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, Potential Device Failures (5.10) 12/2017

----------INDICATIONS AND USAGE----------
Neulasta is a leukocyte growth factor indicated to
- Decrease the incidence of infection, as manifested by febrile neutropenia, in patients with non-myeloid malignancies receiving myelosuppressive anti-cancer drugs associated with a clinically significant incidence of febrile neutropenia. (1.1)
- Increase survival in patients acutely exposed to myelosuppressive doses of radiation (Hematopoietic Subsyndrome of Acute Radiation Syndrome). (1.2)

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

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

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

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

----------WARNINGS AND PRECAUTIONS----------
- Fatal splenic rupture: Evaluate patients who report left upper abdominal or shoulder pain for an enlarged spleen or splenic rupture. (5.1)
- Acute respiratory distress syndrome (ARDS): Evaluate patients who develop fever, lung infiltrates, or respiratory distress. Discontinue Neulasta in patients with ARDS. (5.2)
- Serious allergic reactions, including anaphylaxis: Permanently discontinue Neulasta in patients with serious allergic reactions. (5.3)
- The on-body injector for Neulasta uses acrylic adhesive. For patients who have reactions to acrylic adhesives, use of this product may result in a significant reaction. (5.4)
- Fatal sickle cell crises: Have occurred. (5.5)
- Glomerulonephritis: Evaluate and consider dose-reduction or interruption of Neulasta if causality is likely. (5.6)
- Potential device failures: Instruct patients to notify their healthcare provider if they suspect the on-body injector may not have performed as intended. (5.10)

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

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

----------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: 12/2017

FULL PRESCRIBING INFORMATION: CONTENTS*

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

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

1.1 Patients with Cancer Receiving Myelosuppressive Chemotherapy

Neulasta is indicated to decrease the incidence of infection, as manifested by febrile neutropenia, in patients with non-myeloid malignancies receiving myelosuppressive anti-cancer drugs associated with a clinically significant incidence of febrile neutropenia *[see Clinical Studies (14.1)]*.

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

1.2 Patients with Hematopoietic Subsyndrome of Acute Radiation Syndrome

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

2 DOSAGE AND ADMINISTRATION

2.1 Patients with Cancer Receiving Myelosuppressive Chemotherapy

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

2.2 Patients with Hematopoietic Subsyndrome of Acute Radiation Syndrome

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

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

2.3 Administration

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

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

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.

Pediatric Patients weighing less than 45 kg

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

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

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

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

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

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

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

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

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

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

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

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

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

Refer the patient to the dose delivery information written on the Patient Instructions for Use. Provide training to patients to ensure they understand when the dose delivery of Neulasta will begin and how to monitor the OBI for Neulasta for completed delivery. Ensure patients understand how to identify signs of malfunction of OBI for Neulasta *[see Warnings and Precautions (5.3) and Patient Counseling Information (17)]*. Instruct patients using the OBI to notify their healthcare professional immediately in order to determine the need for a replacement dose of Neulasta if they suspect that the device may not have performed as intended *[see Warnings and Precautions (5.10)]*.

3 DOSAGE FORMS AND STRENGTHS

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

4 CONTRAINDICATIONS

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

5 WARNINGS AND PRECAUTIONS

5.1 Splenic Rupture

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

5.2 Acute Respiratory Distress Syndrome

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

5.3 Serious Allergic Reactions

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

5.4 Allergies to Acrylics

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

5.5 Use in Patients with Sickle Cell Disorders

Severe 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 x 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.

5.10 Potential Device Failures

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

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 2 are from a randomized, double-blind, placebo-controlled study in patients with metastatic or non-metastatic breast cancer receiving docetaxel 100 mg/m^2 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 2. Adverse Reactions with ≥ 5% Higher Incidence in Neulasta Patients Compared to Placebo in Study 3

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

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

6.2 Immunogenicity

As with all therapeutic proteins, there is a potential for immunogenicity. The detection of antibody formation is highly dependent on the sensitivity and specificity of the assay, 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.

Binding antibodies to pegfilgrastim were detected using a BIAcore assay. The approximate limit of detection for this assay is 500 ng/mL. Pre-existing binding antibodies were detected in approximately 6% (51/849) of patients

with metastatic breast cancer. Four of 521 pegfilgrastim-treated subjects who were negative at baseline developed binding antibodies to pegfilgrastim following treatment. None of these 4 patients had evidence of neutralizing antibodies detected using a cell-based bioassay.

