site (may be a sign of infection)
- Severe pain or skin discomfort around your On-body Injector
- Any concern about your medication
- If the needle is exposed after On-body Injector removal

{SIDE 2 Information}

On-body Injector for Neulasta® (nu-las-tah) (pegfilgrastim) Injection Patient Instructions for Use

Dose Delivery Information

Your On-body Injector was applied:

Day	Time	AM / PM
-----	------	---------

Your dose delivery will start around:

Day	Time	AM / PM
-----	------	---------

Name of Healthcare Provider:

Last, First

Healthcare Provider contact number:

On-body Injector lot number:

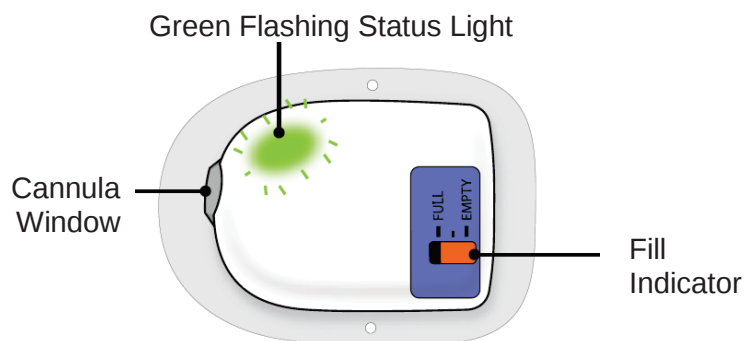
Important Information

- !** This On-body Injector delivers Neulasta with an under-the-skin (subcutaneous) injection. See Patient Information for medicine information.
- !** If you have concerns about your medication, call your healthcare provider immediately. Serious allergic reactions can happen with Neulasta. Ask your caregiver to be nearby for the first use.
- !** Plan to be in a place where you or your caregiver can appropriately monitor the On-body Injector for Neulasta during the approximately 45 minute Neulasta delivery and for an hour after the delivery.
- !** Avoid activities and places that may interfere with monitoring during the dosing of Neulasta administered by the On-body Injector (hours 26-29).

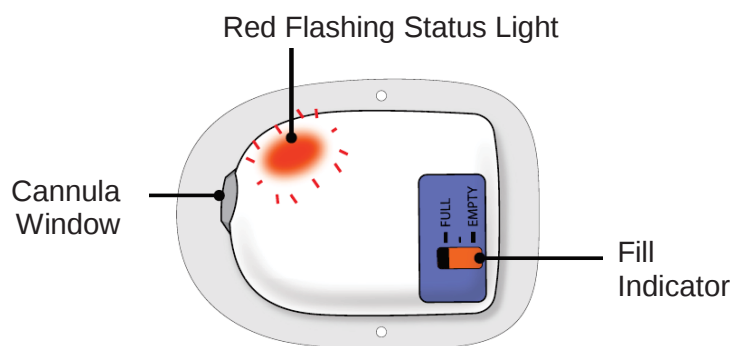
- !** If you have an allergic reaction during the delivery of Neulasta, remove the On-body Injector by grabbing the edge of the adhesive pad and peeling off the On-body Injector. Get emergency medical help right away.
 - !** The On-body Injector should be applied to intact, non-irritated skin on the stomach area (abdomen) or back of the arm. The back of the arm may only be used if there is a caregiver available to monitor the status of the On-body Injector.
 - !** Call your healthcare provider immediately if you have severe pain or skin discomfort around your On-body Injector.
 - !** Be careful not to bump the On-body Injector or knock the On-body Injector off your body.
 - !** Avoid getting body lotions, creams, oils or cleaning agents near the On-body Injector as these products may loosen the adhesive.
 - !** Keep the On-body Injector dry for the last 3 hours prior to the dose delivery start.
 - !** Only expose the On-body Injector to temperatures between 41°F and 104°F (5°C and 40°C).
 - !** After On-body Injector removal, properly dispose of it in a sharps disposal container as instructed by your healthcare provider or by state or local laws.
 - !** Keep the On-body Injector at least 4 inches away from electrical equipment such as cell phones, cordless telephones, microwaves and other common appliances. Failure to keep the On-body Injector at least this recommended distance may interfere with operation and can lead to a missed or incomplete dose of Neulasta.
- ⊘ DO NOT:**
- ×** use hot tubs, whirlpools, or saunas while wearing the On-body Injector. This may affect your medicine.
 - ×** expose the On-body Injector to direct sunlight. If the On-body Injector is exposed to direct sunlight for more than 1 hour, it may affect your medicine. Wear the On-body Injector under clothing.
 - ×** sleep on the On-body Injector or apply pressure during wear, especially during dose delivery. This may affect On-body Injector performance.
 - ×** peel off or disturb the On-body Injector adhesive before your full dose is complete. This may result in a missed or incomplete dose of Neulasta.

A healthcare provider who is familiar with Neulasta should answer your questions. For general questions or support call 1-844-MYNEULASTA (1-844-696-3852) or visit www.neulasta.com.

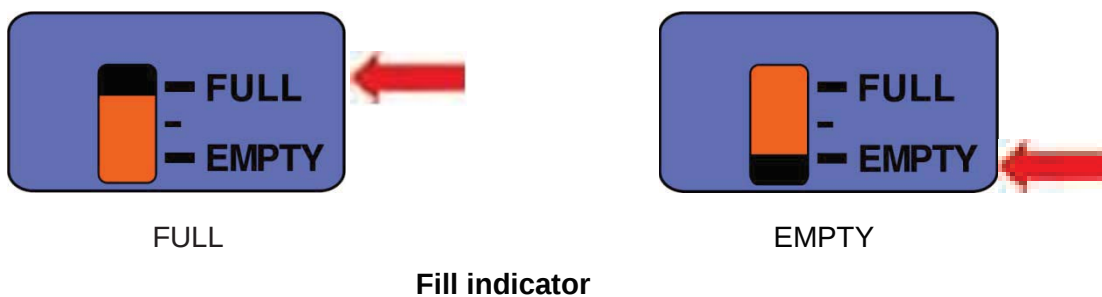
Guide to Parts for On-body Injector for Neulasta



The On-body Injector is working properly.

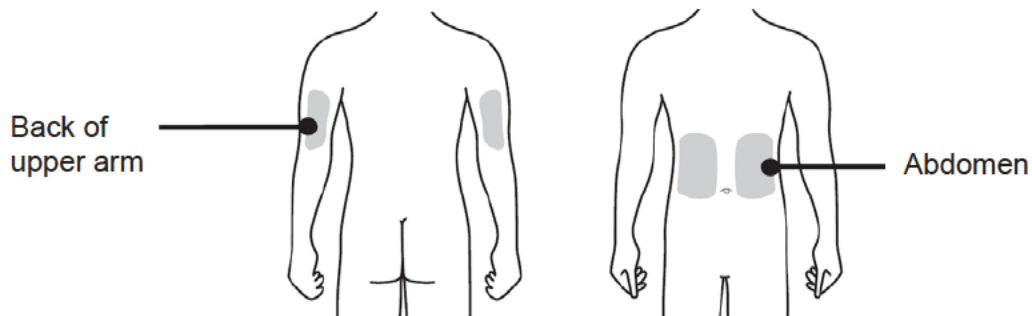


If at any time you hear beeping, check the status light. If it is flashing red, call your healthcare provider immediately.



After your dose delivery is complete, check to see if the black line on your On-body Injector fill indicator is at empty.

On-body Injector Placement



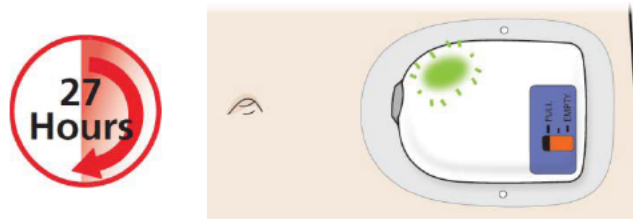
Step 1: Monitor On-body Injector

- A** Check your status light occasionally for approximately 27 hours. Since it flashes slowly, watch for at least 10 seconds. If the status light is flashing green, it is okay.

! If at any time you hear beeping, check the status light. If it is flashing red, call your healthcare provider immediately.

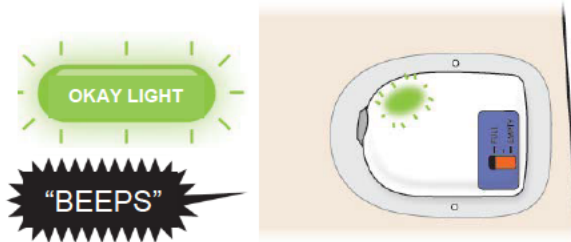


If the On-body Injector for Neulasta was placed on the back of your arm, a caregiver must be available to monitor the status of the On-body Injector.



- B** After approximately 27 hours, your On-body Injector will beep to let you know your dose delivery will begin in 2 minutes. When the dose delivery starts, it will take about 45 minutes to complete. During this time, the On-body Injector will flash a fast green light.

! If at any time you hear beeping, check the status light. If it is flashing red, call your healthcare provider immediately.

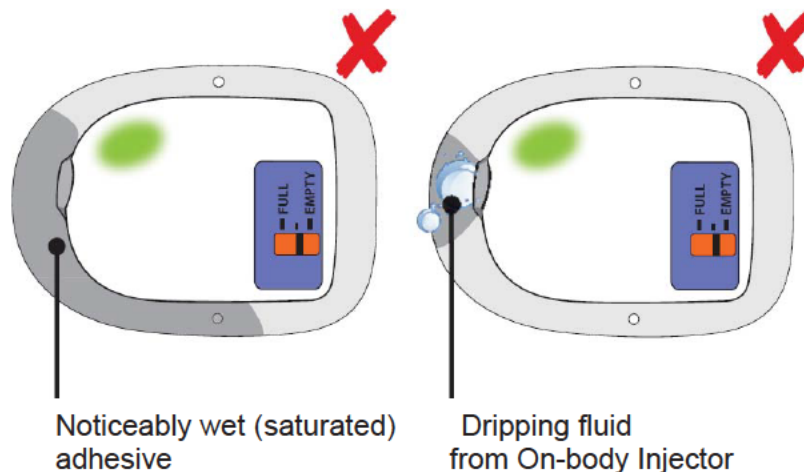


⊘ DO NOT remove the On-body Injector before the dose delivery is complete.

Step 2: Monitor Dose Delivery



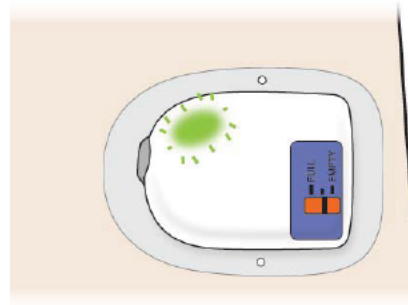
For the next 45 minutes, monitor your On-body Injector frequently for leaks during dose delivery. If the On-body Injector was placed on the back of your arm, a caregiver must be available to monitor your On-body Injector.



If the adhesive becomes noticeably wet (saturated) with fluid, or you see dripping, call your healthcare provider immediately.

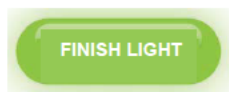
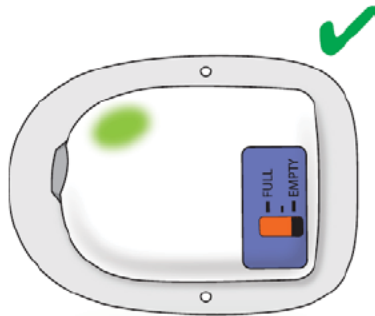
A Your dose delivery will take around 45 minutes to complete.

- You may hear a series of clicks. This is okay.
- A beep will sound when the dose delivery is complete.

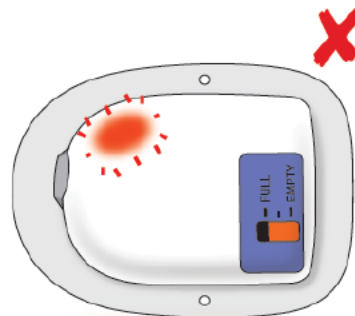


Step 3: Remove On-body Injector When Dose Delivery Is Complete

A When beeping starts, check to see the color of the status light.



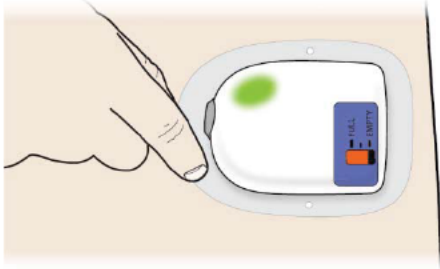
Check to see if the status light is SOLID GREEN or has switched off. This means the dose is complete. Remember, **any time you see a leak, call your healthcare provider immediately.** If the dose is complete, go to the next step.



If you see the status light is flashing red, your On-body Injector is not functioning properly. Call your healthcare provider immediately, as you may not have received a full dose.

B Grab the edge of the adhesive pad. Slowly peel off the On-body Injector.

- If medicine has leaked or the adhesive is noticeably wet (saturated), call your healthcare provider immediately as you may not have received your full dose.
- Remove any extra adhesive using soap and water.



