

## [Neulasta®] (pegfilgrastim)

### 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 *Escherichia 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), sorbitol (30.0 mg), polysorbate 20 (0.02 mg), and sodium (0.02 mg) in water for injection, USP.

### CLINICAL PHARMACOLOGY

Both Filgrastim and pegfilgrastim are Colony Stimulating Factors that act on hematopoietic cells by binding to specific cell surface receptors thereby stimulating proliferation, differentiation, commitment, and end cell functional activation.<sup>1,2</sup> Studies on cellular proliferation, receptor binding, and neutrophil function demonstrate that Filgrastim and pegfilgrastim have the same mechanism of action. Pegfilgrastim has reduced renal clearance and prolonged persistence in vivo as compared to Filgrastim.

### Pharmacokinetics

The pharmacokinetics and pharmacodynamics of Neulasta® were studied in 379 patients with cancer. The pharmacokinetics of Neulasta® were nonlinear in cancer patients and clearance decreased with increases in dose. Neutrophil receptor binding is an important component of the clearance of Neulasta®, and serum clearance is directly related to the number of neutrophils. For example, the concentration of Neulasta® declined rapidly at the onset of neutrophil recovery that followed myelosuppressive chemotherapy. In addition to numbers of neutrophils, body weight appeared to be a factor. Patients with higher body weights experienced higher systemic exposure to Neulasta® after receiving a dose normalized for body weight. A large variability in the pharmacokinetics of Neulasta® was observed in cancer patients. The half-life of Neulasta® ranged from 15 to 80 hours after subcutaneous injection.

## Special Populations

No gender-related differences were observed in the pharmacokinetics of Neulasta<sup>®</sup>, and no differences were observed in the pharmacokinetics of geriatric patients ( $\geq 65$  years of age) compared to younger patients ( $< 65$  years of age) (see **PRECAUTIONS, Geriatric Use**). In a study of 30 patients with varying degrees of renal dysfunction including end-stage renal disease, renal dysfunction had no effect on the pharmacokinetics of pegfilgrastim; thus, dose adjustment in patients with renal dysfunction is not necessary. The pharmacokinetic profile in pediatric populations or in patients with hepatic insufficiency has not been assessed.

## CLINICAL STUDIES

Neulasta<sup>®</sup> was evaluated in three randomized, double-blind, controlled studies. Studies 1 and 2 were active-controlled studies that employed doxorubicin 60 mg/m<sup>2</sup> and docetaxel 75 mg/m<sup>2</sup> 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<sup>®</sup>. 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 (absolute neutrophil count [ANC]  $< 0.5 \times 10^9/L$ ) with a mean duration of 5-7 days, and a 30%-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<sup>®</sup> 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<sup>®</sup> 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<sup>®</sup> 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 primary objective of demonstrating that the mean days of severe neutropenia of Neulasta<sup>®</sup>-treated patients did not exceed that of Filgrastim-treated patients by more than one day in cycle 1 of chemotherapy (see **Table 1**). The rates of febrile neutropenia in the two studies were comparable for Neulasta<sup>®</sup> and Filgrastim (in the range of 10% to 20%). Other secondary endpoints included days of severe neutropenia in cycles 2-4, the depth of ANC nadir in cycles 1-4, and the time to ANC recovery after nadir. In both studies, the results for the secondary endpoints were similar between the two treatment groups.

**Table 1. Mean Days of Severe Neutropenia (in Cycle 1)**

Study	Mean days of severe neutropenia		Difference in means (95% CI)
	Neulasta <sup>®a</sup>	Filgrastim (5 mcg/kg/day)	

Study 1 n = 157	1.8	1.6	0.2 (-0.2, 0.6)
Study 2 n = 310	1.7	1.6	0.1 (-0.2, 0.4)

<sup>a</sup> Study 1 dose = 6 mg x 1; study 2 dose = 100 mcg/kg x 1

Study 3 was a randomized, double-blind, placebo-controlled study that employed docetaxel 100 mg/m<sup>2</sup> 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<sup>®</sup> 6 mg or placebo on day 2 of each chemotherapy cycle. Study 3 met the primary objective 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<sup>®</sup>-treated patients as compared to placebo-treated patients (1% versus 17%,  $p < 0.001$ ). The incidence of hospitalizations (1% versus 14%) and IV anti-infective use (2% versus 10%) for the treatment of febrile neutropenia were also lower in the Neulasta<sup>®</sup>-treated patients compared with the placebo-treated patients.