6.3 Postmarketing Experience

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

- Splenic rupture and splenomegaly (enlarged spleen) *[see Warnings and Precautions (5.1)]*
- Acute respiratory distress syndrome (ARDS) *[see Warnings and Precautions (5.2)]*
- Allergic reactions/hypersensitivity, including anaphylaxis, skin rash, urticaria, generalized erythema, and flushing *[see Warnings and Precautions (5.3)]*
- Sickle cell crisis *[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)]*
- Injection site reactions
- Sweet's syndrome (acute febrile neutrophilic dermatosis), 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 embryolethality 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

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

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

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

8.5 Geriatric Use

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

8.6 Renal Impairment

Renal dysfunction had no effect on the pharmacokinetics of pegfilgrastim. Therefore, pegfilgrastim dose adjustment in patients with renal dysfunction is not necessary *[see Clinical Pharmacology (12.3)]*.

10 OVERDOSAGE

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

11 DESCRIPTION

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 is provided in two presentations:

- Neulasta for manual subcutaneous injection is supplied in 0.6 mL prefilled syringes. The prefilled syringe does not bear graduation marks and is designed to deliver the entire contents of the syringe (6 mg/0.6 mL).
- On-body injector (OBI) for Neulasta is supplied with a prefilled syringe containing 0.64 mL of Neulasta in solution that delivers 0.6 mL of Neulasta in solution when used with the OBI for Neulasta. The syringe does not bear graduation marks and is only to be used with the OBI for Neulasta.

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

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

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

12.2 Pharmacodynamics

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

12.3 Pharmacokinetics

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

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

Renal Impairment
In a study of 30 subjects with varying degrees of renal dysfunction, including end stage renal disease, renal dysfunction had no effect on the pharmacokinetics of pegfilgrastim *[see Use in Specific Populations (8.6)]*.

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

Patients Acutely Exposed to Myelosuppressive Doses of Radiation
The pharmacokinetics of pegfilgrastim is not available in patients acutely exposed to myelosuppressive doses of radiation. Based on limited pharmacokinetic data in irradiated non-human primates, the area under the concentration-time curve (AUC), reflecting the exposure to pegfilgrastim in non-human primates following a 300 mcg/kg dose of Neulasta, appears to be greater than in humans receiving a 6 mg dose. Results from population modeling and simulation indicate that two 6 mg doses of Neulasta administered one week apart in adults result in

clinically relevant effects on duration of grade 3 and 4 neutropenia. In addition, weight based dosing in pediatric patients weighing less than 45 kg *[see Dosage and Administration, Section 2.3, Table 1]* provides exposures comparable to those in adults receiving two 6 mg doses one week apart.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

No carcinogenicity or mutagenesis studies have been performed with pegfilgrastim.

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

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

14.1 Patients with Cancer Receiving Myelosuppressive Chemotherapy

Neulasta was evaluated in three randomized, double-blind, controlled studies. Studies 1 and 2 were active-controlled studies that employed doxorubicin 60 mg/m^2 and docetaxel 75 mg/m^2 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 10^9/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/m^2 administered every 21 days for up to 4 cycles for the treatment of metastatic or non-metastatic breast cancer. In this study, 928 patients were randomized to receive a single subcutaneous injection of Neulasta (6 mg) or placebo on day 2 of each chemotherapy cycle. Study 3 met the major trial outcome measure of demonstrating that the incidence of febrile neutropenia (defined as temperature $\geq$ 38.2°C and ANC $\leq$ 0.5 x 10^9/L) was lower for Neulasta-treated patients as compared to placebo-treated patients (1% versus 17%, respectively, $p < 0.001$). The incidence of hospitalizations (1% versus 14%) and IV anti-infective use (2% versus 10%) for the treatment of febrile neutropenia was also lower in the Neulasta-treated patients compared to the placebo-treated patients.

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

14.2 Patients with Hematopoietic Subsyndrome of Acute Radiation Syndrome

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

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

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

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

16 HOW SUPPLIED/STORAGE AND HANDLING

Neulasta single-dose prefilled syringe for manual use

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

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

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

Neulasta prefilled syringe does not bear graduation marks and is intended only to deliver the entire contents of the syringe (6 mg/0.6 mL) for direct administration. Use of the prefilled syringe is not recommended for direct administration for pediatric patients weighing less than 45 kg who require doses that are less than the full contents of the syringe.

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

Neulasta Onpro® kit

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

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

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

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

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

17 PATIENT COUNSELING INFORMATION

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

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

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

- Glomerulonephritis
- Capillary Leak Syndrome

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

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

- Importance of following the Instructions for Use.
- Dangers of reusing syringes.
- Importance of following local requirements for proper disposal of used syringes.