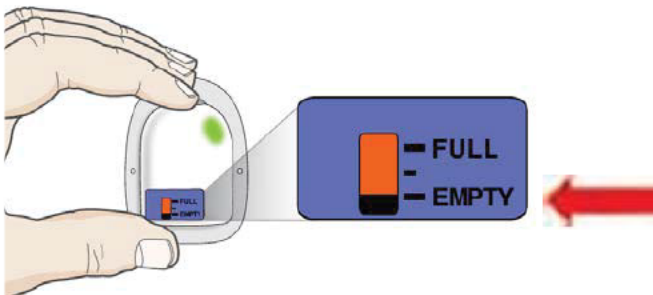
⊘ **DO NOT** grasp the On-body Injector itself to try to pull it off of your body.

Step 4: Finish



Check to see if your On-body Injector is empty.

- You should see a black line next to the EMPTY indicator. If the On-body Injector is not empty, call your healthcare provider immediately.



- Check your status light again. Watch for at least 10 seconds. If the status light is solid green or it has switched off, it is okay.
- If you hear beeping, or when you check the status light and it is flashing red, call your healthcare provider immediately.



After On-body Injector removal, place the On-body Injector in a sharps disposal container whether the needle is exposed or not. If the needle is exposed, call your healthcare provider immediately.

A Record the end state of your On-body Injector.

- Mark the box of the description that represents your On-body Injector after it has been used.

☐ Status light is solid green or the status light has switched off. This means that the delivery is complete.

☐ On-body Injector leaked, call your healthcare provider immediately.

☐ Status light is red, call your healthcare provider immediately.

B Properly dispose of the On-body Injector.

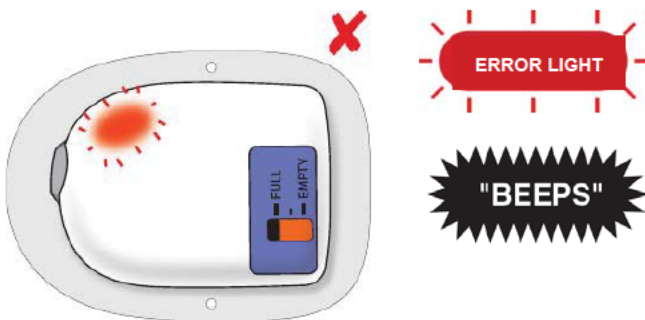
- The On-body Injector contains batteries, electronics, and a needle. Dispose of it in a sharps disposal container as instructed by your healthcare provider or by state or local laws.
- To participate in Amgen's voluntary disposal program, please call 1-844-MYNEULASTA (1-844-696-3852) or visit www.neulasta.com to enroll. For more information about safe sharps disposal, and for specific information about sharps disposal in the state that you live in, go to FDA's website at: <http://www.fda.gov/safesharpsdisposal>.

! Keep children away from the used On-body Injector.

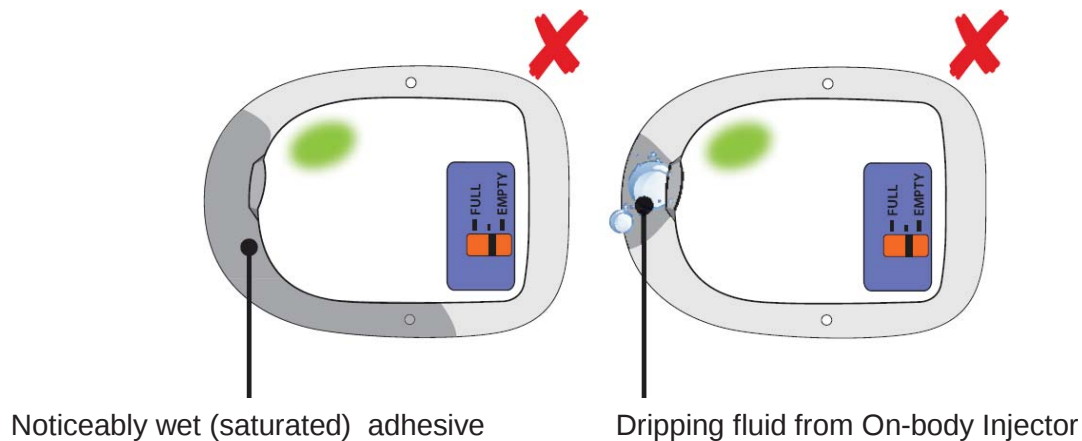
Attention!

What to do if you hear beeping or when you look at the status light and it is flashing red.

! If the status light is flashing red, you may not have received your full dose. Call your healthcare provider immediately.



What to do if the On-body Injector adhesive becomes noticeably wet (saturated) with fluid, or you see dripping.



- !** If the adhesive becomes saturated with fluid, or you see dripping, your medicine may have leaked out.
- !** Even with a leak, the status light may remain green and the fill indicator may be at EMPTY.
- !** Call your healthcare provider immediately as you may not have received your full dose.

Note: It is normal to see a few drops of fluid at the application site, but not normal to see a noticeably wet (saturated) adhesive.

What do I do if the On-body Injector comes off before the full dose is delivered?

Call your healthcare provider immediately if the On-body Injector at any time comes away from your skin before your full dose delivery, **DO NOT** reapply it.

What if there is blood at my application site after the On-body Injector has been removed?

If there is blood, press a clean cotton ball or gauze pad on the application site. Apply an adhesive bandage if needed.

What if my application site is red or tender after On-body Injector removal?

Call your healthcare provider immediately if you experience persistent or worsening redness or tenderness at the application site, as this can be a sign of infection.



Neulasta® (pegfilgrastim)

Manufactured by:

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

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

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www.neulasta.com

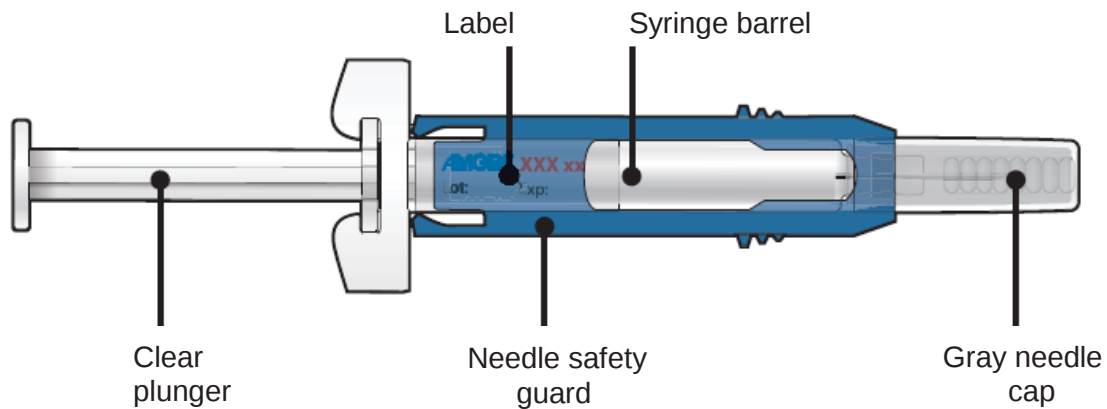
1-844-MYNEULASTA (1-844-696-3852) Issued: 09/2015 vX

Neulasta® (pegfilgrastim) Onpro™ kit

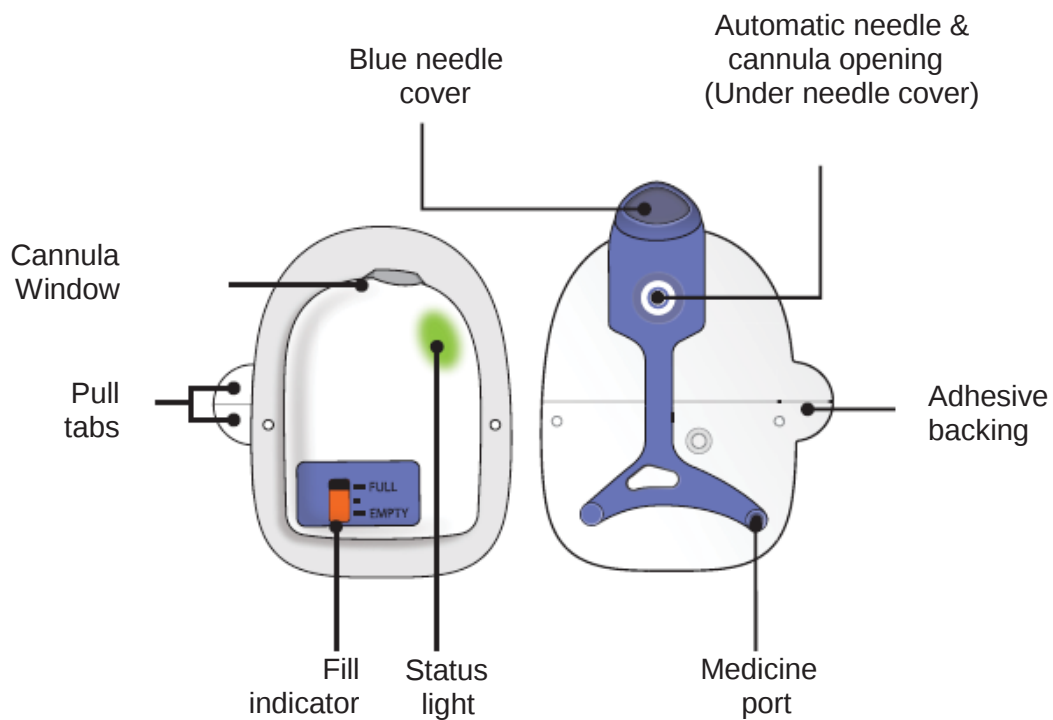
Healthcare Provider Instructions for Use

Guide to Parts

Neulasta Prefilled Syringe with Manual Needle Guard



On-body Injector for Neulasta



Important

READ THE FOLLOWING INSTRUCTIONS BEFORE USING THE ON-BODY INJECTOR

Warning: Do not use Neulasta Onpro kit to deliver any other drug product.

-  See Prescribing Information for information on Neulasta.
-  Store Neulasta Onpro kit in the refrigerator at 36°F to 46°F (2°C to 8°C) until ready for use. If Neulasta Onpro kit is stored at room temperature for more than 12 hours, do not use. Start again with a new Neulasta Onpro kit.
-  Keep the prefilled syringe in the Neulasta Onpro kit carton until use to protect from light.
-  For patients who have had severe skin reactions to acrylic adhesives, consider the benefit:risk profile before administering pegfilgrastim via the On-body Injector for Neulasta.
-  The On-body Injector should be applied to intact, non-irritated skin on the abdomen or back of the arm. The back of the arm may only be used if there is a caregiver available to monitor the status of the On-body Injector.
-  DO NOT:
 -  freeze Neulasta Onpro kit.
 -  shake the prefilled syringe.
 -  separate the components of Neulasta Onpro kit until ready for use.
 -  modify the On-body Injector.
 -  warm Neulasta Onpro kit components using a heat source.
 -  use Neulasta Onpro kit if expiry date on the carton or any of the Neulasta Onpro kit components has passed.
 -  use if the name Neulasta does not appear on the Neulasta Onpro kit carton.
 -  attempt to reapply On-body Injector.
 -  use if either the On-body Injector or prefilled syringe is dropped. Start again with a new Neulasta Onpro kit.

For all questions, call Amgen at 1-800-772-6436. If a patient calls you regarding any On-body Injector problems, call Amgen at 1-800-772-6436.

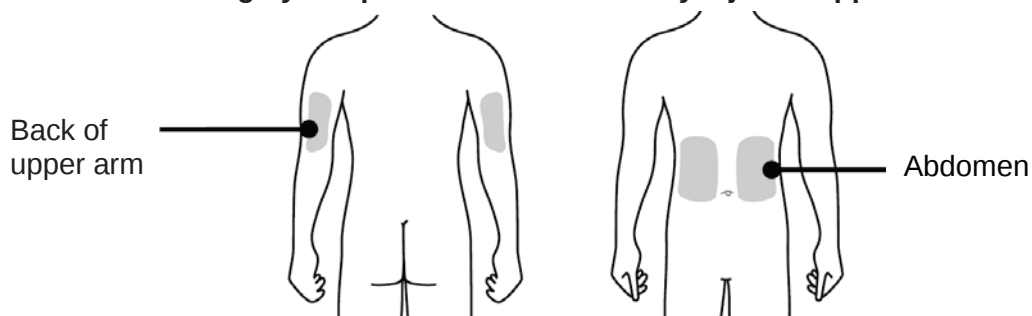
Step 1: Prepare

A Remove Neulasta Onpro kit from refrigerator. Check to make sure it contains:

- One Neulasta prefilled syringe
- One On-body Injector for Neulasta
- Neulasta package insert
- Instructions for use:
 - for healthcare provider
 - for patient
- Reference guide

⊘ DO NOT use On-body Injector if its packaging has been previously opened.

B Wash hands thoroughly. Prepare and clean On-body Injector application site.



Choose the flattest site for On-body Injector application. Consult with your patient regarding their ability to remove and monitor the entire On-body Injector.