## INDICATIONS AND USAGE

Neulasta<sup>®</sup> 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**).

## CONTRAINDICATIONS

Neulasta<sup>®</sup> is contraindicated in patients with known hypersensitivity to *E coli*-derived proteins, pegfilgrastim, Filgrastim, or any other component of the product.

## WARNINGS

### General

The safety and efficacy of Neulasta<sup>®</sup> for peripheral blood progenitor cell (PBPC) mobilization has not been evaluated in adequate and well-controlled studies. Neulasta<sup>®</sup> should not be used for PBPC mobilization.

### Splenic Rupture

**RARE CASES OF SPLENIC RUPTURE HAVE BEEN REPORTED FOLLOWING THE ADMINISTRATION OF NEULASTA<sup>®</sup>. SPLENIC RUPTURE, IN SOME CASES RESULTING IN DEATH, HAS ALSO BEEN ASSOCIATED WITH FILGRASTIM, THE PARENT COMPOUND OF NEULASTA<sup>®</sup>. PATIENTS RECEIVING NEULASTA<sup>®</sup> WHO REPORT LEFT**

**UPPER ABDOMINAL AND/OR SHOULDER TIP PAIN SHOULD BE EVALUATED FOR AN ENLARGED SPLEEN OR SPLENIC RUPTURE.**

**Adult Respiratory Distress Syndrome (ARDS)**

Adult respiratory distress syndrome (ARDS) has been reported in neutropenic patients with sepsis receiving Filgrastim, the parent compound of Neulasta<sup>®</sup>, and is postulated to be secondary to an influx of neutrophils to sites of inflammation in the lungs.

Neutropenic patients receiving Neulasta<sup>®</sup> who develop fever, lung infiltrates, or respiratory distress should be evaluated for the possibility of ARDS. In the event that ARDS occurs, Neulasta<sup>®</sup> should be discontinued and/or withheld until resolution of ARDS and patients should receive appropriate medical management for this condition.

**Allergic Reactions**

Allergic reactions to Neulasta<sup>®</sup>, including anaphylaxis, skin rash, and urticaria, have been reported in postmarketing experience. The majority of reported events occurred upon initial exposure. In some cases, symptoms recurred with rechallenge, suggesting a causal relationship. In rare cases, allergic reactions including anaphylaxis, recurred within days after initial anti-allergic treatment was discontinued. If a serious allergic reaction occurs, appropriate therapy should be administered, with close patient follow-up over several days. Neulasta<sup>®</sup> should be permanently discontinued in patients with serious allergic reactions.

**Sickle Cell Disease**

Severe sickle cell crises have been associated with the use of Neulasta<sup>®</sup> in patients with sickle cell disease. Severe sickle cell crises, in some cases resulting in death, have also been associated with Filgrastim, the parent compound of pegfilgrastim. Only physicians qualified by specialized training or experience in the treatment of patients with sickle cell disease should prescribe Neulasta<sup>®</sup> for such patients, and only after careful consideration of the potential risks and benefits.

**PRECAUTIONS**

**General**

**Use With Chemotherapy and/or Radiation Therapy**

Neulasta<sup>®</sup> should not be administered in the period between 14 days before and 24 hours after administration of cytotoxic chemotherapy (see **DOSAGE AND ADMINISTRATION**) because of the potential for an increase in sensitivity of rapidly dividing myeloid cells to cytotoxic chemotherapy.

The use of Neulasta<sup>®</sup> has not been studied in patients receiving chemotherapy associated with delayed myelosuppression (eg, nitrosoureas, mitomycin C).

The administration of Neulasta<sup>®</sup> concomitantly with 5-fluorouracil or other antimetabolites has not been evaluated in patients. Administration of pegfilgrastim at 0, 1, and 3 days before 5-fluorouracil resulted in increased mortality in mice; administration of pegfilgrastim 24 hours after 5-fluorouracil did not adversely affect survival.

