

PRODUCT MONOGRAPH

PrNEULASTA®

(pegfilgrastim)

Sterile Solution for Injection
(Subcutaneous Use Only)
6 mg (10 mg/mL)

Professed Standard

Hematopoietic Agent
Granulocyte Colony-Stimulating Factor

Manufactured by:

Amgen Manufacturing, Limited,
a subsidiary of Amgen Inc.
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PrNEULASTA®

(pegfilgrastim)

PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	Clinically Relevant Nonmedicinal Ingredients
Subcutaneous	Sterile Solution for Injection / 6 mg (10 mg/mL)	Not Applicable <i>For a complete listing see Dosage Forms, Composition and Packaging section.</i>

DESCRIPTION

Neulasta® (pegfilgrastim) is a long-acting form of recombinant human granulocyte colony-stimulating factor (r-metHuG-CSF) or filgrastim. Neulasta® is composed of filgrastim with a 20,000 dalton polyethylene glycol (PEG) molecule covalently bound to the N-terminal methionine residue. Filgrastim is a 175 amino acid protein with a molecular weight of 18,800 daltons; Neulasta® has a total molecular weight of 39,000 daltons.

INDICATIONS AND CLINICAL USE

Neulasta® (pegfilgrastim) is indicated to decrease the incidence of infection, as manifested by febrile neutropenia, in patients with non-myeloid malignancies receiving myelosuppressive anti-neoplastic drugs.

Pediatrics (< 18 years of age): The safety and effectiveness of Neulasta® in pediatric patients have not been established.

CONTRAINDICATIONS

Neulasta® (pegfilgrastim) is contraindicated in patients with known hypersensitivity to *E. coli*-derived proteins, pegfilgrastim, filgrastim, or any other component of the product. For a complete listing of the components, see the Dosage Forms, Composition and Packaging section of the product monograph.

WARNINGS AND PRECAUTIONS

General

Very rare cases of splenic rupture, including some fatal cases, have been reported following the administration of Neulasta[®] (pegfilgrastim). Patients receiving Neulasta[®] who report left upper abdominal or shoulder tip pain should be evaluated for an enlarged spleen or splenic rupture.

Neulasta[®] (pegfilgrastim) has not been evaluated for PBPC (peripheral blood progenitor cell) mobilization. Therefore, it should not be used in that setting.

Simultaneous Use With Chemotherapy and Radiation Therapy

The safety and efficacy of Neulasta[®] administered concurrently with cytotoxic chemotherapy have not been established. Because of the potential for an increase in sensitivity of rapidly dividing myeloid cells to cytotoxic chemotherapy, Neulasta[®] should not be administered in the period between 14 days before and 24 hours after administration of cytotoxic chemotherapy (see DOSAGE AND ADMINISTRATION).

The safety and efficacy of Neulasta[®] have not been evaluated in patients receiving chemotherapy associated with delayed myelosuppression (e.g., nitrosoureas), mitomycin C, or myelosuppressive doses of anti-metabolites such as 5-fluorouracil (5-FU). Concomitant use of Neulasta[®] with 5-FU or other anti-metabolites has not been evaluated in humans, although it has been studied and shown to potentiate myelosuppression in animal models (see TOXICOLOGY).

The safety and efficacy of Neulasta[®] have not been evaluated in patients receiving radiation therapy.

Carcinogenesis and Mutagenesis

No carcinogenesis or mutagenesis studies were conducted with Neulasta[®].

Potential Effect on Malignant Cells

Neulasta[®] (pegfilgrastim) and filgrastim are growth factors that primarily stimulate production of neutrophils and neutrophil precursors by binding to the G-CSF receptor. Overall, the possibility that Neulasta[®] can act as a growth factor for any tumour type cannot be excluded. Randomized studies have demonstrated that treatment with filgrastim following chemotherapy for AML does not adversely influence the outcome of treatment.¹ The use of Neulasta[®] in AML, chronic myeloid leukemia (CML) and myelodysplasia (MDS) has not been studied.

Hematologic

Sickle cell crises have been associated with the use of Neulasta[®] in patients with sickle cell disease. Physicians should exercise caution in considering the use of Neulasta[®] in patients with sickle cell disease, and only after careful consideration of the potential risks and benefits.

Leukocytosis

In clinical studies with Neulasta[®], white blood cell counts of $100 \times 10^9/L$ or greater have been reported in less than 1% of patients with cancer receiving myelosuppressive chemotherapy (n=930), and were not associated with any reported adverse clinical effects.