You can use:

- Left or right side of abdomen, except for a 2-inch area right around navel.
- Back of upper arm, only if there is a caregiver available to monitor the status of the On-body Injector.

Choose an area larger than the adhesive pad, and clean it with an alcohol swab. Allow skin to completely dry.

⊘ DO NOT touch this area again before attaching On-body Injector.

You should avoid:

- ✗ Areas with scar tissues, moles, or excessive hair. In case of excessive hair, carefully trim hair to get On-body Injector close to skin.
- ✗ Areas where belts, waistbands, or tight clothing may rub against, disturb, or dislodge On-body Injector.
- ✗ Surgical sites.
- ✗ Areas where On-body Injector will be affected by folds in skin.



The following is an overview of On-body Injector preparation steps. Read this section first.

When ready, proceed to Step 2: Get Ready Section.

Before you apply On-body Injector to your patient, locate medicine port on blue needle cover to fill the On-body Injector with Neulasta.

Please note: During filling, beeping will sound and the On-body Injector will be activated.

After activation, you will have 3 minutes to:

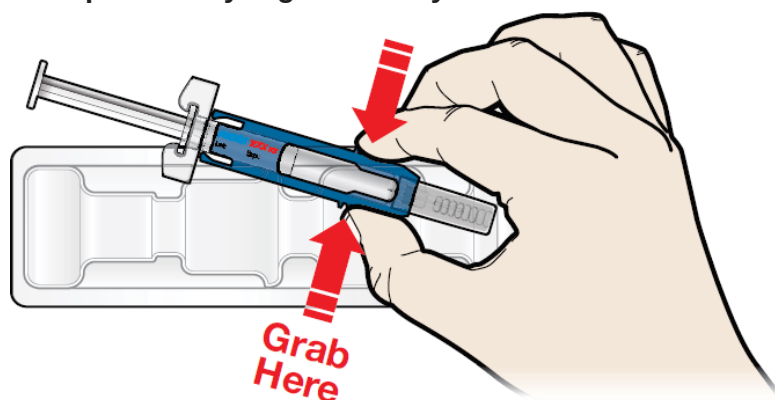
1. Completely empty syringe contents into medicine port.
2. Remove syringe from port and pull down needle safety guard over the exposed needle.
3. Remove blue needle cover from back of On-body Injector.
4. Peel away the two pieces of white adhesive backing from the back of the On-body Injector.
5. Attach On-body Injector to back of patient's upper arm or abdomen.

On-body Injector will deploy cannula in 3 minutes, even if not applied to patient. If not on patient's body in 3 minutes, do not use the On-body Injector. Start again with a new Neulasta Onpro kit.

When you feel you are ready, please continue...

Step 2: Get Ready

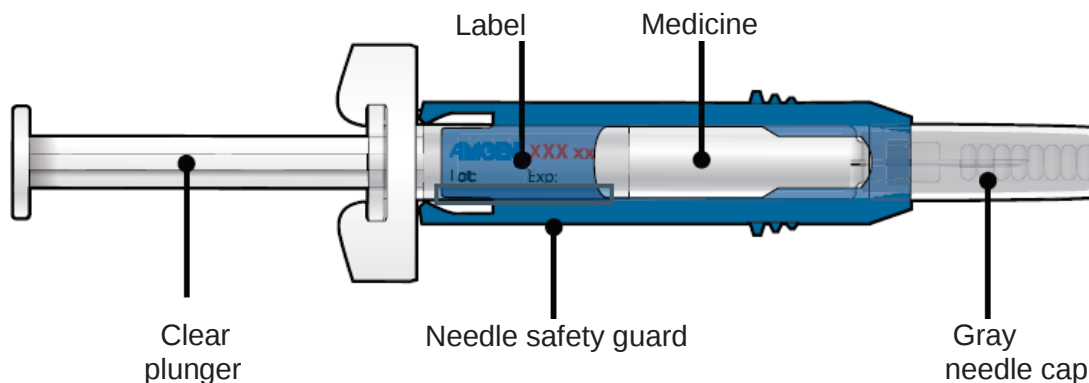
A Remove Neulasta prefilled syringe from tray.



For safety reasons:

- ⊘ DO NOT grasp gray needle cap.
- ⊘ DO NOT put the gray needle cap back onto syringe.
- ⊘ DO NOT grasp clear plunger.

B Inspect medicine and Neulasta prefilled syringe. The Neulasta liquid should always be clear and colorless.

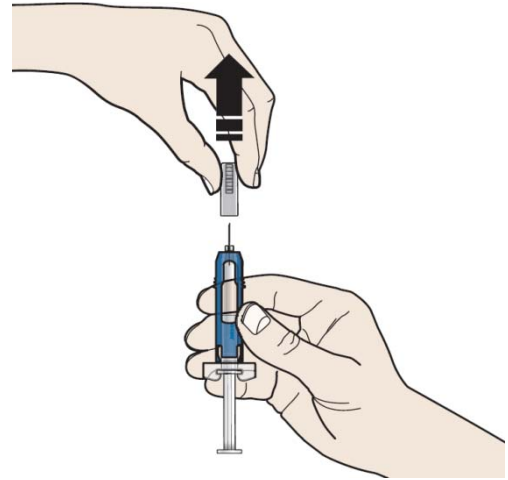


- ⊘ DO NOT use Neulasta prefilled syringe if:
 - ✗ Liquid contains particulate matter or discoloration is observed prior to administration.
 - ✗ Any part appears cracked or broken.
 - ✗ The gray needle cap is missing or not securely attached.
 - ✗ The expiration date printed on the label has passed.
- ⊘ DO NOT remove gray needle cap until ready to fill On-body Injector.
- ⊘ DO NOT pull needle safety guard down over the needle until filling is complete.
- ❗ In all the above cases, start again with a new Neulasta Onpro kit. Call Amgen at 1-800-772-

6436.

! The prefilled syringe gray needle cap contains dry natural rubber, which is derived from latex.

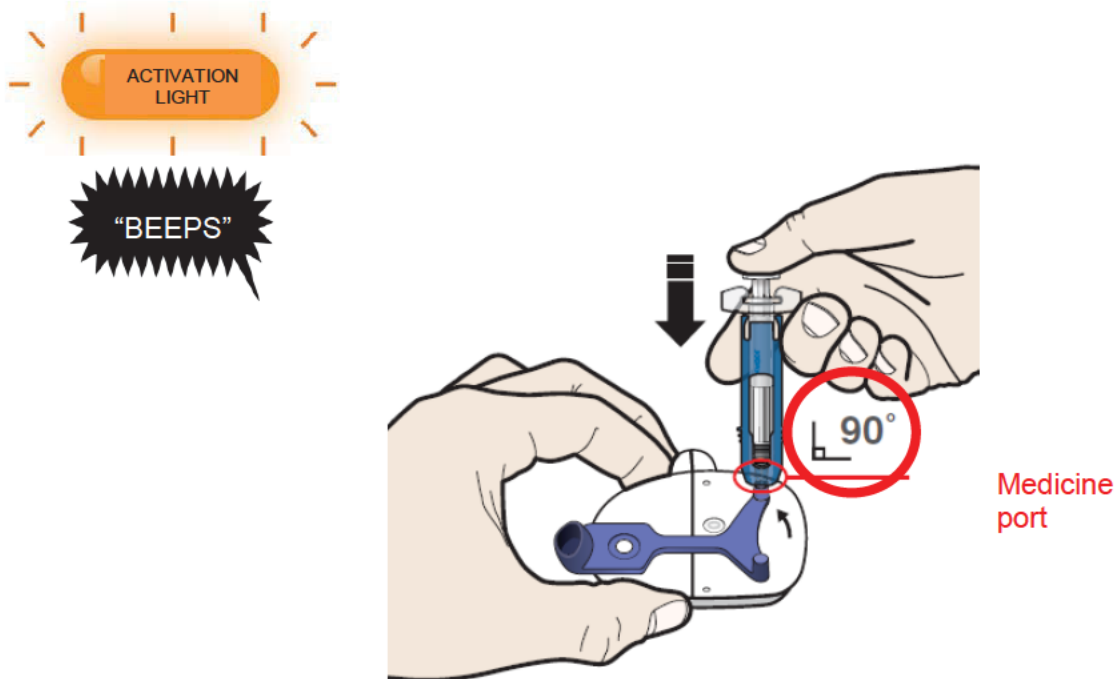
C **Carefully remove gray needle cap straight out from the syringe and away from your body. Check syringe, and remove air bubbles.**



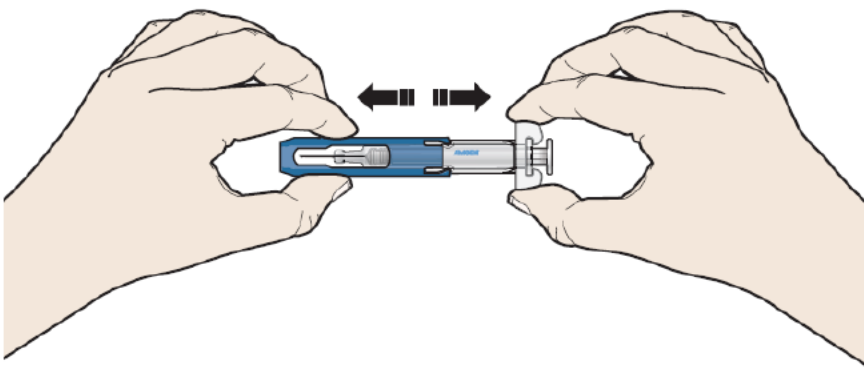
! Take care to expel air only and not medicine.
A small droplet at the tip of the needle during air purging is normal.

⊘ DO NOT recap syringe.

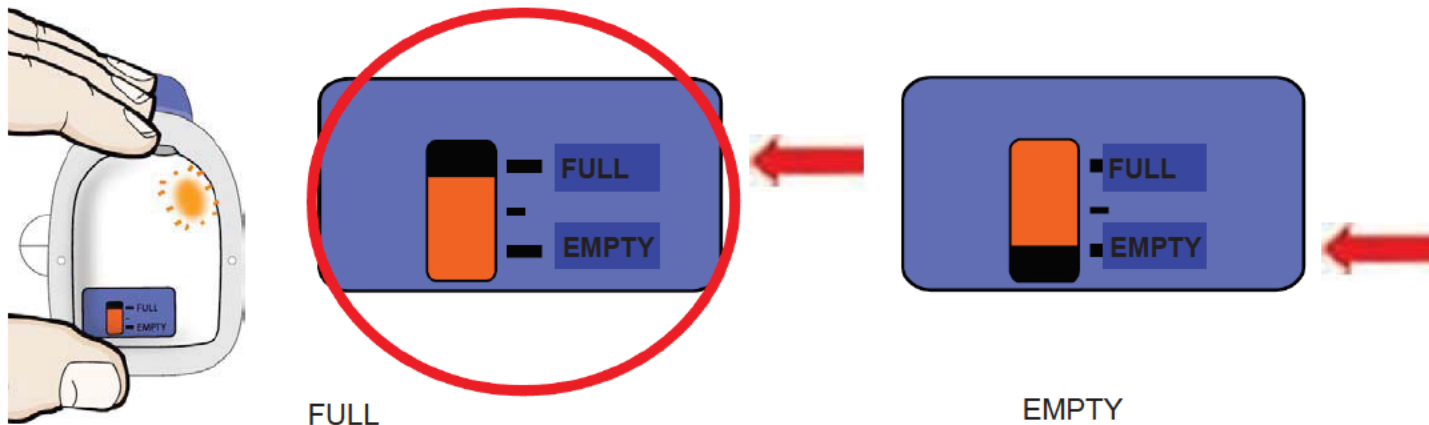
- D** Using blue needle cover, to avoid bending the needle and spilling medicine, insert syringe needle at 90 degrees all the way into medicine port. Slowly empty the entire syringe contents. Remove empty syringe from the medicine port. When beeping sounds and the status light flashes amber, the 3-minute countdown begins.



- ⊘ DO NOT insert needle into medicine port at other than a 90 degree angle
 - ⊘ DO NOT insert needle more than once.
 - ⊘ DO NOT remove blue needle cover before filling the On-body Injector.
- E** Pull needle safety guard down until it clicks and covers needle. Dispose of empty syringe in a sharps container.



F Check to see if the On-body Injector is full.