The use of Neulasta<sup>®</sup> has not been studied in patients receiving radiation therapy.

### **Potential Effect on Malignant Cells**

Pegfilgrastim is a growth factor that primarily stimulates neutrophils and neutrophil precursors; however, the G-CSF receptor through which pegfilgrastim and Filgrastim act has been found on tumor cell lines, including some myeloid, T-lymphoid, lung, head and neck, and bladder tumor cell lines. The possibility that pegfilgrastim can act as a growth factor for any tumor type cannot be excluded. Use of Neulasta<sup>®</sup> in myeloid malignancies and myelodysplasia (MDS) has not been studied. In a randomized study comparing the effects of the parent compound of Neulasta<sup>®</sup>, Filgrastim, to placebo in patients undergoing remission induction and consolidation chemotherapy for acute myeloid leukemia, important differences in remission rate between the two arms were excluded. Disease-free survival and overall survival were comparable; however, the study was not designed to detect important differences in these endpoints.<sup>3</sup>

### **Information for Patients**

Patients should be informed of the possible side effects of Neulasta<sup>®</sup>, and be instructed to report them to the prescribing physician. Patients should be informed of the signs and symptoms of allergic drug reactions and be advised of appropriate actions. Patients should be counseled on the importance of compliance with their Neulasta<sup>®</sup> treatment, including regular monitoring of blood counts.

If it is determined that a patient or caregiver can safely and effectively administer Neulasta<sup>®</sup> (pegfilgrastim) at home, appropriate instruction on the proper use of Neulasta<sup>®</sup> (pegfilgrastim) should be provided for patients and their caregivers, including careful review of the "Information for Patients and Caregivers" insert. Patients and caregivers should be cautioned against the reuse of needles, syringes, or drug product, and be thoroughly instructed in their proper disposal. A puncture-resistant container for the disposal of used syringes and needles should be available.

### **Laboratory Monitoring**

To assess a patient's hematologic status and ability to tolerate myelosuppressive chemotherapy, a complete blood count and platelet count should be obtained before chemotherapy is administered. Regular monitoring of hematocrit value and platelet count is recommended.

## **Drug Interaction**

No formal drug interaction studies between Neulasta<sup>®</sup> and other drugs have been performed. Drugs such as lithium may potentiate the release of neutrophils; patients receiving lithium and Neulasta<sup>®</sup> should have more frequent monitoring of neutrophil counts.

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

## **Carcinogenesis, Mutagenesis, Impairment of Fertility**

No mutagenesis studies were conducted with pegfilgrastim. The carcinogenic potential of pegfilgrastim has not been evaluated in long-term animal studies. In a toxicity study of 6 months duration in rats given once weekly subcutaneous injections of up to 1000 mcg/kg of pegfilgrastim (approximately 23-fold higher than the recommended human dose), no precancerous or cancerous lesions were noted.

When administered once weekly via subcutaneous injections to male and female rats at doses up to 1000 mcg/kg prior to, and during mating, reproductive performance, fertility, and sperm assessment parameters were not affected.

## **Pregnancy Category C**

Pegfilgrastim has been shown to have adverse effects in pregnant rabbits when administered subcutaneously every other day during gestation at doses as low as 50 mcg/kg/dose (approximately 4-fold higher than the recommended human dose). Decreased maternal food consumption, accompanied by a decreased maternal body weight gain and decreased fetal body weights were observed at 50 to 1000 mcg/kg/dose. Pegfilgrastim doses of 200 and 250 mcg/kg/dose resulted in an increased incidence of abortions. Increased post-implantation loss due to early resorptions was observed at doses of 200 to 1000 mcg/kg/dose, and decreased numbers of live rabbit fetuses were observed at pegfilgrastim doses of 200 to 1000 mcg/kg/dose, given every other day.

Subcutaneous injections of pegfilgrastim of up to 1000 mcg/kg/dose every other day during the period of organogenesis in rats were not associated with an embryotoxic or fetotoxic outcome. However, an increased incidence (compared to historical controls) of wavy ribs was observed in rat fetuses at 1000 mcg/kg/dose every other day. Very low levels (< 0.5%) of pegfilgrastim crossed the placenta when administered subcutaneously to pregnant rats every other day during gestation.