In studies of Neulasta[®] administration after chemotherapy, most reported side effects were consistent with those usually seen as a result of cytotoxic chemotherapy (see ADVERSE REACTIONS). Because of the potential for patients to receive full doses of chemotherapy on the prescribed schedule, patients may be at greater risk of thrombocytopenia, anemia, and non-hematologic consequences of increased chemotherapy doses (please refer to the prescribing information for specific chemotherapy agents). Regular monitoring of hematocrit value and platelet count is recommended. Furthermore, care should be exercised in the administration of Neulasta[®] in conjunction with drugs known to lower platelet count.

Respiratory

Adult respiratory distress syndrome (ARDS) has been reported following administration of Neulasta[®] and is postulated to be secondary to an influx of neutrophils to sites of inflammation in the lungs. Neutropenic patients receiving Neulasta[®] who develop fever, lung infiltrates, or respiratory distress should be evaluated for the possibility of ARDS. In the event that ARDS occurs, Neulasta[®] should be discontinued and/or withheld until resolution of ARDS and patients should receive appropriate medical management for this condition.

Sensitivity/Resistance

Allergic-type reactions, including anaphylaxis, skin rash, and urticaria, occurring on initial or subsequent treatment have been reported both with Neulasta[®] and filgrastim. In some cases, symptoms have recurred with rechallenge, suggesting a causal relationship. If a serious allergic reaction or an anaphylactic reaction occurs, appropriate therapy should be administered and further use of Neulasta[®] should be discontinued. Antibodies to filgrastim or pegfilgrastim have been reported, although no neutralizing antibodies have been reported (see ADVERSE REACTIONS; Immunogenicity).

Sexual Function/Reproduction

No studies evaluating sexual function or reproduction in humans were conducted with Neulasta[®].

Special Populations

Pregnant Women: There were no pregnant women exposed to Neulasta[®] in clinical trials. Neulasta[®] should be used during pregnancy only if the potential benefit outweighs the risk to the fetus (see TOXICOLOGY).

Nursing Women: It is not known whether Neulasta[®] is excreted in human milk. Because many drugs are excreted in human milk, Neulasta[®] is not recommended for women who are breast feeding. Neulasta[®] should only be administered to a nursing woman if the potential benefit outweighs the risk.

Pediatrics (< 18 years of age): The safety and effectiveness of Neulasta[®] in pediatric patients have not been established.

Geriatrics (>65 years of age): Of the total number of subjects with cancer who received Neulasta[®] in clinical studies (n=930), 139 subjects (15%) were 65 years or older and 18 subjects (2%) were 75 years or older. No overall differences in safety or effectiveness were observed between these patients and younger patients, and other reported clinical experience has not

identified differences in responses between the elderly and younger patients; however, due to the small number of elderly subjects, small but clinically relevant differences cannot be excluded.

Monitoring and Laboratory Tests

To assess a patient's hematologic status and ability to tolerate myelosuppressive chemotherapy, a complete blood count (CBC) and platelet count should be obtained before chemotherapy is administered. Neulasta[®] produced ANC (absolute neutrophil count) profiles similar to daily filgrastim, including earlier ANC nadir, shorter duration of severe neutropenia, and accelerated ANC recovery, compared with ANC profiles observed without growth factor support. Regular monitoring of hematocrit value, white blood cell count and platelet count, as clinically indicated, is recommended.

ADVERSE REACTIONS

Adverse Drug Reaction Overview

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

Clinical Trial Adverse Drug Reactions

Because clinical trials are conducted under very specific conditions the adverse reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse drug reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates.

Safety data are based on 7 randomized clinical trials involving 932 patients with lymphoma and solid tumours (breast and thoracic) who received Neulasta[®] (pegfilgrastim) after non-myeloablative cytotoxic chemotherapy. Common adverse events occurred at similar rates between the treatment arms in both the filgrastim-controlled trials (Neulasta[®], n = 465; filgrastim, n = 331) and the placebo-controlled trial (Neulasta[®], n = 467; placebo, n = 461). Most adverse experiences were attributed by the investigator as the sequelae of the underlying malignancy or cytotoxic chemotherapy. In the filgrastim-controlled trials, these adverse experiences occurred at rates between 15% and 72% 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. A summary of the most frequently reported adverse reactions in these randomized clinical trials can be found in Table 1 and 2.