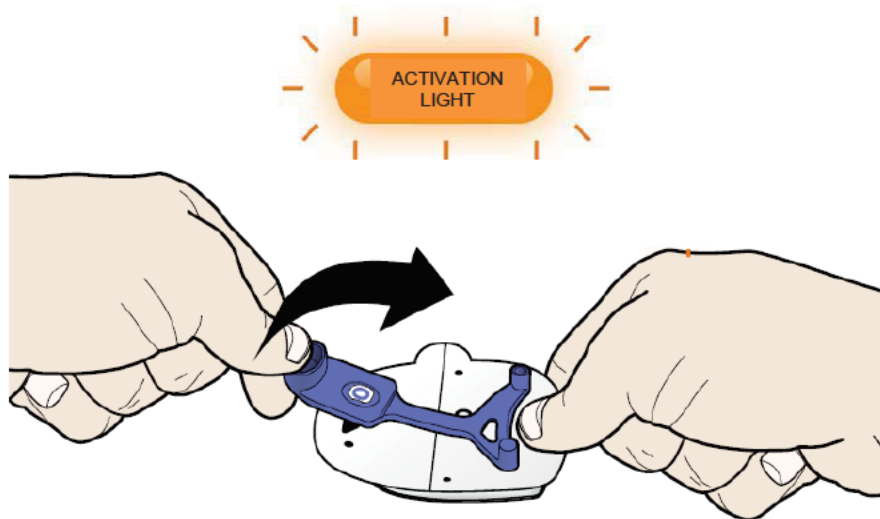
You should see:

- amber status light flashing.
- black line next to FULL on the fill indicator

If this is not the case, do not use. Start again with a new Neulasta Onpro kit, and call Amgen at 1-800-772-6436.

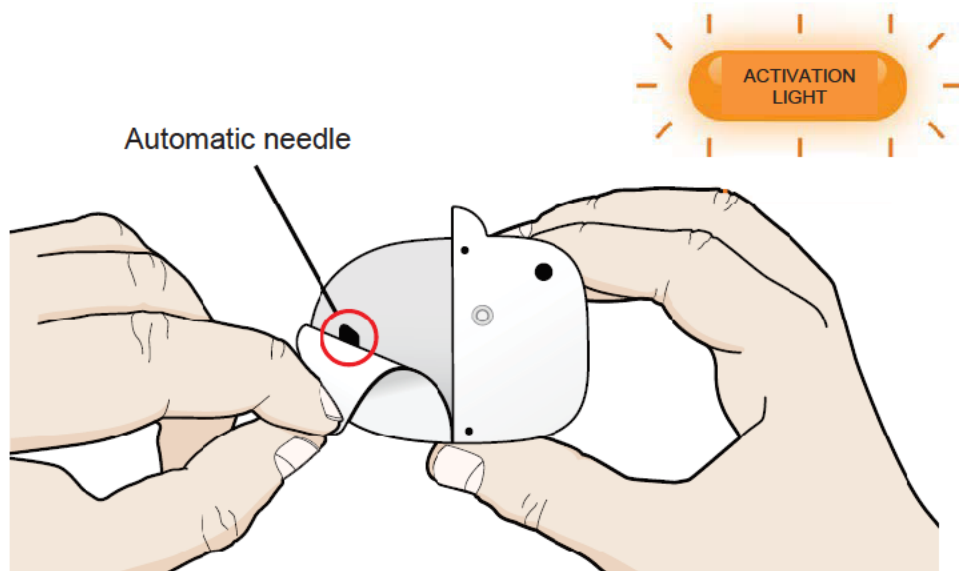
Step 3: Apply

A Firmly lift and remove blue needle cover away from On-body Injector.



A drop of medicine may be visible on needle tip when blue needle cover is removed.

- B To expose the adhesive pad, use both pull tabs, one at a time, to peel the two pieces of white adhesive backing away from On-body Injector.**

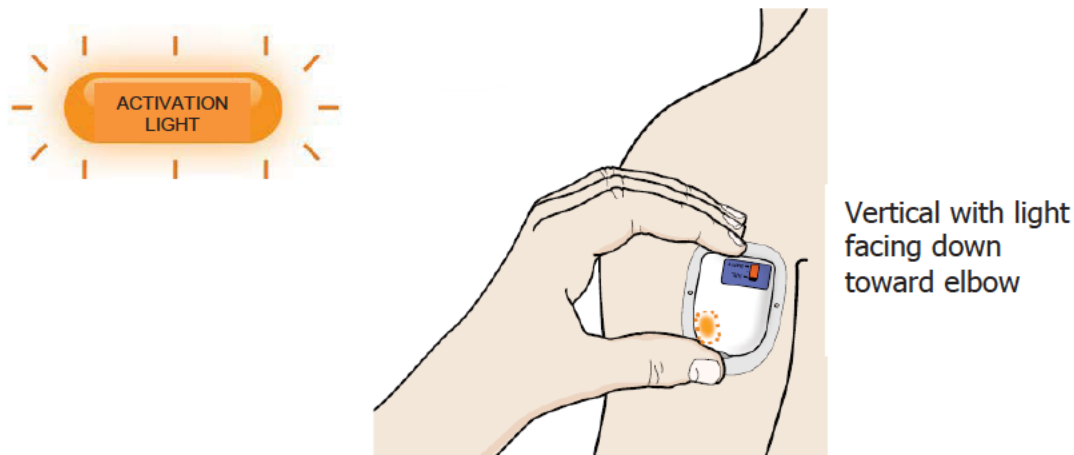


- ⊘ DO NOT touch or contaminate automatic needle area.
- ⊘ DO NOT pull off adhesive pad or fold it.
- ⊘ DO NOT use if the needle or cannula is extended past the adhesive or is extended before the On-body Injector is placed on patient.

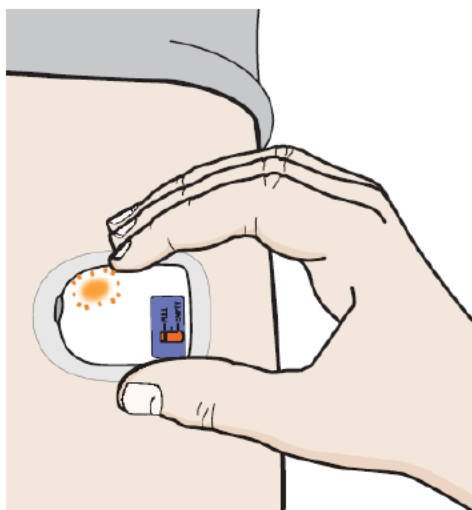
! In all cases, start again with a new Neulasta Onpro kit. Call Amgen at 1-800-772-6436.

- C Apply On-body Injector securely to patient with entire On-body Injector visible so it can be monitored by patient or caregiver.**
Before cannula deploys, place On-body Injector on your selected site, and run your finger around entire adhesive pad to make sure it is securely attached.

Back of Upper Arm



Horizontal
with light
facing
navel

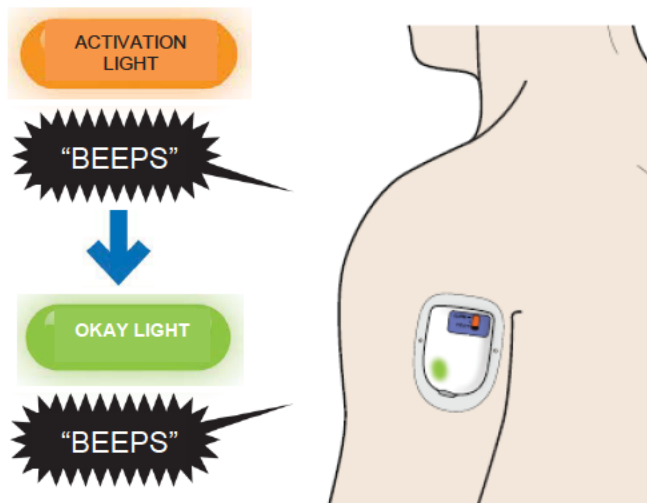


Abdomen



STOP! Do not worry if On-body Injector is quiet. When 3 minutes are up, On-body Injector will beep.

- D** Beeping will tell you the cannula is about to insert. You may hear a series of clicks. This is okay.
A long beep will sound, and the status light will turn to green. This means the cannula insertion is complete.



If the adhesive folds over near the cannula window or there are folds anywhere that prevent the On-body Injector from securely adhering, remove the On-body Injector. Start again with a new Neulasta Onpro kit and call Amgen at 1-800-772-6436.

Step 4: Finish

- A Fill in the Dose Delivery Information section in the patient instructions. Be sure to include when the On-body Injector was applied, when the dose will begin, and your contact information. Review this information with the patient.**

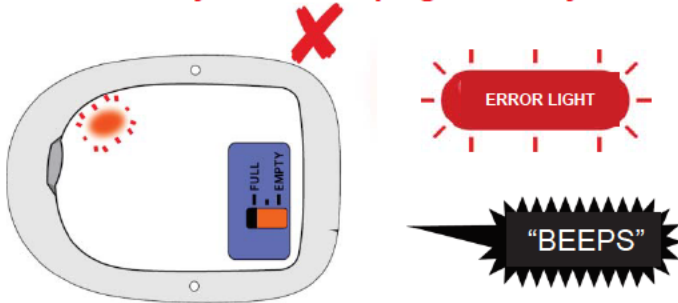
Review each step in the patient instructions with your patient. Give your patient the instructions, and reference guide to take home.

Before your patient goes home, make sure your patient understands:

- The On-body Injector will always flash a slow green light to let them know it is working properly.
- **After approximately 27 hours, beeps will signal that the dose delivery will begin in 2 minutes.**
- **When the dose delivery starts it will take about 45 minutes to complete. During this time, the On-body Injector will flash a fast green light.**
- The patient should remain in a place where they can monitor the On-body Injector for the entire dose delivery. The patient should avoid activities and settings that may interfere with monitoring during the dosing of Neulasta administered by the On-body Injector. For example, avoid traveling, driving, or operating heavy machinery during hours 26-29 following application of the On-body Injector (this includes the approximately 45-minute delivery period plus an hour post-delivery).
- If the patient has an allergic reaction during the delivery of Neulasta, the patient should remove the On-body Injector and call his or her healthcare provider or seek emergency care right away.
- If placed on the back of the arm, remind the patient that a caregiver must be available to monitor the On-body Injector.
- When the dose delivery is complete, the patient or caregiver will hear a beep and see a solid green light.
- Always dispose of the empty On-body Injector in a sharps disposal container as instructed by your healthcare provider or by state or local laws.
- Keep the On-body Injector at least 4 inches away from electrical equipment such as cell phones, cordless telephones, microwaves and other common appliances. Failure to keep the On-body Injector at least this recommended distance may interfere with operation and can lead to a missed or incomplete dose of Neulasta.

Attention!

What to do if you hear beeping or when you look at status light and it is flashing red.

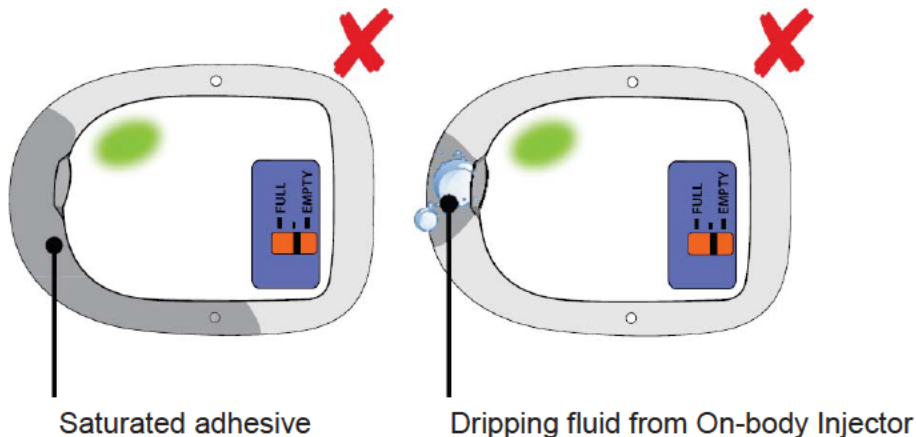


If at any time the On-body Injector beeps continuously for 5 minutes, and the status light is flashing red, take the On-body Injector off of the patient.

- ⊗ DO NOT apply On-body Injector to patient if red error light is on.
- ⊗ DO NOT leave On-body Injector on patient if red error light is on.

In all cases, do not use. Start over with a new Neulasta Onpro kit, and call Amgen at 1-800-772-6436.

What to do if the adhesive becomes saturated with fluid or the On-body Injector is dripping.



If patient reports an On-body Injector leak, they might not have received full dose. Schedule a follow-up appointment, and report the incident to Amgen at 1-800-772-6436.

Neulasta® (pegfilgrastim)

Manufactured by:

Amgen Inc.

One Amgen Center Drive

Thousand Oaks, California 91320-1799

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www.neulasta.com 1-800-772-6436 (1-800-77-AMGEN)

Issued: 09/2015

vX

Do not expose the On-body Injector for Neulasta to the following environments as the On-body Injector may be damaged and the patient could be injured:

- MRI
- X-ray
- CT-Scan
- Ultrasound
- Oxygen rich environments such as hyperbaric chambers

Symbol	Meaning
	Do not reuse this On-body Injector. Single-use only
	Refer to Instructions for Use
	Do not use if packaging is damaged.
	Temperature Limitation
	Humidity Limitation
	Expiration Date (use by date)
	Reference/model number
	Lot Number
	Type BF medical device (protection from electrical shock)
	Sterilized by ethylene oxide
	Waterproof up to 8 feet for 1 hour
	Prescription use only
	Not MRI-safe
	On-body Injector for Neulasta® (pegfilgrastim)
	Neulasta® (pegfilgrastim) Prefilled Syringe

Electromagnetic Compatibility

The information contained in this section (such as separation distances) is, in general, specifically written in regard to the On-body Injector for Neulasta. The numbers provided will not guarantee faultless operation but should provide reasonable assurance of such. This information may not be applicable to other medical electrical equipment; older equipment may be particularly susceptible to interference.