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

- Review the Patient Information and Patient Instructions for Use with the patient and provide the instructions to the patient.
- Refer the patient to the dose delivery information written on the Patient Instructions for Use.
- Tell the patient when their dose delivery of Neulasta will begin and when their dose delivery should be completed.
- Advise the patient that serious allergic reactions can happen with Neulasta. Patients should have a caregiver nearby for the first use. Patients should plan to be in a place where they can appropriately monitor the OBI for Neulasta during the approximately 45 minute Neulasta delivery and for an hour after the delivery. Advise the patient to avoid traveling, driving, or operating heavy machinery during hours 26-29 following application of the OBI for Neulasta.
- If the OBI for Neulasta is placed on the back of the arm, remind the patient that a caregiver must be available to monitor the OBI for Neulasta.
- If a patient calls the healthcare provider regarding any OBI for Neulasta problems, the healthcare provider is advised to call Amgen at 1-800-772-6436.
- Advise the patient:
    - to call their healthcare provider immediately if the status light on the OBI for Neulasta is flashing red (see the Patient Instructions for Use).
    - to inform their healthcare provider if the adhesive on the OBI for Neulasta becomes saturated with fluid, or there is dripping, as this may be evidence of significant product leakage, resulting in inadequate or missed dose (see the Patient Instructions for Use).
    - to keep the OBI for Neulasta dry for approximately the last 3 hours prior to the dose delivery start to better enable potential leak detection.
    - that the OBI for Neulasta should only be exposed to temperatures between 41°F and 104°F (5°C-40°C).
    - to keep the OBI for Neulasta at least 4 inches away from electrical equipment such as cell phones, cordless telephones, microwaves, and other common appliances. Failure to keep the OBI for Neulasta at least this recommended distance may interfere with operation and can lead to a missed or incomplete dose of Neulasta.
    - that if the needle is exposed after OBI for Neulasta removal, place the used OBI for Neulasta in a sharps disposal container to avoid accidental needle stick and call their healthcare provider immediately.

- to remove the OBI for Neulasta after the green light shines continuously and to place the used OBI for Neulasta in a sharps disposal container (see the Patient Instructions for Use).

- Advise the patient:
  - do not reapply the OBI for Neulasta if the OBI for Neulasta comes off before full dose is delivered and instead call their healthcare provider immediately.
  - avoid bumping the OBI for Neulasta or knocking the OBI for Neulasta off the body.
  - do not expose the OBI 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 OBI for Neulasta damage and patient injury.
- Advise the patient to avoid:
  - airport X-ray scans and request a manual pat down instead; remind patients who elect to request a manual pat down to exercise care to avoid having the OBI for Neulasta dislodged during the pat down process.
  - sleeping on the OBI for Neulasta or applying pressure on the OBI for Neulasta as this may affect OBI for Neulasta performance.
  - getting body lotions, creams, oils, and cleaning agents near the OBI for Neulasta as these products may loosen the adhesive.
  - using hot tubs, whirlpools, or saunas and avoid exposing the OBI for Neulasta to direct sunlight as these may affect the drug.
  - peeling off or disturbing the OBI for Neulasta adhesive before delivery of full dose is complete.

AMGEN®

Neulasta® (pegfilgrastim)