In clinical trials comparing Neulasta[®] to filgrastim, medullary bone pain was reported in 26% of Neulasta[®]-treated patients, which was comparable to the incidence in filgrastim-treated patients. In the study comparing Neulasta[®] to placebo, the incidence of bone pain was 23% vs. 16%, respectively. This bone pain was generally reported to be of mild-to-moderate severity. Approximately 17% (for all bone pain type AEs; 10% for specifically “bone pain”) of all subjects utilized non-narcotic analgesics and less than 6% utilized

narcotic analgesics in association with bone pain. No patient withdrew from study due to bone pain.

Across all studies, no life-threatening or fatal adverse events were attributed to Neulasta[®]. There was only one serious adverse event (dyspnea) reported as possibly related to Neulasta[®] in a single patient. No events of pleuritis, pericarditis, or other major systemic reactions to Neulasta[®] were reported.

No clinically significant changes in vital signs were observed. No evidence of interaction of Neulasta[®] with other drugs was observed in the course of clinical trials (see WARNINGS AND PRECAUTIONS).

Table 1. Most Frequently* Reported Adverse Reactions in Randomized Clinical Trials with Filgrastim as Comparator

Body System and Preferred Term	Neulasta® (pegfilgrastim) (n=465)	Filgrastim (n=331)
Application Site		
Injection Site Pain	16 (3%)	9 (3%)
Body as a whole		
Pain	8 (2%)	4 (1%)
Chest Pain (Non-Cardiac)	4 (1%)	3 (1%)
Edema Periorbital	3 (1%)	0 (0%)
Fever	3 (1%)	4 (1%)
CNS/PNS		
Headache	20 (4%)	12 (4%)
Musculo-skeletal		
Skeletal Pain	96 (21%)	89 (27%)
Myalgia	32 (7%)	25 (8%)
Arthralgia	27 (6%)	19 (6%)
Back Pain	19 (4%)	26 (8%)
Limb Pain	12 (3%)	7 (2%)
Musculo-Skeletal Pain	5 (1%)	4 (1%)
Neck Pain	4 (1%)	3 (1%)

* Most frequently reported events were considered to be those events reported in $\geq 1\%$ of the patients in the Neulasta® group.

Table 2. Most Frequently* Reported Adverse Reactions in Randomized Clinical Trials with Placebo Control

Body System and Preferred Term	Neulasta® (pegfilgrastim) (n=467)	Placebo (n=461)
Blood and Lymphatic System Disorders		
Leukocytosis	5 (1%)	1 (0%)
Gastrointestinal Disorders		
Diarrhea	9 (2%)	10 (2%)
General Disorders and Administration Site Conditions		
Pyrexia	8 (2%)	9 (2%)
Fatigue	3 (1%)	5 (1%)
Infections and Infestations		
Influenza	6 (1%)	5 (1%)
Musculoskeletal and Connective Tissue Disorders		
Bone Pain	62 (13%)	41 (9%)
Myalgia	26 (6%)	23 (5%)
Arthralgia	32 (7%)	19 (4%)
Polymyalgia	8 (2%)	7 (2%)
Musculoskeletal Pain	14 (3%)	5 (1%)
Pain in Limb	11 (2%)	5 (1%)
Back Pain	8 (2%)	4 (1%)
Polyarthralgia	5 (1%)	0 (0%)
Nervous System Disorders		
Headache	6 (1%)	2 (0%)
Skin and Subcutaneous Tissue Disorders		
Alopecia	8 (2%)	9 (2%)

* Most frequently reported events were considered to be those events reported in $\geq 1\%$ of the patients in the Neulasta® group.

Less Common Clinical Trial Adverse Drug Reactions (<1%)

The following adverse drug reactions were reported at an incidence of <1% in controlled clinical studies (occurring in more than 1 patient, with higher frequency than filgrastim):

General Disorders and Administration Site Conditions: injection site bruising;

Infections and Infestations: rhinitis;

Nervous System Disorders: hypertonia;

Skin and Subcutaneous Tissue Disorders: periorbital edema.

The following adverse drug reactions were reported at an incidence of <1% in controlled clinical studies (occurring in more than 1 patient, with higher frequency than placebo):

General Disorders and Administration Site Conditions: chest pain, pain.