General Notes:
Medical electrical equipment requires special precautions regarding electromagnetic compatibility (EMC), and needs to be installed and put into service according to the EMC information provided in this document.

Portable and mobile RF communications equipment can affect medical electrical equipment.

Cables and accessories not specified within the instructions for use are not authorized. Using cables and/or accessories may adversely impact safety, performance, and electromagnetic compatibility (increased emission and decreased immunity).

Care should be taken if the On-body Injector for Neulasta is used adjacent to other electrical equipment; if adjacent use is inevitable, the On-body Injector for Neulasta should be observed to verify normal operation in this setting.

Electromagnetic Emissions		
The On-body Injector for Neulasta is intended for use in the electromagnetic environment specified below. The user of the On-body Injector for Neulasta should ensure that it is used in such an environment.		
Emissions	Compliance according to	Electromagnetic environment
RF Emissions (CISPR 11)	Group 1	The On-body Injector for Neulasta uses RF energy only for its internal function. Therefore, its RF emissions are very low and are not likely to cause any interference in nearby equipment.
CISPR B Emissions Classification	Class B	

Electromagnetic Immunity			
The On-body Injector for Neulasta is intended for use in the electromagnetic environment specified below. The user of this equipment should ensure that it is used in such an environment.			
Immunity Test	IEC 60601 Test Level	Compliance Level	Electromagnetic Environment – Guidance
ESD IEC 61000-4-2	±6kV Contact ±8kV Air	6kV Contact ±8kV Air	Floors should be wood, concrete or ceramic tile. If floors are synthetic, the r/h should be at least 30%.
Power Frequency 50/60 Hz Magnetic Field IEC 61000-4-8	3A/m	3A/m	Power frequency magnetic fields should be that of typical commercial or hospital environment.
Radiated RF Fields 61000-4-3	3 V/m 80 MHz to 2.5 GHz	(E1)=3V/m	Portable and mobile communications equipment should be separated from the On-body Injector for Neulasta by no less than the distances calculated/listed below: $D = (3.5/V1)(\sqrt{P})$ 150 kHz to 80 MHz $D = (3.5/E1)(\sqrt{P})$ 80 to 800 MHz $D = (7/E1)(\sqrt{P})$ 800 MHz to 2.5 GHz Where P is the max power in watts and D is the recommended separation distance in meters. Field strengths from fixed transmitters, as determined by an electromagnetic site survey, should be less than the compliance levels (V1 and E1). Interference may occur in the vicinity of equipment containing a transmitter.

Recommended separation distances between portable and mobile RF communications equipment and the On-body Injector for Neulasta

You can help prevent electromagnetic interference by maintaining a minimum distance between portable and mobile RF communications equipment (transmitters) and the On-body Injector for Neulasta, as recommended below, according to the maximum power of the communication equipment.

Rated maximum output power of transmitter, in watts	Separation distance according to frequency of transmitter, in meters		
	150 kHz to 80 MHz $D=(3.5/V1)(\sqrt{P})$	80 to 800 MHz $D=(3.5/E1)(\sqrt{P})$	800 MHz to 2.5 GHz $D=(7/E1)(\sqrt{P})$
0.01	0.11667	0.11667	0.23333
0.1	0.36894	0.36894	0.73785
1	1.1667	1.1667	2.3333
10	3.6894	3.6894	7.3785
100	11.667	11.667	23.333

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

125031Orig1s181

OTHER REVIEW(S)

FILE MEMORANDUM

MEMO DATE: 9/2/15

Regarding: PAS Label Supplement Neulasta
Submission: BLA 125031 s 170; s 179; s 181
Submission Date: 3/24/14 / 2/5/15 / 2/5/15
Submitted by: Amgen
FDA Received Date: 3/24/14; 2/5/15; 2/5/15
FDA Goal Date: 9/24/14; 8/5/15; 8/5/15
Date Review Completed: 9/2/15

FROM: Patricia Dinndorf, MD, Medical Officer; Division of
Hematology Products (DHP), OHOP; CDER

THROUGH: Albert Deisseroth, MD PhD, Team Leader; Division of
Hematology Products (DHP), OHOP; CDER

THROUGH: Ann Farrell, MD, Division Director; Division of
Hematology Products (DHP), OHOP; CDER

SUBJECT: PAS Label Supplement

ISSUE:

There are 3 submissions with pending items presented in the table

BLA 125031 Neulasta Pending Supplements			
Supplement #	Received	Due:	Content
170	3/24/2014	9/24/2014	PAS: Revise USPI and USPPI to add information about splenomegaly and leukocytosis
170 FDA Request 5/22/14			Revise the Neulasta label to include reference to Capillary Leak Syndrome to the WARNINGS AND PRECAUTIONS and POST-MARKETING EXPERIENCE sections of the PI.
179	2/5/2015	8/5/2015	Addition of Glomerulonephritis to the Warnings and Precautions and Adverse Reactions sections
181	2/5/2015	8/5/2015	Proposing the proprietary name "Neulasta OnPRO" for the Neulasta Delivery Kit

SUMMARY OF REVIEWER FINDINGS:

Review of Amgen's Justification for Adding Leukocytosis & Splenomegaly (copied from T Herndon review of 4/28/14)

The Safety Assessments submitted for Leukocytosis and Splenomegaly were reviewed.

Leukocytosis

There were 32 cases of leukocytosis in patients receiving Neupogen and 30 cases of leukocytosis in patient receiving Neulasta. The event of leukocytosis was defined as one or more lab values $\geq 100 \times 10^9/L$. In these patients, the increase in WBC was an asymptomatic, isolated, and transient lab finding, not associated with AEs. Confounding factors in causal assessment of the events in these cases included a history of leukocytosis, concurrent AML, MDS, and bone metastasis, and concomitant administration of corticosteroids, and overdose. Thirty eight of 62 events with Neupogen and Neulasta were serious. Of the 8 cases with fatal outcome, none of the fatal events appeared to be related to Neupogen or Neulasta. In the placebo-controlled clinical trials of Neupogen in CIN (Chemotherapy- Induced Neutropenia), the incidence rate of leukocytosis was 4.1% versus placebo 0%. In the placebo-controlled clinical trials of Neupogen in the Bone Marrow Transplant, Acute Myeloid leukemia, HIV and Healthy Donors patients, the incidence rate of leukocytosis on Neupogen was 8.8% versus placebo 9.7%. In the pegfilgrastim, placebo-controlled clinical trials, the incidence of leukocytosis on pegfilgrastim was 0 % versus placebo <1%.

The addition of leukocytosis to Section 5 was questioned as it is unclear what action the provider should take with this agent since patients only receive 1 dose and there is no specific action to suggest to caretakers.

FDA provided the following comment to Amgen:

To Applicant: The Agency agrees with everything except hyperleukocytosis. The Agency thinks this is an appropriate warning for Neupogen because there is an important intervention, stopping Neupogen, but for Neulasta this action is not feasible.

Amgen's Response:

Note to FDA: It is Amgen's position that the addition of Leukocytosis in Section 5 - Warnings and Precautions, Section 6 – Adverse Reactions and Section 6.3 Postmarketing Experience supports the Core Safety Information for Neulasta in the current indications. As such, Amgen proposes to retain Leukocytosis in the Warnings and Precautions, Adverse Reactions and the Postmarketing Experience sections. The addition of leukocytosis is supported by the Safety Assessment Report – Leukocytosis in Patients treated with Neupogen (filgrastim) and Neulasta (pegfilgrastim) submitted 24 March 2014 (Sequence No. 0181) and the Response to Request for Information of 22 May 2014 submitted 12 June 2014 (Sequence No. 0190) to BLA 125031/170.

ASSESSMENT

FDA will agree to include this statement in Warning and Precautions section. Although there is not specific intervention, hyperleukocytosis can be consequence of pegfigrastim.

Splenomegaly

In the Amgen clinical trials database, no events of splenomegaly, splenic rupture or other spleen disorder were identified. The search of the Amgen Global Safety Database identified a total of 65 cases. After excluding 4 duplicate cases, 1 case from an ongoing trial, and 10 cases with very limited information, 50 cases remained for further analysis: splenomegaly was reported in 26 cases, splenic rupture in 18 cases, and other diagnoses in 7 cases. One case reported 2 adverse events (splenomegaly and splenic rupture) and is counted twice. Fatal outcome occurred in 3 cases: 1 splenomegaly case and 2 splenic rupture cases. Massive leukocytosis was reported in 2 of the cases and “very high” WBC count was reported in the third case. Fatality occurred in the context of severe comorbidities in the 2 cases where detailed information was available. Leukocytosis, sometimes massive, was reported in almost 80% of all cases of splenomegaly, splenic rupture and other splenic events, when the information was available; more specifically, leukocytosis was reported in association with splenic rupture and splenic hematoma in all cases when this information was available.

ASSESSMENT

Review supports revising section 6.3:

From: Gastrointestinal disorders: Splenic rupture

To: Gastrointestinal disorders: Splenic rupture and splenomegaly (enlarged spleen)

Review of Amgen’s Justification for Adding Capillary Leak Syndrome

Amgen evaluated capillary leak syndrome prompted by an internal observation of 2 cases and a request by the European Medicines Agency (EMA) to evaluate for filgrastim and pegfilgrastim. The review identified a total of 39 filgrastim cases and 5 pegfilgrastim cases that were consistent with clinical presentation of capillary leak syndrome. Based on this review EMA requested Amgen update the product information for Neupogen and Neulasta.

ASSESSMENT

Add capillary leak syndrome to section 5 Warnings and Precautions; section 6 Adverse Reactions; and section 6.3 Postmarketing Experience

Review of Amgen’s Justification for Adding Glomerulonephritis

A literature article triggered Amgen’s evaluation of the association of pegfilgrastim therapy and glomerulonephritis. The case report described a 51-year old female with breast cancer receiving chemotherapy with pegfilgrastim support. She developed two episodes of proteinuria, hematuria and azotemia with a temporal relationship to cycles of pegfilgrastim exposure. Mesangioproliferative glomerulonephritis was demonstrated on kidney biopsy. She did not develop renal symptoms with subsequent cycles of chemotherapy without pegfilgrastim. (Arora 2012)

Amgen review of the literature included 13 published articles involving the development of glomerulonephritis in subjects treated with filgrastim or pegfilgrastim. Seven were

individual case reports, the remaining six were review articles. Of the seven case reports, one was the pegfilgrastim index case which involved a subject with breast cancer receiving chemotherapy with pegfilgrastim support and the second pegfilgrastim case involving a male HIV patient. Of the five filgrastim case reports two involved PBSC donors, two involved SCN [severe chronic neutropenia] subjects and one PBPC [peripheral blood progenitor cell] donor. Of the six review articles, four involved patients with SCN, one involved a patient with cyclic neutropenia and one involved a patient with agranulocytosis.

The clinical course of these patients included development of macroscopic hematuria, variable proteinuria, increased creatinine and decreased glomerular filtration rate. Renal biopsy was most commonly described as mesangial proliferative glomerulonephritis. In a majority of cases, renal function improved following withdrawal of filgrastim,

ASSESSMENT

There is adequate information suggesting a relationship between pegfilgrastim exposure and glomerulonephritis to include this in the label. Add glomerulonephritis to section 5 Warnings and Precautions; section 6 Adverse Reactions; and section 6.3 Postmarketing Experience.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

PATRICIA A DINNDORF
09/02/2015

ALBERT B DEISSEROTH
09/02/2015

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

125031Orig1s181

PROPRIETARY NAME REVIEW(S)

PROPRIETARY NAME REVIEW

Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

***** This document contains proprietary information that cannot be released to the public*****

Date of This Review:	March 13, 2015
Application Type and Number:	BLA 125031/S-181
Product Name and Strength:	Neulasta (pegfilgrastim) OnPro Injection, 6 mg/0.64 mL
Product Type:	Combination Product (Drug-Device)
Rx or OTC:	Rx
Applicant/Sponsor Name:	Amgen
Panorama #:	2015-48755
DMEPA Primary Reviewer:	Neil Vora, PharmD, MBA
DMEPA Team Leader:	Yelena Maslov, PharmD

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1 INTRODUCTION

This review evaluates the proposed proprietary name, Neulasta OnPro, from a safety and misbranding perspective. The sources and methods used to evaluate the proposed name are outlined in the reference section and Appendix A respectively. The Applicant submitted an external name study, conducted by (b) (4) for this product.

1.1 PRODUCT INFORMATION

The following product information is provided in the February 5, 2015 proprietary name submission.