Once weekly subcutaneous injections of pegfilgrastim to female rats from day 6 of gestation through day 18 of lactation at doses up to 1000 mcg/kg/dose did not result in any adverse maternal effects. There were no deleterious effects on the growth and development of the offspring and no adverse effects were found upon assessment of fertility indices.

There are no adequate and well-controlled studies in pregnant women. Neulasta<sup>®</sup> should be used during pregnancy only if the potential benefit to the mother justifies the potential risk to the fetus.

### **Nursing Mothers**

It is not known whether pegfilgrastim is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when Neulasta<sup>®</sup> is administered to a nursing woman.

### **Pediatric Use**

The safety and effectiveness of Neulasta<sup>®</sup> in pediatric patients have not been established. The 6 mg fixed dose single-use syringe formulation should not be used in infants, children, and smaller adolescents weighing less than 45 kg.

### **Geriatric Use**

Of the 932 patients with cancer who received Neulasta<sup>®</sup> 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.

## **ADVERSE REACTIONS**

See WARNINGS sections regarding Splenic Rupture, ARDS, Allergic Reactions, and Sickle Cell Disease.

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of Neulasta<sup>®</sup> cannot be directly compared to rates in the clinical trials of other drugs and may not reflect the rates observed in practice. The adverse reaction information from clinical trials does, however, provide a basis for identifying the adverse events that appear to be related to Neulasta<sup>®</sup> use and for approximating rates.

The data described below reflect exposure to Neulasta<sup>®</sup> in 932 patients. Neulasta<sup>®</sup> was studied in placebo- and active-controlled trials (n = 467, and n = 465, respectively). The population encompassed an age range of 21 to 88 years. Ninety-two percent of patients were female. The ethnicity of the patients was as follows: 75% Caucasian, 18% Hispanic, 5% Black, and 1% Asian. Patients with solid tumors (breast [n = 823], lung and thoracic tumors [n = 53]) or lymphoma (n = 56) received Neulasta<sup>®</sup> 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.

In the placebo-controlled trial, bone pain occurred at a higher incidence in Neulasta<sup>®</sup>-treated patients as compared to placebo-treated patients. The incidence of other commonly reported adverse events were similar in the Neulasta<sup>®</sup>- and placebo-treated

patients, and were consistent with the underlying cancer diagnosis and its treatment with chemotherapy. The data in Table 2 reflect those adverse events occurring in at least 10% of patients treated with Neulasta<sup>®</sup> in the placebo-controlled study.

**Table 2. Adverse Events Occurring in  $\geq 10\%$ <sup>a</sup> of Patients in the Placebo-Controlled Study.**

Event	Neulasta <sup>®</sup> (n = 467)	Placebo (n = 461)
Alopecia	48%	47%
Bone Pain <sup>b</sup>	31%	26%
Diarrhea	29%	28%
Pyrexia (not including febrile neutropenia)	23%	22%
Myalgia	21%	18%
Headache	16%	14%
Arthralgia	16%	13%
Vomiting	13%	11%
Asthenia	13%	11%
Edema peripheral	12%	10%
Constipation	10%	6%

<sup>a</sup> Events occurring in  $\geq 10\%$  of Neulasta<sup>®</sup>-treated patients and at a higher incidence as compared to placebo-treated patients.

<sup>b</sup> Bone pain is limited to the specified adverse event term "bone pain."

In the active controlled studies, common adverse events occurred at similar rates and severities in both treatment arms (Neulasta<sup>®</sup>, n = 465; Filgrastim, n = 331). These adverse experiences occurred at rates between 72% and 15% and included: nausea, fatigue, alopecia, diarrhea, vomiting, constipation, fever, anorexia, skeletal pain, headache, taste perversion, dyspepsia, myalgia, insomnia, abdominal pain, arthralgia, generalized weakness, peripheral edema, dizziness, granulocytopenia, stomatitis, mucositis, and neutropenic fever.

### **Bone Pain**

The analysis of bone pain described below is based on a composite analysis using multiple, related, adverse event terms.