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

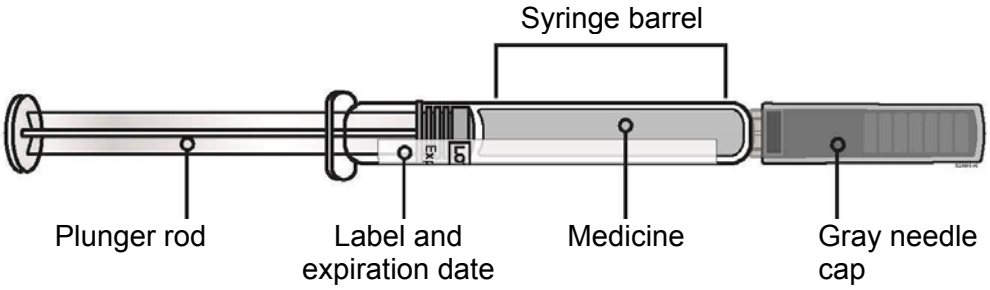
Patent: http://pat.amgen.com/onpro/

www.neulasta.com
1-800-77-AMGEN (1-800-772-6436)
v8

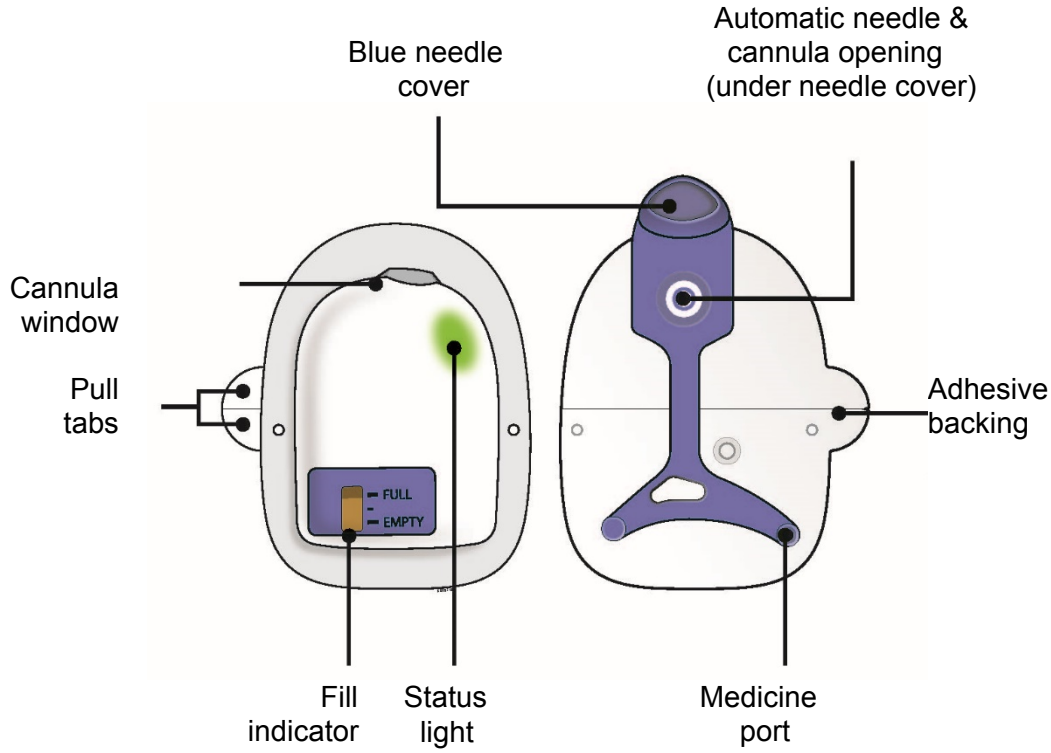
Neulasta® (pegfilgrastim) Onpro® kit
Healthcare Provider Instructions for Use

Guide to Parts

Neulasta Prefilled Syringe



On-body Injector for Neulasta



Important

READ THE FOLLOWING INSTRUCTIONS BEFORE USING NEULASTA ONPRO KIT

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

- See Prescribing Information for information on Neulasta.
- The On-body Injector is for adult patients only.
- The On-body Injector is not recommended for patients with Hematopoietic Subsyndrome of Acute Radiation Syndrome.
- 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 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.
- **Do not** shake the prefilled syringe.
- **Do not** separate the components of Neulasta Onpro kit until ready for use.
- **Do not** modify the On-body Injector.
- **Do not** warm Neulasta Onpro kit components using a heat source.
- **Do not** use Neulasta Onpro kit if expiry date on the carton or any of Neulasta Onpro kit components has passed.
- **Do not** use if the name Neulasta does not appear on Neulasta Onpro kit carton.
- **Do not** attempt to reapply On-body Injector.
- **Do not** 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.

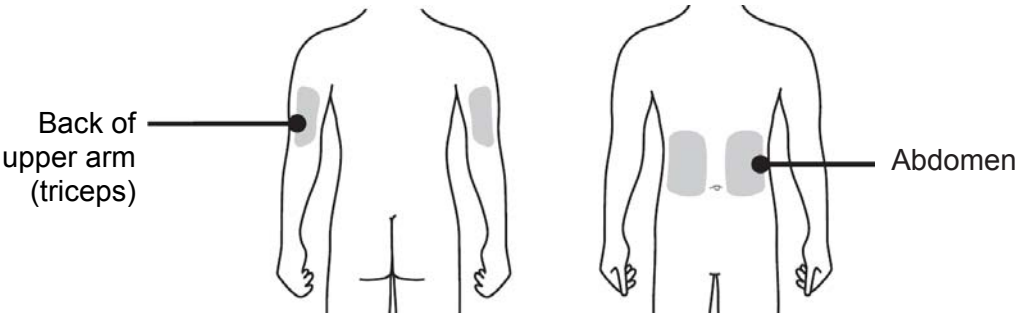
Step 1: Prepare

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

- One Neulasta prefilled syringe
- One On-body Injector for Neulasta
- Neulasta Patient Information
- Neulasta Prescribing Information
- Instructions for use for healthcare provider
- Instructions for use for patient
- Reference Guide

Do not use the On-body Injector if its packaging has been previously opened.

B **Choose the patient's injection site.**



Choose the flattest site for the On-body Injector application.

Consult with the patient regarding their ability to remove and monitor the entire On-body Injector.

- You can use the left or right side of the abdomen, except for a two-inch area right around navel.
- You can use the back of upper arm only if there is a caregiver available to monitor the status of the On-body Injector.
- **Do not** apply the On-body Injector on areas with scar tissue, moles, or excessive hair. In case of excessive hair, carefully trim hair to get the On-body Injector close to the skin.
- **Do not** apply the On-body Injector on areas where belts, waistbands, or tight clothing may rub against, disturb, or dislodge the On-body Injector.
- **Do not** apply the On-body Injector on surgical sites.
- **Do not** apply the On-body Injector on areas where the On-body Injector will be affected by folds in the 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 the On-body Injector to the patient, locate the medicine port on the 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 three minutes to:

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

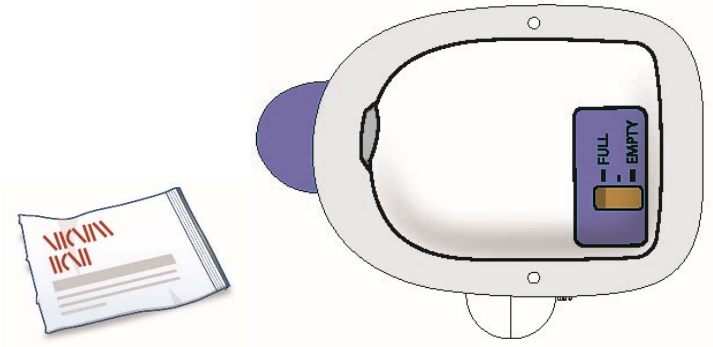
The On-body Injector will deploy the cannula in three minutes, even if not applied to the patient. If not on patient's body in three minutes, do not use the On-body Injector. Start again with a new Neulasta Onpro kit.

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

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

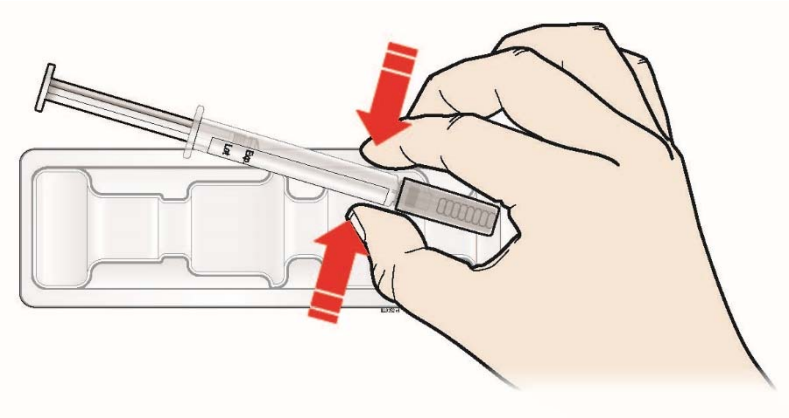
Choose an area larger than the adhesive backing, and clean it with an alcohol swab.

- Thoroughly clean the application site as this will help the On-body Injector adhere to the skin.
- **Do not** use any cleaner other than alcohol, especially those containing lotions or aloe.
- Allow the skin to completely dry.
- **Do not** touch this area again before attaching the On-body Injector.



Step 2: Get Ready

A Remove Neulasta prefilled syringe from tray.

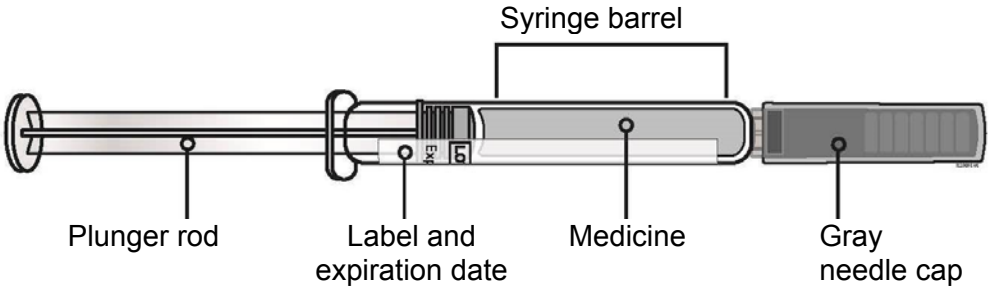


Grab Here

For safety reasons:

- **Do not** grasp the gray needle cap.
- **Do not** remove the gray needle cap until ready to fill the On-body Injector.
- **Do not** grasp the plunger rod.

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

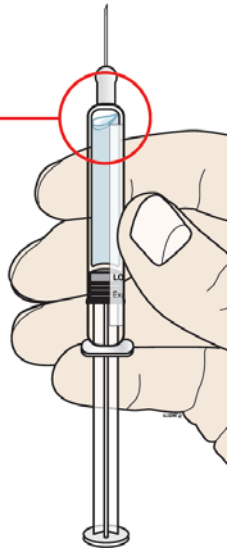


- **Do not** use if the liquid contains particulate matter or discoloration is observed prior to administration.
- **Do not** use if any part appears cracked or broken.
- **Do not** use if the gray needle cap is missing or not securely attached.
- **Do not** use if the expiration date printed on the label has passed.
- **Do not** remove the gray needle cap until ready to fill the On-body Injector.

In all the above cases, start again with a new kit. Call Amgen at 1-800-772-6436.