- Intended Pronunciation: nu-**las**-tah **on**-pro
- Active Ingredient: pegfilgrastim
- Indication of Use: 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.
- Route of Administration: Subcutaneous Injection
- Dosage Form: Delivery device and prefilled syringe
- Strength: 6 mg/0.64 mL
- Dose and Frequency: 6 mg once per chemotherapy cycle. Do not administer between 14 days before and 24 hours after administration of cytotoxic chemotherapy.
- How Supplied: The kit is supplied with a prefilled single use syringe containing 0.64 mL with 0.6 mL of deliverable pegfilgrastim, used with Neulasta on-body injector and supplied with a 27-gauge, 1/2 –inch needle with UltraSafe® Needle Guard. The needle cap of the prefilled syringe contains dry natural rubber (a derivative of latex). The Neulasta OnPRO device kit is provided in a carton containing one sterile 0.64 mL prefilled syringe and one sterile on-body injector delivery device.
- Storage: Store the kit in the refrigerator at 36°F to 46°F (2°C to 8°C) until ready for use. Because the device is at room temperature during the period of use, the kit should not be held at room temperature longer than 12 hours prior to use. Discard the kit if stored at room temperature for more than 12 hours.

2 RESULTS

The following sections provide information obtained and considered in the overall evaluation of the proposed proprietary name.

2.1 MISBRANDING ASSESSMENT

The Office of Prescription Drug Promotion (OPDP) determined that the proposed name would not misbrand the proposed product. DMEPA and the Division of Hematology Products (DHP) concurred with the findings of OPDP's assessment of the proposed name.

2.2 SAFETY ASSESSMENT

The following aspects were considered in the safety evaluation of the name.

2.2.1 *United States Adopted Names (USAN) Search*

There is no USAN stem present in the proprietary name¹.

2.2.2 *Components of the Proposed Proprietary Name*

The Applicant indicated in their submission that the proposed name, Neulasta OnPro, is a delivery kit comprised of a single-use prefilled syringe co-packaged with the On-body Injector for Neulasta. The use of the word 'On' refers to the application of the on-body injector and to the fact that injector is adhered to the patient's skin until injection is complete. The use of the word 'PRO' indicates that the on-body injector must be applied to the patient's skin by a healthcare professional (HCP) in the HCP office. This proprietary name is comprised of a multiple words that do not contain any components (i.e. a modifier, route of administration, dosage form, etc.) that are misleading or can contribute to medication error.

2.2.3 *Medication Error Data Selection of Cases*

We searched the FDA Adverse Event Reporting System (FAERS) database using the strategy listed in Table 2 (see Appendix A1 for a description of FAERS database) for name confusion errors involving XX which would be relevant for this review.

Table 2. FAERS Search Strategy	
Date	March 6, 2015
Drug Name(Product Name)	Neulasta
MedDRA Event Search	Product Name Confusion - PT
Time/Date Limits	Open date range

Our search did not yield any results.

¹USAN stem search conducted on March 5, 2015.

2.2.4 FDA Name Simulation Studies

One hundred and three practitioners participated in DMEPA's prescription studies. The responses did not overlap with any currently marketed products nor did the responses sound or look similar to any currently marketed products or any products in the pipeline. Below is a summary of the prescription study results:

- In the voice prescription study, 11 of the 41 participants correctly interpreted the prescription.
- In the written inpatient prescription study, 11 of the 41 participants correctly interpreted the prescription.
- In the outpatient prescription study, 19 of the 41 participants correctly interpreted the prescription.

Common misinterpretations in the outpatient study include:

- Omission of the modifier, "OnPRO"
- A space inserted between "On" and "PRO"

Common misinterpretations in the inpatient study include:

- Omission of the letter "a" from the proprietary name Neulasta
- Omission of the modifier, "OnPRO"
- "o" for "a"
- "r" for "i"
- "a" for "o" in Neulasta
- "u" for "w"
- "Ne" for "tr"

Common misinterpretations in the voice study include:

- A space inserted between "On" and "PRO"
- "u" for "w"
- Omission of the letter "e" from Neulasta

Appendix B contains the results from the verbal and written prescription studies.

2.2.5 Comments from Other Review Disciplines at Initial Review

In response to the OSE, February 27, 2015 e-mail, the Division of Hematology Products (DHP) did not forward any comments or concerns relating to the proposed proprietary name at the initial phase of the review.

2.2.6 Phonetic and Orthographic Computer Analysis (POCA) Search Results

Table 1 lists the number of names with the combined orthographic and phonetic score of $\geq 50\%$ retrieved from our POCA search² organized as highly similar, moderately similar or low similarity for further evaluation. Table 1 also includes names identified from the FDA Prescription Simulation and by (b) (4)

Table 1. POCA Search Results	Number of Names
Highly similar name pair: combined match percentage score $\geq 70\%$	4
Moderately similar name pair: combined match percentage score $\geq 50\%$ to $\leq 69\%$	40
Low similarity name pair: combined match percentage score $\leq 49\%$	5

2.2.7 Safety Analysis of Names with Potential Orthographic, Spelling, and Phonetic Similarities

Our analysis of the 50 names contained in Table 1 determined none of the names will pose a risk for confusion as described in Appendices C through H.

2.2.8 Communication of DMEPA's Analysis at Midpoint of Review

DMEPA communicated our findings to the Division of Hematology Products (DHP) via e-mail on March 10, 2015. At that time we also requested additional information or concerns that could inform our review. Per e-mail correspondence from the DHP on March 12, 2015 they stated no additional concerns with the proposed proprietary name, Neulasta OnPro.

3 CONCLUSIONS

The proposed proprietary name is acceptable.

If you have further questions or need clarifications, please contact Sarah Harris, OSE project manager, at 240-402-4774.

3.1 COMMENTS TO THE APPLICANT

If any of the proposed product characteristics as stated in your February 5, 2015 submission are altered prior to approval of the marketing application, the name must be resubmitted for review.

² POCA search conducted on March 5, 2015.

4 REFERENCES

1. **USAN Stems** (<http://www.ama-assn.org/ama/pub/physician-resources/medical-science/united-states-adopted-names-council/naming-guidelines/approved-stems.page>)

USAN Stems List contains all the recognized USAN stems.

2. Phonetic and Orthographic Computer Analysis (POCA)

POCA is a system that FDA designed. As part of the name similarity assessment, POCA is used to evaluate proposed names via a phonetic and orthographic algorithm. The proposed proprietary name is converted into its phonemic representation before it runs through the phonetic algorithm. Likewise, an orthographic algorithm exists that operates in a similar fashion. POCA is publicly accessible.

Drugs@FDA

Drugs@FDA is an FDA Web site that contains most of the drug products approved in the United States since 1939. The majority of labels, approval letters, reviews, and other information are available for drug products approved from 1998 to the present.

Drugs@FDA contains official information about FDA-approved *brand name* and *generic drugs*; *therapeutic biological products*, *prescription* and *over-the-counter* human drugs; and *discontinued drugs* (see Drugs @ FDA Glossary of Terms, available at http://www.fda.gov/Drugs/InformationOnDrugs/ucm079436.htm#ther_biological).

RxNorm

RxNorm contains the names of prescription and many OTC drugs available in the United States. RxNorm includes generic and branded:

- Clinical drugs – pharmaceutical products given to (or taken by) a patient with therapeutic or diagnostic intent
- Drug packs – packs that contain multiple drugs, or drugs designed to be administered in a specified sequence

Radiopharmaceuticals, contrast media, food, dietary supplements, and medical devices, such as bandages and crutches, are all out of scope for RxNorm (<http://www.nlm.nih.gov/research/umls/rxnorm/overview.html#>).

Division of Medication Errors Prevention and Analysis proprietary name consultation requests

This is a list of proposed and pending names that is generated by the Division of Medication Error Prevention and Analysis from the Access database/tracking system.

APPENDICES

Appendix A

FDA's Proprietary Name Risk Assessment evaluates proposed proprietary names for misbranding and safety concerns.

1. **Misbranding Assessment:** For prescription drug products, OPDP assesses the name for misbranding concerns. . For over-the-counter (OTC) drug products, the misbranding assessment of the proposed name is conducted by DNCE. OPDP or DNCE evaluates proposed proprietary names to determine if the name is false or misleading, such as by making misrepresentations with respect to safety or efficacy. For example, a fanciful proprietary name may misbrand a product by suggesting that it has some unique effectiveness or composition when it does not (21 CFR 201.10(c)(3)). OPDP or DNCE provides their opinion to DMEPA for consideration in the overall acceptability of the proposed proprietary name.
2. **Safety Assessment:** The safety assessment is conducted by DMEPA, and includes the following:
 - a. Preliminary Assessment: We consider inclusion of USAN stems or other characteristics that when incorporated into a proprietary name may cause or contribute to medication errors (i.e., dosing interval, dosage form/route of administration, medical or product name abbreviations, names that include or suggest the composition of the drug product, etc.) See prescreening checklist below in Table 2*. DMEPA defines a medication error as any preventable event that may cause or lead to inappropriate medication use or patient harm while the medication is in the control of the health care professional, patient, or consumer.³

³ National Coordinating Council for Medication Error Reporting and Prevention.
<http://www.nccmerp.org/aboutMedErrors.html>. Last accessed 10/11/2007.

***Table 2- Prescreening Checklist for Proposed Proprietary Name**

	Answer the questions in the checklist below. Affirmative answers to any of these questions indicate a potential area of concern that should be carefully evaluated as described in this guidance.
Y/N	Is the proposed name obviously similar in spelling and pronunciation to other names?
	Proprietary names should not be similar in spelling or pronunciation to proprietary names, established names, or ingredients of other products.
Y/N	Are there medical and/or coined abbreviations in the proprietary name?
	Proprietary names should not incorporate medical abbreviations (e.g., QD, BID, or others commonly used for prescription communication) or coined abbreviations that have no established meaning.
Y/N	Are there inert or inactive ingredients referenced in the proprietary name?
	Proprietary names should not incorporate any reference to an inert or inactive ingredient in a way that might create an impression that the ingredient's value is greater than its true functional role in the formulation (21 CFR 201.10(c)(4)).
Y/N	Does the proprietary name include combinations of active ingredients?
	Proprietary names of fixed combination drug products should not include or suggest the name of one or more, but not all, of its active ingredients (see 21 CFR 201.6(b)).
Y/N	Is there a United States Adopted Name (USAN) stem in the proprietary name?
	Proprietary names should not incorporate a USAN stem in the position that USAN designates for the stem.
Y/N	Is this proprietary name used for another product that does not share at least one common active ingredient?
	Drug products that do not contain at least one common active ingredient should not use the same (root) proprietary name.
Y/N	Is this a proprietary name of a discontinued product?
	Proprietary names should not use the proprietary name of a discontinued product if that discontinued drug product does not contain the same active ingredients.

b. Phonetic and Orthographic Computer Analysis (POCA): Following the preliminary screening of the proposed proprietary name, DMEPA staff evaluates the proposed name against potentially similar names. In order to identify names with potential similarity to the proposed proprietary name, DMEPA enters the proposed proprietary name in POCA and queries the name against the following drug reference databases, Drugs@fda, CernerRxNorm, and names in the review pipeline using a 50% threshold in POCA. DMEPA reviews the combined orthographic and phonetic matches and group the names into one of the following three categories:

- Highly similar pair: combined match percentage score $\geq 70\%$.
- Moderately similar pair: combined match percentage score $\geq 50\%$ to $\leq 69\%$.
- Low similarity: combined match percentage score $\leq 49\%$.

Using the criteria outlined in the check list (Table 3-5) that corresponds to each of the three categories (highly similar pair, moderately similar pair, and low similarity), DMEPA evaluates the name pairs to determine the acceptability or non-acceptability of a proposed proprietary name. The intent of these checklists is to increase the transparency and predictability of the safety determination of whether a proposed name is vulnerable to confusion from a look-alike or sound-alike perspective. Each bullet below corresponds to the name similarity category cross-references the respective table that addresses criteria that DMEPA uses to determine whether a name presents a safety concern from a look-alike or sound-alike perspective.

- For highly similar names, differences in product characteristics often cannot mitigate the risk of a medication error, including product differences such as strength and dose. Thus, proposed proprietary names that have a combined score of ≥ 70 percent are at risk for a look-alike sound-alike confusion which is an area of concern (See Table 3).
- Moderately similar names with overlapping or similar strengths or doses represent an area for concern for FDA. The dosage and strength information is often located in close proximity to the drug name itself on prescriptions and medication orders, and it can be an important factor that either increases or decreases the potential for confusion between similarly named drug pairs. The ability of other product characteristics to mitigate confusion (e.g., route, frequency, dosage form, etc.) may be limited when the strength or dose overlaps. We review such names further, to determine whether sufficient differences exist to prevent confusion. (See Table 4).
- Names with low similarity that have no overlap or similarity in strength and dose are generally acceptable (See Table 5) unless there are data to suggest that the name might be vulnerable to confusion (e.g., prescription simulation study suggests that the name is likely to be misinterpreted as a marketed product). In these instances, we would reassign a low similarity name to the moderate similarity category and review according to the moderately similar name pair checklist.

- c. FDA Prescription Simulation Studies: DMEPA staff also conducts a prescription simulation studies using FDA health care professionals.

Three separate studies are conducted within the Centers of the FDA for the proposed proprietary name to determine the degree of confusion of the proposed proprietary name with marketed U.S. drug names (proprietary and established) due to similarity in visual appearance with handwritten prescriptions or verbal pronunciation of the drug name. The studies employ healthcare professionals (pharmacists, physicians, and nurses), and attempts to simulate the prescription ordering process. The primary Safety Evaluator uses the results to identify orthographic or phonetic vulnerability of the proposed name to be misinterpreted by healthcare practitioners.