In the placebo-controlled study, the incidence of bone pain was 57% in Neulasta<sup>®</sup>-treated patients compared to 50% in placebo-treated patients. Bone pain was generally reported to be of mild-to-moderate severity.



Among patients experiencing bone pain, approximately 37% of Neulasta<sup>®</sup> - and 31% of placebo-treated patients utilized non-narcotic analgesics and 10% of Neulasta<sup>®</sup> - and 9% of placebo-treated patients utilized narcotic analgesics.

In the active-controlled studies, the use of non-narcotic and narcotic analgesics in association with bone pain was similar between Neulasta<sup>®</sup> - and Filgrastim-treated patients. No patient withdrew from study due to bone pain.

### **Laboratory Abnormalities**

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<sup>®</sup>. Leukocytosis was not associated with any adverse effects.

In the placebo-controlled study, reversible elevations in LDH, alkaline phosphatase, and uric acid that did not require treatment occurred at similar rates in Neulasta<sup>®</sup> - and placebo-treated patients.

### **Immunogenicity**

As with all therapeutic proteins, there is a potential for immunogenicity. The incidence of antibody development in patients receiving Neulasta<sup>®</sup> has not been adequately determined. While available data suggest that a small proportion of patients developed binding antibodies to Filgrastim or pegfilgrastim, the nature and specificity of these antibodies has not been adequately studied. No neutralizing antibodies have been detected using a cell-based bioassay in 46 patients who apparently developed binding antibodies. 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 sample handling, concomitant medications, and underlying disease. Therefore, comparison of the incidence of antibodies to Neulasta<sup>®</sup> with the incidence of antibodies to other products may be misleading.

Cytopenias resulting from an antibody response to exogenous growth factors have been reported on rare occasions in patients treated with other recombinant growth factors. There is a theoretical possibility that an antibody directed against pegfilgrastim may cross-react with endogenous G-CSF, resulting in immune-mediated neutropenia, but this has not been observed in clinical studies.

### **OVERDOSAGE**

The maximum amount of Neulasta<sup>®</sup> 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 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. Leukapheresis should be considered in the management of symptomatic individuals.

## **DOSAGE AND ADMINISTRATION**

The recommended dosage of Neulasta<sup>®</sup> is a single subcutaneous injection of 6 mg administered once per chemotherapy cycle. Neulasta<sup>®</sup> should not be administered in the period between 14 days before and 24 hours after administration of cytotoxic chemotherapy (see **PRECAUTIONS**).

The 6 mg fixed-dose formulation should not be used in infants, children, and smaller adolescents weighing less than 45 kg.

No dosing adjustment is necessary for renal dysfunction (see **CLINICAL PHARMACOLOGY, Special Populations**).

Neulasta<sup>®</sup> should be visually inspected for discoloration and particulate matter before administration. Neulasta<sup>®</sup> should not be administered if discoloration or particulates are observed.

For method of administration please see patient package insert.

### **Storage**

Neulasta<sup>®</sup> should be stored refrigerated at 2° to 8°C (36° to 46°F); syringes should be kept in their carton to protect from light until time of use. Shaking should be avoided. Before injection, Neulasta<sup>®</sup> may be allowed to reach room temperature for a maximum of 48 hours but should be protected from light. Neulasta<sup>®</sup> left at room temperature for more than 48 hours should be discarded. Freezing should be avoided; however, if accidentally frozen, Neulasta<sup>®</sup> should be allowed to thaw in the refrigerator before administration. If frozen a second time, Neulasta<sup>®</sup> should be discarded.

### **HOW SUPPLIED**

Neulasta<sup>®</sup> is supplied as a preservative-free solution containing 6 mg (0.6 mL) of pegfilgrastim (10 mg/mL) in a single-dose syringe with a 27-gauge, 1/2-inch needle with an UltraSafe<sup>®</sup> Needle Guard.

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

Neulasta<sup>®</sup> is provided in a dispensing pack containing one syringe (NDC 55513-190-01).

### **Rx Only**

This product, its production, and/or its use may be covered by one or more US Patents, including US Patent Nos. 5,824,784; 4,810,643; 4,999,291; 5,582,823; 5,580,755 as well as other patents or patents pending.

