

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

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

6 mg per 0.6 mL in single use prefilled syringe. (3)

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 can occur. Evaluate for splenomegaly or splenic rupture in patients with left upper abdominal or shoulder pain. (5.1)

- Acute respiratory distress syndrome (ARDS) can occur. Evaluate for ARDS in patients who develop fever, lung infiltrates, or respiratory distress. Discontinue Neulasta in patients with ARDS. (5.2)
- Serious allergic reactions, including anaphylaxis, can occur. Permanently discontinue Neulasta in patients with serious allergic reactions. (5.3)
- Severe and sometimes fatal sickle cell crises can occur. (5.4)

ADVERSE REACTIONS

Most common adverse reactions (≥ 5% difference in incidence) in placebo controlled clinical trials are bone pain and pain in extremity. (6)

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. Physicians are encouraged to enroll pregnant patients in Amgen’s Pregnancy Surveillance Program by calling 1-800-772-6436 (1-800-77-AMGEN). (8.1)
- Nursing Mothers: Caution should be exercised when administered to a nursing woman. (8.3)
- Pediatric Use: The safety and effectiveness of Neulasta have not been established. (8.4)
- Geriatric Use: No overall differences in safety or effectiveness were observed in patients age 65 and older. (8.5)
- Renal Impairment: No dose adjustment required. (8.6)

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

Revised: 02/2010

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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

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.

Visually inspect parenteral drug products for particulate matter and discoloration prior to administration, whenever solution and container permit. Do not administer Neulasta if discoloration or particulates are observed.

NOTE: The needle cover on the single-use prefilled syringe contains dry natural rubber (latex); persons with latex allergies should not administer this product.

3 DOSAGE FORMS AND STRENGTHS

6 mg per 0.6 mL in single use prefilled syringe.

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 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.

5.5 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)*]
- Use in Patients with Sickle Cell Disorders [*See Warnings and Precautions (5.4)*]
- Potential for Tumor Growth Stimulatory Effects on Malignant Cells [*See Warnings and Precautions (5.5)*]

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

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.

Bone pain and pain in extremity occurred at a higher incidence in Neulasta-treated patients as compared with placebo-treated patients.

Table 1. Adverse Reactions With $\geq 5\%$ 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 $> 100 \times 10^9/L$) was observed in less than 1% of 932 patients with non-myeloid malignancies receiving Neulasta. No complications attributable to leukocytosis were reported in clinical studies.

6.2 Immunogenicity

As with all therapeutic proteins, there is a potential for immunogenicity. 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 [see Warnings and Precautions (5.1)]

Blood and lymphatic system disorder: Sickle cell crisis [see Warnings and Precautions (5.4)]

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

General disorders and administration site conditions: Injection site reactions

Skin and subcutaneous tissue disorders: Allergic reactions/hypersensitivity, including anaphylaxis, skin rash, and urticaria, Sweet's syndrome, generalized erythema and flushing [see Warnings and Precautions (5.3)]

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)*].

Women who become pregnant during Neulasta treatment are encouraged to enroll in Amgen's Pregnancy Surveillance Program. Patients or their physicians should call 1-800-77-AMGEN (1-800-772-6436) to enroll.

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-inf}) 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 is supplied in 0.6 mL prefilled syringes for subcutaneous injection. Each syringe 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.

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

16 HOW SUPPLIED/STORAGE AND HANDLING

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

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

Neulasta is provided in a dispensing pack containing one syringe (NDC 55513-190-01).

Store refrigerated between 2° to 8°C (36° to 46°F) 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.

17 PATIENT COUNSELING INFORMATION

Advise patients of the following risks:

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

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



Neulasta® (pegfilgrastim)

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This product, its production, and/or its use may be covered by one or more US Patents, including US Patent Nos. 5,824,784; 5,582,823; 5,580,755, as well as other patents or patents pending.

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v 11.0