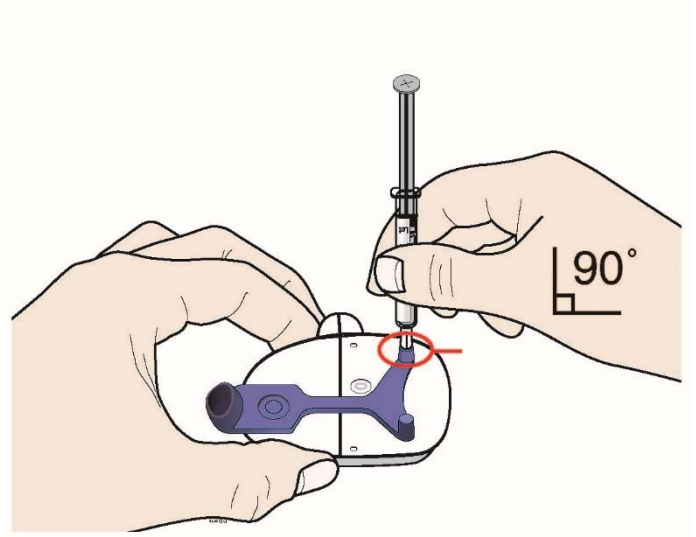
Neulasta prefilled syringe gray needle cap contains dry natural rubber, which is derived from latex.

C Remove air bubbles in syringe without expelling medicine.



- Carefully remove the gray needle cap straight out and away from your body.
- Gently tap the syringe with your finger until air bubbles rise to the top.
- Slowly push air out of the syringe, taking care to expel air only, not medicine.
- A small droplet at the tip of the needle during air purging is normal.
- **Do not** recap the syringe.

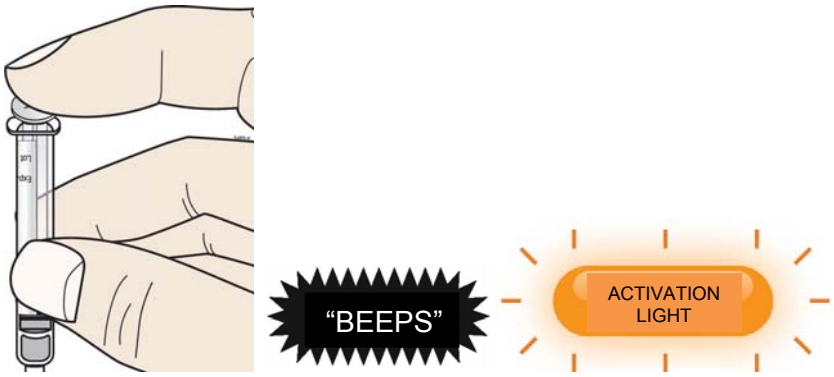
D Center the needle directly over the medicine port at a 90 degree angle. Insert all the way into the port, avoiding sides.



Insert needle into medicine port at a 90 degree angle only.

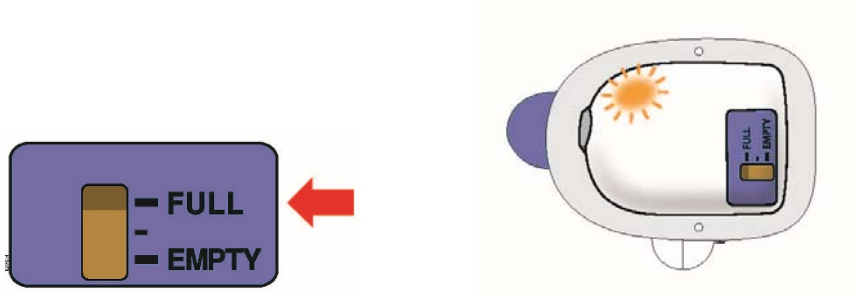
- **Do not** insert the needle more than once.
- **Do not** bend the needle. Avoid spilling the medicine.
- **Do not** remove the blue needle cover before filling the On-body Injector.

E Push the plunger rod to empty entire syringe contents. During filling, you will hear beeping. The status light will flash amber, indicating you now have three minutes to apply the On-body Injector to the patient.



Discard used syringe in sharps container.

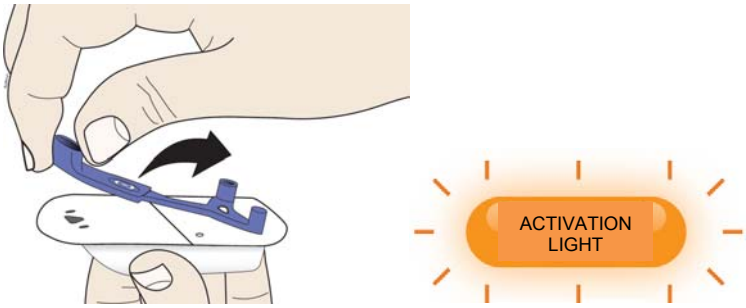
F Check to see if the On-body Injector is full and the amber light is flashing.



You should see the amber status light flashing and a 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.