## REFERENCES

1. Morstyn G, Dexter T, Foote M. *Filgrastim (r-metHuG-CSF) in clinical practice*. 2nd ed. 1998;3:51-71.
2. Valerius T, Elsasser D, Repp R, et al. HLA Class-II antibodies recruit G-CSF activated neutrophils for treatment of B-cell malignancies. *Leukemia and Lymphoma*. 1997;26, 261-269.
3. Heil G, Hoelzer D, Sanz MA, et al. A randomized, double-blind, placebo-controlled, phase III study of Filgrastim in remission induction and consolidation therapy for adults with de novo Acute Myeloid Leukemia. *Blood*. 1997;90:4710-4718.

[Amgen Logo]

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**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 *E coli*. G-CSF is a substance naturally 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.

**What is Neulasta® used for?**

Neulasta® is used to treat neutropenia (nu-tro-peen-ee-ah), a condition where the body makes too few white blood cells. Neutropenia can be caused by drugs used to treat cancer.

**How does Neulasta® work?**

Neulasta® works by stimulating the growth of neutrophils, a type of white blood cell. To make sure Neulasta® is working, the doctor will ask that the patient have blood tests to count the number of white blood cells. It is important to follow the doctor's instructions about these tests.

**Who should not take Neulasta®?**

Do not take Neulasta® if you are:

- Allergic to Neulasta® (pegfilgrastim) or any of its ingredients, or to NEUPOGEN® (Filgrastim). See the end of this leaflet for a list of ingredients in Neulasta®.
- Allergic to other medicines made using the bacteria *E coli*. Ask your doctor if you are not sure.

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

Neulasta® can reduce the risk of infection, but it may not prevent all infections. An infection can still happen during the time when your white blood cell levels are low. You must be alert and look for some of the common signs of infection, such as fever, chills, rash, sore throat, diarrhea, or redness, swelling, or pain around a cut or sore. If you

notice any of these symptoms during treatment with Neulasta<sup>®</sup>, tell your doctor or nurse immediately.

Occasionally a reaction may develop 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.

If you have sickle cell disease, make sure that your doctor knows about it before using Neulasta<sup>®</sup>. It is important that you drink plenty of fluids if you receive Neulasta<sup>®</sup>. If you have a sickle cell crisis after getting Neulasta<sup>®</sup>, you need to tell your doctor right away.

Make sure your doctor knows about all medications you are taking before starting Neulasta<sup>®</sup> injections. If you are taking lithium, you may need more frequent blood tests.

The doctor, nurse, or caregiver will usually inject the dose of Neulasta<sup>®</sup> a day after the last dose of chemotherapy in each cycle. Neulasta<sup>®</sup> should only be injected on the day the doctor has determined and should not be injected until approximately 24 hours after receiving chemotherapy.

More information about Neulasta<sup>®</sup> is available in the Physician Package Insert. If you have any questions, talk to your doctor.

#### **What are possible or reasonable likely side effects of Neulasta<sup>®</sup>?**

Your spleen may become enlarged and, in rare instances, may rupture while taking Neulasta<sup>®</sup>. The spleen is located in the upper left section of your stomach area. Call your doctor right away if you have pain in your left upper stomach area or left shoulder tip area. This pain could mean your spleen is enlarged or ruptured.

Neulasta<sup>®</sup> can cause serious allergic reactions. These reactions can cause a rash over the whole body, shortness of breath, wheezing, dizziness (a drop in blood pressure), swelling around the mouth or eyes, fast pulse, and/or sweating. Sometimes these symptoms could come back within days after stopping treatment for the allergic reaction. If you get these symptoms at any time, stop using Neulasta<sup>®</sup> and call a doctor or get emergency care right away. If you have an allergic reaction during the injection of Neulasta<sup>®</sup>, stop the injection right away.

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.

Some people experience redness, swelling, or itching at the site of injection. This may be an allergy to the ingredients in Neulasta<sup>®</sup>, or it may be a local reaction. If you notice signs of a local reaction, call your doctor.