Abnormal Hematologic and Clinical Chemistry Findings

Spontaneously reversible elevations in LDH, alkaline phosphatase, and uric acid of mild-to-moderate severity were observed. Most changes have been attributed to post-cytokine bone marrow expansion as well as to chemotherapy and metastatic disease. The incidences of these changes, presented for Neulasta[®] versus filgrastim and placebo, were: LDH (18% versus 29% and 18%), alkaline phosphatase (11% versus 16% and 12%), and uric acid [10% versus 9% and 13% (1% of uric acid reported cases for filgrastim and Neulasta[®] treatment groups were classified as severe)].

In clinical studies with Neulasta[®], white blood cell counts of $100 \times 10^9/L$ or greater have been reported in less than 1% of patients with cancer receiving myelosuppressive chemotherapy (n=930), and were not associated with any reported adverse clinical effects.

Immunogenicity

As with all therapeutic proteins, there is a potential for immunogenicity. The incidence of antibody development in patients receiving Neulasta[®] has not been adequately determined. While available data suggest that a small proportion of patients developed binding antibodies to filgrastim or Neulasta[®], 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 (9%, n = 534) 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[®] 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 Neulasta[®] may cross-react with endogenous G-CSF, resulting in immune-mediated neutropenia, but this has not been observed in clinical studies.

Post-Market Adverse Drug Reactions

Allergic Reaction

In post-marketing experience, allergic-type reactions, including anaphylaxis, skin rash, and urticaria, occurring on initial or subsequent treatment have been reported both with Neulasta[®] and filgrastim. In some cases, symptoms have recurred with rechallenge, suggesting a causal relationship (see WARNINGS AND PRECAUTIONS).

DRUG INTERACTIONS

Overview

Drug interactions between Neulasta[®] (pegfilgrastim) and other drugs have not been studied.

Drugs such as lithium that may potentiate the release of neutrophils should be used with caution; such patients should have more frequent monitoring of their neutrophil counts.

Drug-Drug Interactions

Interactions with other drugs have not been established.

Drug-Food Interactions

Interactions with food have not been established.

Drug-Herb Interactions

Interactions with herbal products have not been established.

Drug-Laboratory Interactions

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.

DOSAGE AND ADMINISTRATION

Dosing Considerations

Neulasta[®] (pegfilgrastim) should be administered no sooner than 24 hours after the administration of cytotoxic chemotherapy (see WARNINGS AND PRECAUTIONS).

Renal impairment, including end-stage renal disease, appears to have no effect on the pharmacokinetics of Neulasta[®] and no dosage adjustment is required.

Recommended Dose and Dosage Adjustment

The recommended dosage of Neulasta[®] is a single subcutaneous injection of 6 mg, administered once per cycle of chemotherapy. Neulasta[®] should be administered no sooner than 24 hours after the administration of cytotoxic chemotherapy (see WARNINGS AND PRECAUTIONS).

Missed Dose

If a scheduled dose is missed, Neulasta[®] should not be administered less than 14 days before subsequent administration of cytotoxic chemotherapy.

Administration

Neulasta[®] is intended for subcutaneous injection only and should not be given by any other route of administration. Neulasta[®] should not be mixed with any diluents.

Neulasta[®] should not be vigorously shaken.

Following administration of Neulasta[®] from the single-use prefilled syringe, the patient should activate the UltraSafe[®] Needle Guard by placing their hands behind the needle, grasping the guard with one hand, and sliding the guard forward until the needle is completely covered and the guard clicks into place. NOTE: If an audible click is not heard, the needle guard may not be completely activated.

OVERDOSAGE

The maximum tolerated dose of Neulasta[®] (pegfilgrastim) has not been determined in humans. Neulasta[®] administered at a dose of 300 mcg/kg (n = 12), approximately three times the recommended dose, exhibited an adverse event profile similar to that observed at the recommended dose.

ACTION AND CLINICAL PHARMACOLOGY

Mechanism of Action

Both Neulasta[®] (pegfilgrastim) and filgrastim 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.²⁻³ 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.

Pharmacodynamics and Pharmacokinetics

The pharmacokinetics and pharmacodynamics of Neulasta[®] (pegfilgrastim) were studied in patients with cancer. The pharmacokinetics of pegfilgrastim were nonlinear in cancer patients and clearance decreased with increases in dose. Neutrophil-mediated clearance is an important component of the clearance of pegfilgrastim, and serum clearance is related to the number of neutrophils. For example, the concentration of pegfilgrastim declined rapidly at the onset of neutrophil recovery that followed myelosuppressive chemotherapy.⁴ 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 in cancer patients. The half-life of pegfilgrastim ranged from 25 to 49 hours after SC injection. (see DETAILED PHARMACOLOGY)