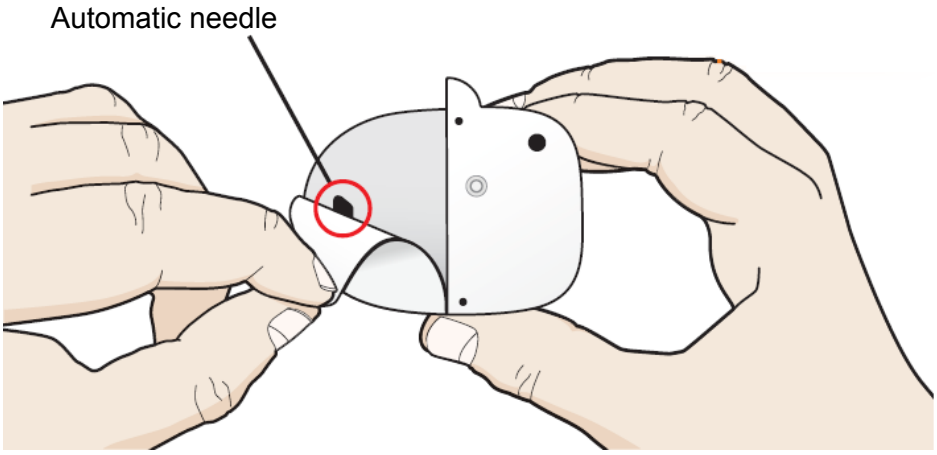
G Firmly lift and remove the blue needle cover away from the On-body Injector.



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

Step 3: Apply

A **Peel away both pull tabs to show the adhesive. Never touch hands or gloves to the adhesive.**



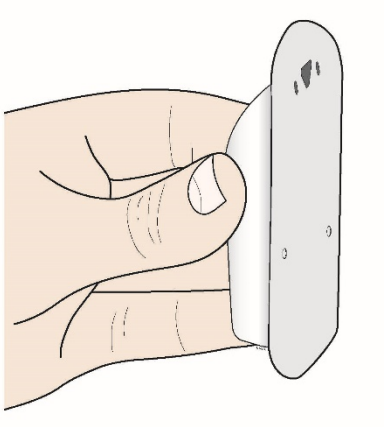
- **Do not** touch or contaminate the automatic needle area.
- **Do not** pull off the adhesive pad or fold it.
- **Do not** use if the needle or cannula is extended past the adhesive or is extended before the On-body Injector is placed on the patient.
- **Do not place adhesive on skin that is damp.**

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

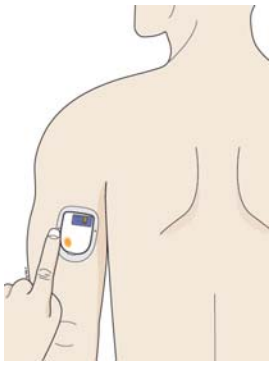
B Before the cannula deploys, securely apply the On-body Injector so it is visible and can be monitored by the patient or caregiver.

You now have time to carefully apply the On-body Injector without folding or wrinkling the adhesive.

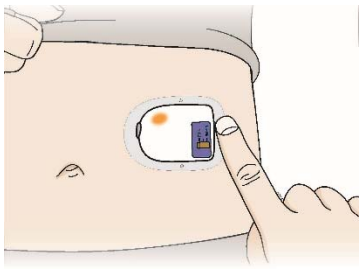
- **Do not** touch the adhesive. Grasp the On-body Injector's plastic case with your fingertips and only by sides, keeping fingers off of the adhesive.
- **Do not** let the adhesive bend or curl while applying the On-body Injector to skin.
- Once on the skin, gently pat around the entire adhesive so it lies down without folds or wrinkles.
- Then, gently hold the top of the On-body Injector and run finger around the adhesive to create a secure attachment.