#### **What about pregnancy or breastfeeding?**

Neulasta<sup>®</sup> has not been studied in pregnant women, and its effects on unborn babies are not known. If you take Neulasta<sup>®</sup> 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<sup>®</sup> can get into human breast milk. If you are pregnant, plan to become pregnant, think you may be pregnant, or are breast feeding, you should tell your doctor before using Neulasta<sup>®</sup>.

## HOW TO PREPARE AND GIVE A NEULASTA® INJECTION

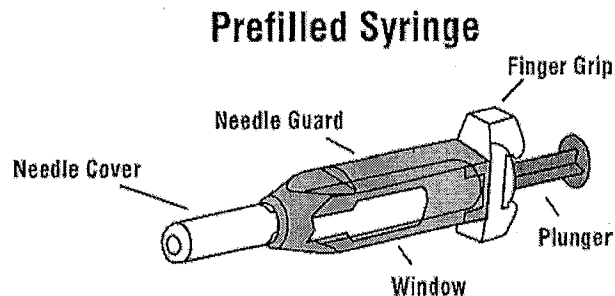
Neulasta® is provided in a prefilled syringe. **Neulasta® should be stored in its carton to protect from light until use.** If you are giving someone else Neulasta® injections, it is important that you know how to inject Neulasta®. Before getting your Neulasta® injection, always check to see that:

- 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.**

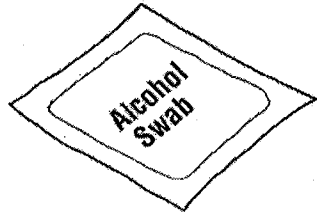
### Setting up for an injection

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



- An alcohol swab and a cotton ball or gauze

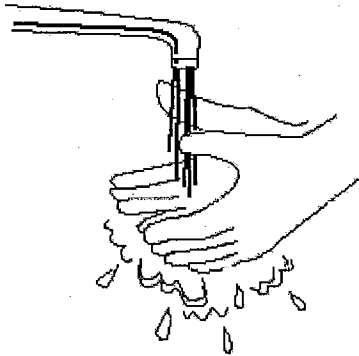
## Alcohol Swab



## Cotton Ball



- puncture-proof disposal container
4. Wash your hands with soap and warm water.



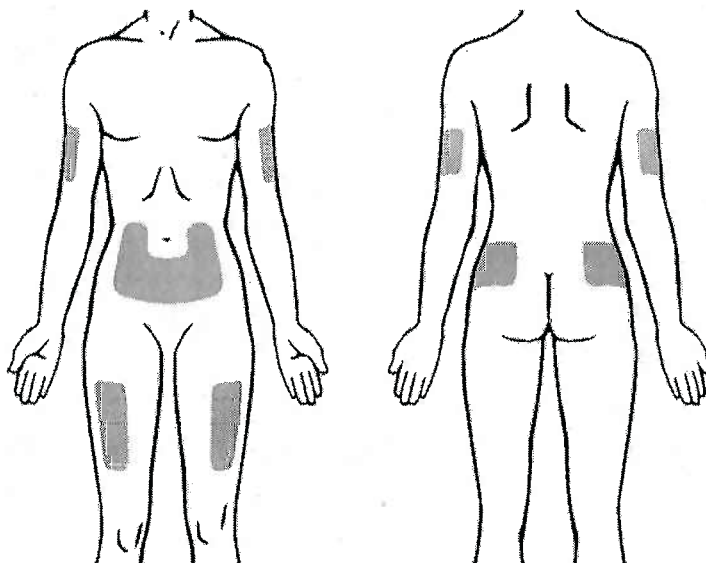
### HOW TO PREPARE FOR INJECTION OF NEULASTA®

5. Remove the 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 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:

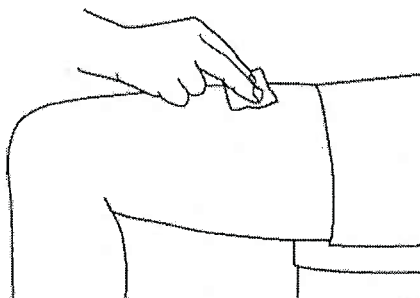
- The outer area of the upper arms
- The abdomen, except for the two inch area around the navel
- The front of the middle thighs
- The upper outer areas of the buttocks