In order to evaluate the potential for misinterpretation of the proposed proprietary name in handwriting and verbal communication of the name, inpatient medication orders and/or outpatient prescriptions are written, each consisting of a combination of marketed and unapproved drug products, including the proposed name. These orders are optically scanned and one prescription is delivered to a random sample of participating health professionals via e-mail. In addition, a verbal prescription is recorded on voice mail. The voice mail messages are then sent to a random sample of the participating health professionals for their interpretations and review. After receiving either the written or verbal prescription orders, the participants record their interpretations of the orders which are recorded electronically.

- d. Comments from Other Review Disciplines: DMEPA requests the Office of New Drugs (OND) and/or Office of Generic Drugs (OGD), ONDQA or OBP for their comments or concerns with the proposed proprietary name, ask for any clinical issues that may impact the DMEPA review during the initial phase of the name review. Additionally, when applicable, at the same time DMEPA requests concurrence/non-concurrence with OPDP's decision on the name. The primary Safety Evaluator addresses any comments or concerns in the safety evaluator's assessment.

The OND/OGD Regulatory Division is contacted a second time following our analysis of the proposed proprietary name. At this point, DMEPA conveys their decision to accept or reject the name. The OND or OGD Regulatory Division is requested to provide any further information that might inform DMEPA's final decision on the proposed name.

Additionally, other review disciplines opinions such as ONDQA or OBP may be considered depending on the proposed proprietary name.

When provided, DMEPA considers external proprietary name studies conducted by or for the Applicant/Sponsor and incorporates the findings of these studies into the overall risk assessment.

The DMEPA primary reviewer assigned to evaluate the proposed proprietary name is responsible for considering the collective findings, and provides an overall risk assessment of the proposed proprietary name.

Table 3. Highly Similar Name Pair Checklist (i.e., combined Orthographic and Phonetic score is $\geq 70\%$).

Answer the questions in the checklist below. Affirmative answers to some of these questions suggest that the pattern of orthographic or phonetic differences in the names may render the names less likely to confusion, provided that the pair do not share a common strength or dose.			
<u>Orthographic Checklist</u>		<u>Phonetic Checklist</u>	
Y/N	Do the names begin with different first letters? <i>Note that even when names begin with different first letters, certain letters may be confused with each other when scripted.</i>	Y/N	Do the names have different number of syllables?
Y/N	Are the lengths of the names dissimilar* when scripted? <i>*FDA considers the length of names different if the names differ by two or more letters.</i>	Y/N	Do the names have different syllabic stresses?
Y/N	Considering variations in scripting of some letters (such as z and f), is there a different number or placement of upstroke/downstroke letters present in the names?	Y/N	Do the syllables have different phonologic processes, such vowel reduction, assimilation, or deletion?
Y/N	Is there different number or placement of cross-stroke or dotted letters present in the names?	Y/N	Across a range of dialects, are the names consistently pronounced differently?
Y/N	Do the infixes of the name appear dissimilar when scripted?		

Y/N	Do the suffixes of the names appear dissimilar when scripted?		
-----	---	--	--

Table 4: Moderately Similar Name Pair Checklist (i.e., combined score is $\geq 50\%$ to $\leq 69\%$).

Step 1	Review the DOSAGE AND ADMINISTRATION and HOW SUPPLIED/STORAGE AND HANDLING sections of the prescribing information (or for OTC drugs refer to the Drug Facts label) to determine if strengths and doses of the name pair overlap or are very similar. Different strengths and doses for products whose names are moderately similar may decrease the risk of confusion between the moderately similar name pairs. Name pairs that have overlapping or similar strengths or doses have a higher potential for confusion and should be evaluated further (see Step 2). Because the strength or dose could be used to express an order or prescription for a particular drug product, overlap in one or both of these components would be reason for further evaluation. For single strength products, also consider circumstances where the strength may not be expressed. For any i.e. drug products comprised of more than one active ingredient, consider whether the strength or dose may be expressed using only one of the components. To determine whether the strengths or doses are similar to your proposed product, consider the following list of factors that may increase confusion: ○ Alternative expressions of dose: 5 mL may be listed in the prescribing information, but the dose may be expressed in metric weight (e.g., 500 mg) or in non-metric units (e.g., 1 tsp, 1 tablet/capsule). Similarly, a strength or dose of 1000 mg may be expressed, in practice, as 1 g, or vice versa. ○ Trailing or deleting zeros: 10 mg is similar in appearance to 100 mg which may potentiate confusion between a name pair with moderate similarity. ○ Similar sounding doses: 15 mg is similar in sound to 50 mg
--------	--

Step 2	Answer the questions in the checklist below. Affirmative answers to some of these questions suggest that the pattern of orthographic or phonetic differences in the names may reduce the likelihood of confusion for moderately similar names <u>with</u> overlapping or similar strengths or doses.	
	Orthographic Checklist (Y/N to each question) - Do the names begin with different first letters? Note that even when names begin with different first letters, certain letters may be confused with each other when scripted. - Are the lengths of the names dissimilar* when scripted? *FDA considers the length of names different if the names differ by two or more letters. - Considering variations in scripting of some letters (such as z and f), is there a different number or placement of upstroke/downstroke letters present in the names? - Is there different number or placement of cross-stroke or dotted letters present in the names? - Do the infixes of the name appear dissimilar when scripted? - Do the suffixes of the names appear dissimilar when scripted?	Phonetic Checklist (Y/N to each question) - Do the names have different number of syllables? - Do the names have different syllabic stresses? - Do the syllables have different phonologic processes, such as vowel reduction, assimilation, or deletion? - Across a range of dialects, are the names consistently pronounced differently?

Table 5: Low Similarity Name Pair Checklist (i.e., combined score is $\leq 49\%$).

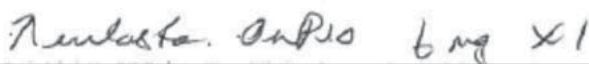
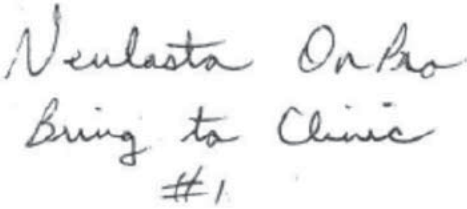
In most circumstances, these names are viewed as sufficiently different to minimize confusion. Exceptions to this would occur in circumstances where, for example, there are data that suggest a name with low similarity is nonetheless misinterpreted as a marketed product name in a prescription simulation study. In such instances, FDA would reassign a low similarity name to the moderate similarity category and review according to the moderately similar name pair checklist.

Appendix A1: Description of FAERS

The FDA Adverse Event Reporting System (FAERS) is a database that contains information on adverse event and medication error reports submitted to FDA. The database is designed to support the FDA's postmarket safety surveillance program for drug and therapeutic biologic products. The informatic structure of the FAERS database adheres to the international safety reporting guidance issued by the International Conference on Harmonisation. FDA's Office of Surveillance and Epidemiology codes adverse events and medication errors to terms in the Medical Dictionary for Regulatory Activities (MedDRA) terminology. Product names are coded using the FAERS Product Dictionary. More information about FAERS can be found at: <http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Surveillance/AdverseDrugEffects/default.htm>.

Appendix B: Prescription Simulation Samples and Results

Figure 1. Neulasta OnPro Study (Conducted on February 20, 2015)

Handwritten Requisition Medication Order	Verbal Prescription
<u>Medication Order:</u> 	Neulasta OnPRO Bring to clinic #1
<u>Outpatient Prescription:</u> 	

FDA Prescription Simulation Responses (Aggregate 1 Rx Studies Report)

251 People Received Study

103 People Responded

Study Name: Neulasta OnPro

Total	37	30	36	
INTERPRETATION	OUTPATIENT	VOICE	INPATIENT	TOTAL
NELASTA ONPRO	1	1	0	2
NENLASTA ONPRO	0	0	1	1
NEUBASTA INPRO	0	0	1	1
NEULAST ON PRO	0	0	1	1
NEULAST ONPRO	0	0	1	1
NEULASTA	4	0	2	6
NEULASTA AMPRO	0	0	1	1
NEULASTA ANPRO	0	0	2	2
NEULASTA ON PRO	13	2	0	15
NEULASTA ONCPRO	0	0	1	1
NEULASTA ONEPRO	0	0	1	1
NEULASTA ONPIO	0	0	3	3
NEULASTA ONPRO	19	11	11	41
NEULASTA QUPRO	0	0	1	1

NEULASTO	0	0	2	2
NEURLASTA PRO	0	1	0	1
NEVLASTA ANPRO	0	0	1	1
NEVLASTA ONPRO	0	0	1	1
NEWLASTA ANPIO	0	0	1	1
NEWLASTA ONPRO	0	3	0	3
NUELAST ONPRO	0	1	0	1
NUELASTA OMPRO	0	1	0	1
NUILASTA	0	0	1	1
NULASTA ON PRO	0	1	0	1
NULASTA ONPRO	0	7	0	7
NULASTA ON-PRO	0	1	0	1
NULASTOUNPRO	0	1	0	1
RHOFADE	0	0	1	1
TEULASTA ONPIO	0	0	1	1
TEVLASTA ON PRO	0	0	1	1
TRULASTA ANPRO	0	0	1	1

Appendix C: Highly Similar Names (e.g., combined POCA score is $\geq 70\%$)

No.	Proposed name: Neulasta OnPro Established name: pegfilgrastim Dosage form: Delivery device and prefilled syringe Strength(s): 6 mg/0.64 mL Usual Dose: 6 mg once per chemotherapy cycle. Do not administer between 14 days before and 24 hours after administration of cytotoxic chemotherapy.	POCA Score (%)	Orthographic and/or phonetic differences in the names sufficient to prevent confusion Other prevention of failure mode expected to minimize the risk of confusion between these two names.
1.	Compro	73	The prefix of this name pair has sufficient orthographic differences. The first syllable of this name pair sounds different.
2.	Empro	73	The prefix of this name pair has sufficient orthographic differences. The first syllable of this name pair sounds different. Furthermore, Empro has been discontinued with no generic equivalent available.
3.	Nupro	70	The suffix of this name pair has sufficient orthographic differences. The second syllable of this name pair sounds different. Also, no information could be found on Nupro after checking both internal and external databases.
4.	Uni-Pro	70	The prefix of this name pair has sufficient orthographic differences. The first syllable of this name pair sounds different.

Appendix D: Moderately Similar Names (e.g., combined POCA score is $\geq 50\%$ to $\leq 69\%$)
with no overlap or numerical similarity in Strength and/or Dose

No.	Name	POCA Score (%)
1.	Clinpro 5000	61
2.	Avapro	55
3.	Cipro	55
4.	Oleptro	54
5.	Lidopro	53
6.	Qinprezo ***	52
7.	Reopro	52
8.	(b) (4)	51
9.	Prempro	51
10.	Benzepro	50
11.	Omtryg	50

Appendix E: Moderately Similar Names (e.g., combined POCA score is $\geq 50\%$ to $\leq 69\%$) with overlap or numerical similarity in Strength and/or Dose

No.	Proposed name: Neulasta OnPro Established name: pegfilgrastim Dosage form: Delivery device and prefilled syringe Strength(s): 6 mg/0.64 mL Usual Dose: 6 mg once per chemotherapy cycle. Do not administer between 14 days before and 24 hours after administration of cytotoxic chemotherapy.	POCA Score (%)	Prevention of Failure Mode In the conditions outlined below, the following combination of factors, are expected to minimize the risk of confusion between these two names
1.	Neupro	68	The prefix of this name pair has sufficient orthographic differences. The first syllable of this name pair sounds different.
2.	Orfro	66	The first syllable of this name pair sounds different. Furthermore, Orfro is dosed every 12 hours.
3.	Onxol	53	The suffix of this name pair has sufficient orthographic differences. The second syllable of this name pair sound different.
4.	Daypro	52	The prefix of this name pair has sufficient orthographic differences. The first syllable of this name pair sounds different.

Appendix F: Low Similarity Names (e.g., combined POCA score is $\leq 49\%$)

No.	Name	POCA Score (%)
1.	Lunesta	30
2.	Lupron	30
3.	OraPred	23
4.	Onglyza	18
5.	Ortho	13

Appendix G: Names not likely to be confused or not used in usual practice settings for the reasons described.

No.	Name	POCA Score (%)	Failure preventions
1.	IB Pro	68	Name found in RxNorm. No product characteristics available in common drug references.
2.	AKpro	64	Discontinued product with no generic equivalent available.
3.	AK-pro	64	Discontinued product with no generic equivalent available.
4.	Dipro	62	Name found in RxNorm. No product characteristics available in common drug references.
5.	Pro 12	59	Name found in RxNorm. No product characteristics available in common drug references.
6.	Bovapro	58	Name found in RxNorm. No product characteristics available in common drug references.