Back of upper arm (triceps)
Vertical with the light facing down toward the elbow

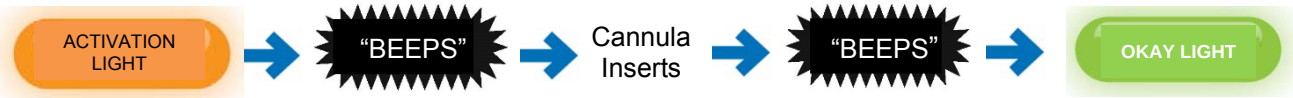


Abdomen
Horizontal with the light facing up and visible to the patient



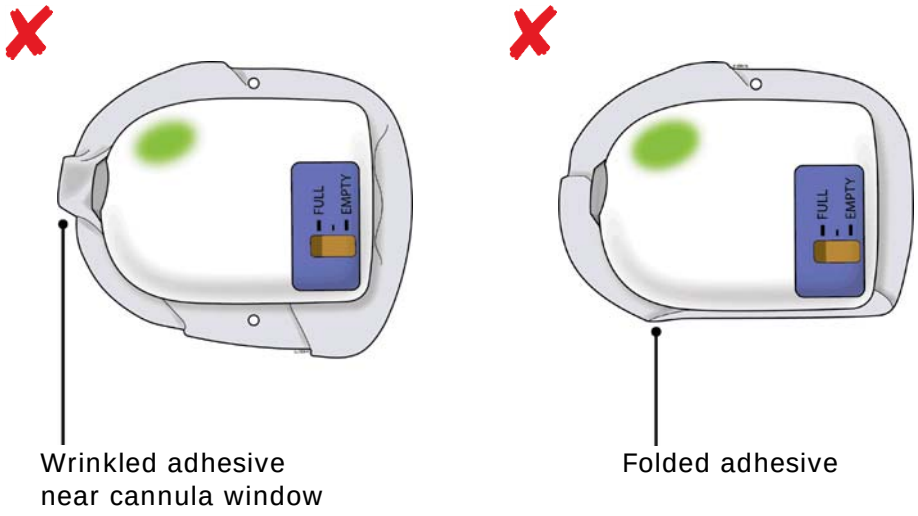
Do not worry if the On-body Injector is quiet. When three minutes are up, the On-body Injector will beep telling you the cannula is about to insert.

C **Wait for the status light to turn green. This means the cannula has been inserted.**
Do not remove the On-body Injector during cannula insertion to avoid needle stick injury to you or to the patient.



Check the quality of adhesion before sending the patient home.

If the adhesive is wrinkled in front of the cannula window or has folds anywhere that prevent the On-body Injector from securely adhering, remove the On-body Injector. Start again with a new 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.

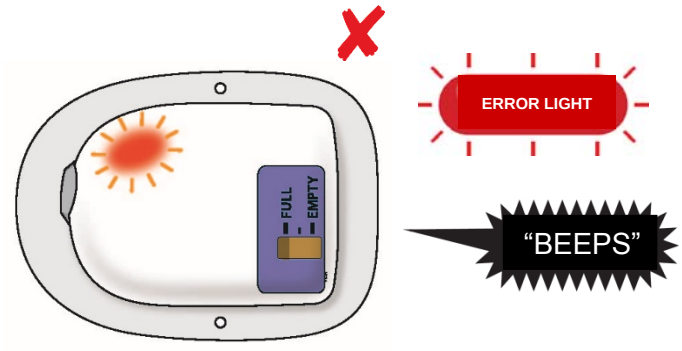
Review each step in the patient instructions with the patient. Give the patient the instructions for use, reference guide, patient information and prescribing information to take home.

Before the patient goes home, make sure the 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 two 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 four 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.

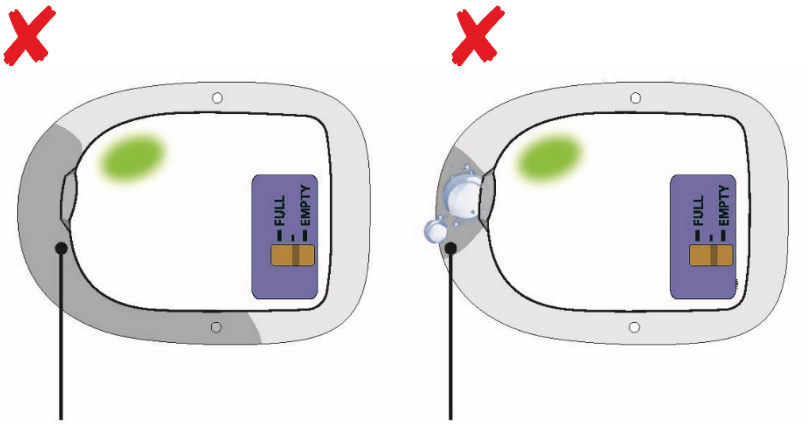


If at any time the On-body Injector beeps continuously for five minutes, and the status light is flashing red, take the On-body Injector off of the patient.

- **Do not** apply the On-body Injector to the patient if red error light is on.
- **Do not** leave the On-body Injector on the 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.



Saturated adhesive Dripping fluid from On-body Injector

If the 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
US License No. 1080

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

www.neulasta.com 1-844-MYNEULASTA (1-844-696-3852)
Issued: 12/2016
v7

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.
	Refer to Instructions for Use
	Do not use if packaging is damaged.
	Temperature Limitation
	Humidity Limitation
	Expiration Date (use by date)
REF	Reference/model number
LOT	Lot Number
	Type BF medical device (protection from electrical shock)
STERILE EO	Sterilized by ethylene oxide
IPX8	Waterproof up to 8 feet for 1 hour
℞ Only	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	±6 kV Contact ±8 kV Air	6 kV Contact ±8 kV 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	3 A/m	3 A/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)=3 V/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)(√P)150 kHz to 80 MHz D=(3.5/E1)(√P)80 to 800 MHz D=(7/E1)(√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 MHz 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