**Front**

**Back**

10. Clean the injection site with an alcohol swab.

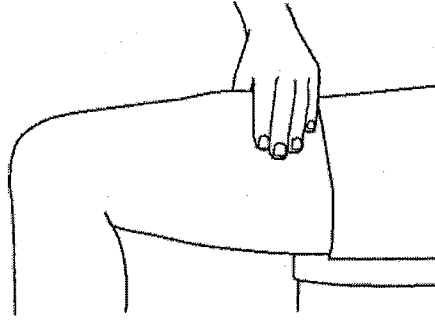


### Injecting the dose of Neulasta®

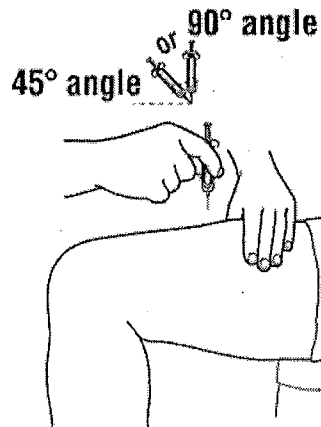
11. Pick up the prefilled syringe from your clean flat working surface by grabbing the sides of the needle guard with your thumb and forefinger.



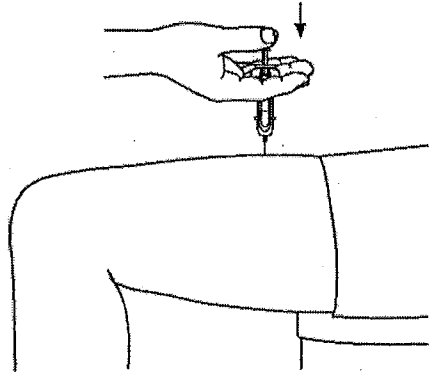
12. Hold the syringe in the hand you will use to inject Neulasta®. Use the other hand to pinch a fold of skin at the cleaned injection site. Note: Hold the syringe barrel through the needle guard windows when giving the injection.



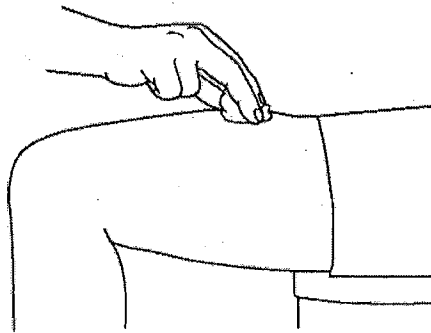
13. Holding the syringe like a pencil, use a quick “dart-like” motion to insert the needle either straight up and down (90 degree angle) or at a slight angle (45 degrees) into the skin.



14. After the needle is inserted, let go of the skin. Pull the plunger back slightly. If no blood appears, slowly push down on the plunger all the way, until all the Neulasta<sup>®</sup> is injected. **If blood comes into the syringe, do not inject Neulasta<sup>®</sup>, because the needle has entered a blood vessel.** Withdraw the syringe and discard it in the puncture-proof container. Repeat the steps to prepare a new prefilled syringe and choose and clean a new injection site. Remember to check again for blood before injecting Neulasta<sup>®</sup>.



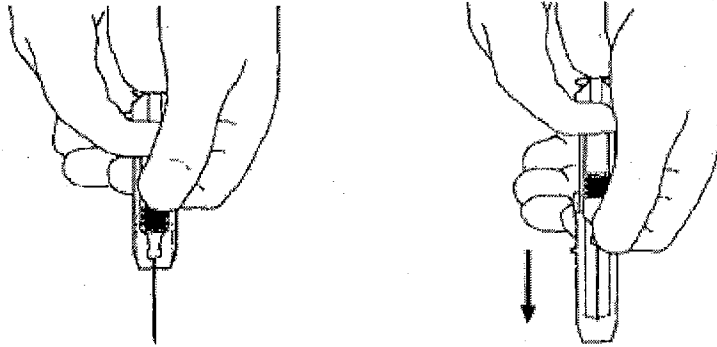
15. When the syringe is empty, pull the needle out of the skin and place a cotton ball or gauze over the injection site and press for several seconds.



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 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.

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.

[Amgen Logo]

**Manufactured by:**

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