Table 3. Summary of Pharmacokinetic Parameters of pegfilgrastim in Cancer Patients After SC Administration

	C _{max}	t _½	AUC _{0-∞}	Clearance
Single dose* Median	78.3-175 ng/mL	25-49 hr	5640-15000 ng·hr/mL	6.68-17.7 mL/hr/kg

* Doses of 100 µg/kg and 6 mg

Special Populations and Conditions

No gender-related differences were observed in the pharmacokinetics of Neulasta[®] (pegfilgrastim), and no differences were observed in the pharmacokinetics of geriatric patients with cancer (≥ 65 years of age) compared to younger patients (< 65 years of age) (see WARNINGS AND PRECAUTIONS, Special Populations, Geriatrics). Renal impairment,

including end-stage renal disease, appears to have no effects on the pharmacokinetics of pegfilgrastim. The pharmacokinetic profile in pediatric populations or in patients with hepatic insufficiency has not been assessed. The effect of race on pharmacokinetics has not been adequately assessed.

STORAGE AND STABILITY

Neulasta[®] (pegfilgrastim) should be stored refrigerated at 2° to 8°C (36° to 46°F) and protected from light. Before injection, Neulasta[®] may be allowed to reach room temperature for a maximum of 72 hours. Neulasta[®] left at room temperature for more than 72 hours should be discarded. Freezing should be avoided; however, if accidentally frozen Neulasta[®] should be allowed to thaw in the refrigerator before administration. If frozen a second time, Neulasta[®] should be discarded.

Neulasta[®] should be visually inspected for discoloration and particulate matter before administration. Neulasta[®] should not be administered if discoloration or particulates are observed.

SPECIAL HANDLING INSTRUCTIONS

Neulasta[®] (pegfilgrastim) should not be vigorously shaken.

DOSAGE FORMS, COMPOSITION AND PACKAGING

Neulasta[®] (pegfilgrastim) is a sterile, clear, colourless, preservative-free liquid for SC administration. Each single-use syringe (0.6 mL) of Neulasta[®] (10 mg/mL) contains 6 mg of pegfilgrastim (based on protein mass only). The product is formulated at pH 4.0 in 10 mM acetate, 30.0 mg sorbitol and 0.02 mg polysorbate 20. The quantitative composition (per 0.6 mL prefilled syringe) of Neulasta[®] is:

Pegfilgrastim	6 mg
Acetate	0.35 mg
Sorbitol	30.0 mg
Polysorbate 20	0.02 mg
Sodium	0.021 mg
Water for Injection USP q.s.	0.6 mL

Availability of Dosage Forms

Neulasta[®] is supplied as a preservative-free solution (0.6 mL) containing 6 mg of pegfilgrastim (10 mg/mL) in a single-dose syringe with a 27 gauge, ½ inch needle, with an UltraSafe[®] Needle Guard.

The needle cover on the single-use prefilled syringe contains dry natural rubber (a derivative of latex), which may cause allergic reactions and should not be handled by individuals who are sensitive to latex.

To reduce the risk of accidental needle sticks to users, each single-use prefilled syringe is equipped with an UltraSafe[®] Needle Guard that is manually activated to cover the needle during disposal.

Neulasta[®] is provided in a dispensing pack containing one syringe.

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

Drug Substance

Proper name: pegfilgrastim

Chemical name: recombinant methionyl human granulocyte colony-stimulating factor

Molecular formula and molecular mass: Pegfilgrastim has a total molecular weight of 39,000 daltons.

Structural formula: Pegfilgrastim is composed of filgrastim (recombinant methionyl human G-CSF) with a 20,000 dalton polyethylene glycol (PEG) molecule covalently bound to the N-terminal methionine residue. Filgrastim is a 175 amino acid protein manufactured by recombinant DNA technology. Filgrastim is produced by *Escherichia coli* (*E. coli*) bacteria into which the human G-CSF gene has been inserted. Filgrastim has an amino acid sequence that is identical to the natural sequence predicted by human DNA sequence analysis, except for the addition of an N-terminal methionine necessary for expression in *E. coli*. Because filgrastim is produced in *E. coli*, the protein is nonglycosylated and thus differs from G-CSF isolated from a human cell.

Product Characteristics

Neulasta[®] (pegfilgrastim) is a sterile, clear colourless liquid.