7.	Amprol	56	Name found in RxNorm. No product characteristics available in common drug references.
8.	Amprol 128	56	Name found in RxNorm. No product characteristics available in common drug references.
9.	Onzetra ***	53	Name found in RxNorm. No product characteristics available in common drug references.
10.	Onsior	52	Name found in RxNorm. No product characteristics available in common drug references.
11.	Accupro	51	International product, not marketed in the U.S.

Appendix H: Names not likely to be confused due to notable spelling, orthographic and phonetic differences.

No.	Name	POCA Score (%)
1.	Introl	58
2.	Vontrol	58
3.	Anoro ***	57
4.	Ancrod	56
5.	Encron	56
6.	Inspira	54
7.	Xtoro	54
8.	(b) (4)	52
9.	Antara	50
10.	(b) (4)	50
11.	Enbrel	50
12.	Entre-B	50

13.	Entre-S	50
14.	(b) (4)	50

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

NEIL H VORA
03/13/2015

YELENA L MASLOV
03/13/2015

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

125031Orig1s181

**ADMINISTRATIVE and CORRESPONDENCE
DOCUMENTS**

Sensie, Tinya

From: Sensie, Tinya
Sent: Wednesday, September 02, 2015 11:17 AM
To: 'Yu, Tai'
Subject: BLA 125031/S-170, 179 & 181/Neulasta- Final PI
Attachments: NLS-US-PI-tradename-GN-leuko-spleno-CLS-2015-0901-R.DOCX

Follow Up Flag: Follow up
Flag Status: Flagged

Dear Tai,

We have completed another review of your revised PI and the Agency finds the inclusion of leukocytosis acceptable. Please find enclosed the final PI with all edits accepted and comments deleted.

Please official submit to the BLA all final PI and additional final labeling information by noon, Friday, September 4, 2015.

Thank you,

Tinya

Tinya Sensie, M.H.A.

Regulatory Health Project Manager | DHP | OHOP | CDER | FDA
P: 240-402-4230 | F: 301-796-9849 | e: tinya.sensie@fda.hhs.gov

From: Yu, Tai [<mailto:tyu@amgen.com>]
Sent: Tuesday, September 01, 2015 11:51 AM
To: Sensie, Tinya
Subject: RE: BLA 125031/S-170, 179 & 181/Neulasta- FDA Revised PI #2

Dear Tinya,

Attached please find Amgen's redline version of the PI. Amgen respectfully disagrees with the Agency's recommendation with the removal of leukocytosis. Please see detail comments in the attached.

Please let me know if you have any questions.

Regards,
Tai H. Yu, MS
Regulatory Affairs
AMGEN
One Amgen Center Drive
17-2-A
Thousand Oaks, CA 91320
work: 805.447.2748
mobile: (b) (6)
email: tyu@amgen.com

25 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

TINYA J SENSIE
09/02/2015

From: Sensie, Tinya [<mailto:Tinya.Sensie@fda.hhs.gov>]
Sent: Friday, August 28, 2015 8:27 AM
To: Yu, Tai
Subject: BLA 125031/S-170, 179 & 181/Neulasta- FDA Revised PI #2

Dear Tai,

We have completed another review of the PI, on-body injector PPI and pre-filled syringe PPI submitted as part of BLA 125031/S-179 for Neulasta on July 10, 2015. The Agency finds your changes to the PPIs acceptable.

Please review the changes/comments in the attached draft PI and do the following to the same draft:

- Accept any changes that you agree with
- Edit over the ones that you do not agree with (do not reject any changes that the FDA proposed)

After you have made the changes, please send me the revised track changes version before you make your official submission electronically.

Please provide a response by **noon, Tuesday, September 1, 2015.**

Thank you,

Tinya

Tinya Sensie, M.H.A.

Regulatory Health Project Manager
Division of Hematology Products | Office of Hematology and Oncology Products
Center for Drug Evaluation and Research | U.S. Food and Drug Administration
10903 New Hampshire Ave., WO22, Rm 2379
Silver Spring, MD 20903

P: 240-402-4230 | F: 301-796-9849 | e: tinya.sensie@fda.hhs.gov

12 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

Sensie, Tinya

From: Sensie, Tinya
Sent: Friday, August 28, 2015 11:27 AM
To: Yu, Tai (tyu@amgen.com)
Subject: BLA 125031/S-170, 179 & 181/Neulasta- FDA Revised PI #2
Attachments: NLS-US-PI-tradename-GN-leuko-spleno-CLS-2015-0825-R.DOCX; NLS-US-PPI-OB-
tradename-GN-leuko-spleno-CLS-2015-0825-R.DOC; NLS-US-PPI-PFS-tradename-GN-
leuko-spleno-CLS-2015-0825-R.DOC

Follow Up Flag: Follow up
Flag Status: Flagged

Dear Tai,

We have completed another review of the PI, on-body injector PPI and pre-filled syringe PPI submitted as part of BLA 125031/S-179 for Neulasta on July 10, 2015. The Agency finds your changes to the PPIs acceptable.

Please review the changes/comments in the attached draft PI and do the following to the same draft:

- Accept any changes that you agree with
- Edit over the ones that you do not agree with (do not reject any changes that the FDA proposed)

After you have made the changes, please send me the revised track changes version before you make your official submission electronically.

Please provide a response by **noon, Tuesday, September 1, 2015.**

Thank you,

Tinya

Tinya Sensie, M.H.A.
Regulatory Health Project Manager
Division of Hematology Products | Office of Hematology and Oncology Products
Center for Drug Evaluation and Research | U.S. Food and Drug Administration
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/s/

TINYA J SENSIE
08/28/2015

Sensie, Tinya

From: Sensie, Tinya
Sent: Monday, August 17, 2015 1:50 PM
To: Yu, Tai (tyu@amgen.com)
Subject: BLA 125031/S-170, 179 & 181/Neulasta- FDA Revised Package Insert
Attachments: BLA 125031-170-179-181_PI.docx

Dear Tai,

We have completed a review of the revised Package Insert submitted as part of BLA 125031/S-179 for Neulasta on July 10, 2015.

Please review the changes/comments in the attached draft and do the following to the same draft:

- Accept any changes that you agree with
- Edit over the ones that you do not agree with (do not reject any changes that the FDA proposed)

After you have made the changes, please send me the revised track changes version before you make your official submission electronically.

Please note that FDA finds your last submitted HCP IFU, Patient IFU and PPI acceptable for supplement 179.

Please provide a response by noon, Tuesday, August 24, 2015.

Thank you,

Tinya

Tinya Sensie, M.H.A.

Regulatory Health Project Manager

Division of Hematology Products | Office of Hematology and Oncology Products

Center for Drug Evaluation and Research | U.S. Food and Drug Administration

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/s/

TINYA J SENSIE
08/17/2015

Sensie, Tinya

From: Sensie, Tinya
Sent: Friday, June 12, 2015 8:33 AM
To: 'Chi, Telly'
Subject: RE: BLA 125031/S-179 & 181/Neulasta- Labeling Information Request

Follow Up Flag: Follow up
Flag Status: Flagged

Hi Telly,

I meant Tuesday, July 7th. Sorry for any confusion.

Best,

Tinya

Tinya Sensie, M.H.A.

Regulatory Health Project Manager | DHP | OHOP | CDER | FDA
P: 240-402-4230 | F: 301-796-9849 | e: tinya.sensie@fda.hhs.gov

From: Chi, Telly [<mailto:tchi@amgen.com>]
Sent: Thursday, June 11, 2015 4:48 PM
To: Sensie, Tinya
Subject: RE: BLA 125031/S-179 & 181/Neulasta- Labeling Information Request

Hi Tinya,

In regards to the due date of the information request, do you mean Friday, **July 10th**? Can you please confirm?

Thanks and look forward in hearing back from you,

Telly

Telly Chi, PharmD, MS, RAC
Director, Global Regulatory Affairs
Hematology and Oncology Therapeutics

Amgen Inc.
Direct: (805) 313-4451
Mobile: (b) (6)
Email: tchi@amgen.com

From: Sensie, Tinya [<mailto:Tinya.Sensie@fda.hhs.gov>]
Sent: Thursday, June 11, 2015 8:03 AM
To: Chi, Telly
Cc: Chow, Janet
Subject: BLA 125031/S-179 & 181/Neulasta- Labeling Information Request
Importance: High

Good Morning,

Reference is made to BLA 125031/S-179 & 181 submitted on February 5, 2015, where you provided updates to the Neulasta labeling with information regarding glomerulonephritis and proposed proprietary name "Neulasta OnPRO™" for the Neulasta Delivery Kit. Please respond to this information request by **Friday, July 7, 2015 at 1:30 PM** (for time, please respond by email, in addition to officially submitting your response to the BLA).

RECOMMENDATION FOR THE APPLICANT:

1. Carton Labeling

- a. The modifier "OnPRO" for Neulasta is presented with the letters 'PRO' capitalized. This mixed case type of presentation is typically reserved for differentiating known look-alike and sound-alike established name pairs or in rare circumstances for proprietary names to help reduce the risk of wrong drug name errors. Since Onpro is not a name that has been involved in drug name confusion or wrong drug errors, the capitalization of the letter "PRO" is inappropriately applied. The entire proprietary name "Neulasta Onpro" should appear together without any intervening matter and with equal prominence. Currently, the root name "Neulasta" is more prominent and separated from the modifier "Onpro" by an illustration of a person in a circle.

Kindly confirm receipt of this message.

Thanks,

Tinya

Tinya Sensie, M.H.A.

Regulatory Health Project Manager

Division of Hematology Products | Office of Hematology and Oncology Products

Center for Drug Evaluation and Research | U.S. Food and Drug Administration

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/s/

TINYA J SENSIE
06/12/2015

Sensie, Tinya

From: Sensie, Tinya
Sent: Thursday, June 11, 2015 11:03 AM
To: Chi, Telly (tchi@amgen.com)
Cc: Chow, Janet (jchow@amgen.com)
Subject: BLA 125031/S-179 & 181/Neulasta- Labeling Information Request

Follow Up Flag: Follow up
Flag Status: Flagged

Good Morning,

Reference is made to BLA 125031/S-179 & 181 submitted on February 5, 2015, where you provided updates to the Neulasta labeling with information regarding glomerulonephritis and proposed proprietary name "Neulasta OnPRO™" for the Neulasta Delivery Kit. Please respond to this information request by **Friday, July 7, 2015 at 1:30 PM** (for time, please respond by email, in addition to officially submitting your response to the BLA).

RECOMMENDATION FOR THE APPLICANT:

1. Carton Labeling
 - a. The modifier "OnPRO" for Neulasta is presented with the letters 'PRO' capitalized. This mixed case type of presentation is typically reserved for differentiating known look-alike and sound-alike established name pairs or in rare circumstances for proprietary names to help reduce the risk of wrong drug name errors. Since Onpro is not a name that has been involved in drug name confusion or wrong drug errors, the capitalization of the letter "PRO" is inappropriately applied. The entire proprietary name "Neulasta Onpro" should appear together without any intervening matter and with equal prominence. Currently, the root name "Neulasta" is more prominent and separated from the modifier "Onpro" by an illustration of a person in a circle.

Kindly confirm receipt of this message.

Thanks,

Tinya

Tinya Sensie, M.H.A.

Regulatory Health Project Manager

Division of Hematology Products | Office of Hematology and Oncology Products

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/s/

TINYA J SENSIE
06/11/2015



DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Silver Spring, MD 20993

BLA 125031/S-181

**PROPRIETARY NAME REQUEST
CONDITIONALLY ACCEPTABLE**

Amgen Inc.
One Amgen Center Drive
Mail Stop: 17-2-A
Thousand Oaks, CA 91320-1799

ATTENTION: Janet Chow, PhD, RAC
Manager, Regulatory Affairs

Dear Dr. Chow:

Please refer to your Supplemental Biologics License Application (sBLA) dated and received February 5, 2015, submitted under section 351(a) of the Public Health Service Act for Pegfilgrastim, 6 mg/0.64 mL.

We also refer to your correspondence, dated and received February 5, 2015, requesting review of your proposed proprietary name, Neulasta OnPro.

We have completed our review of the proposed proprietary name, Neulasta OnPro and have concluded that it is conditionally acceptable.

If any of the proposed product characteristics as stated in your February 5, 2015, submission are altered prior to approval of the marketing application, the proprietary name should be resubmitted for review.

If you require information on submitting requests for proprietary name review or PDUFA performance goals associated with proprietary name reviews, we refer you to the following:

- Guidance for Industry Contents of a Complete Submission for the Evaluation of Proprietary Names
(<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM075068.pdf>)
- PDUFA Reauthorization Performance Goals and Procedures Fiscal Years 2013 through 2017,
(<http://www.fda.gov/downloads/ForIndustry/UserFees/PrescriptionDrugUserFee/UCM270412.pdf>)

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, contact Sarah Harris, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (240) 402-4774. For any other information regarding this application, contact Tinya Sensie, Regulatory Project Manager in the Office of New Drugs, at (240) 402-4230.

Sincerely,

{See appended electronic signature page}

Todd Bridges, RPh
Deputy Director
Division of Medication Error Prevention and Analysis
Office of Medication Error Prevention and Risk Management
Office of Surveillance and Epidemiology
Center for Drug Evaluation and Research

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/s/

TODD D BRIDGES
03/16/2015