CLINICAL TRIALS

Study demographics and trial design

Table 4. Summary of patient demographics for clinical trials in specific indication

Study #	Trial design	Dosage, route of administration and duration	Study subjects (n=number)	Mean age (Range) years	Gender
980226	Phase 3, double-blind, randomized, filgrastim controlled	Single SC dose of 100 µg/kg/day pegfilgrastim or daily SC dose of 5 µg/kg/day filgrastim, up to 4 cycles	310 (154 pegfilgrastim, 156 filgrastim)	50.9 (25-81) pegfilgrastim 51.8 (26-87) filgrastim	306 female, 4 male
990749	Phase 3, double-blind, randomized, filgrastim controlled	6 mg single dose of pegfilgrastim SC or 5 µg/kg/day filgrastim up to 14 days, up to 4 cycles	157 (80 pegfilgrastim, 77 filgrastim)	51.9 (31-75) pegfilgrastim 52.6 (30-74) filgrastim	156 female, 1 male
20010144	Phase 3, double-blind, placebo-controlled, randomized	Pegfilgrastim, 6 mg SC, single dose every 3 weeks, up to 12 weeks	928 (463 pegfilgrastim, 465 placebo)	51.9 (21-88) pegfilgrastim 52.1 (24-76) placebo	99% female

Study results

Clinical Experience: Response to Neulasta[®] (pegfilgrastim)

Neulasta[®] (pegfilgrastim) administered as a single SC injection, after each cycle of chemotherapy, has been shown to be safe and effective in reducing neutropenia and associated clinical sequelae in a variety of chemotherapy settings.

Neulasta[®] has been evaluated in three Phase III, randomized, double-blind, controlled studies. Results from two active controlled studies (n= 467) conducted in patients with breast cancer undergoing up to 4 cycles of chemotherapy with doxorubicin and docetaxel demonstrated non-inferiority of Neulasta[®] to filgrastim. A clinically and statistically similar reduction in the duration of severe neutropenia (absolute neutrophil count [ANC] < 0.5 x 10⁹/L; WHO grade 4) was seen in patients who received a single injection of Neulasta[®], either 6 mg fixed dose⁵ or 100 mcg/kg⁶, compared with patients who received a mean of 11 daily injections (cycle 1) of filgrastim 5 mcg/kg/day.

The mean (std dev) duration of severe neutropenia in cycle 1 in patients who received a single fixed-dose (6 mg) SC injection of Neulasta[®] (n=68) was 1.8 (1.4) days compared with 1.6 (1.1) days in patients who received daily injections (range: 7-14 injections) of filgrastim (n=62). The difference in means was 0.18 days (95% CI of -0.23 to 0.61). Durations of severe neutropenia were also comparable between treatment groups in all subsequent cycles. The rate of febrile neutropenia (temperature ≥ 38.2°C with an ANC < 0.5 x 10⁹/L) across all cycles was lower for

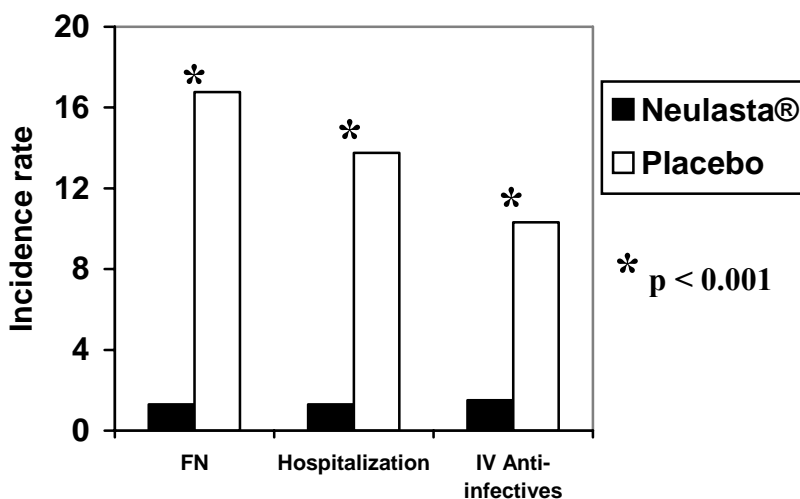
patients receiving Neulasta[®] (13%) compared to patients receiving filgrastim (20%) (-7% difference; 95% CI of -19% to +5%). A single SC injection of Neulasta[®] per chemotherapy cycle was safe and well tolerated (see ADVERSE REACTIONS).

The third study employed a placebo control and evaluated the effect of Neulasta[®] on the incidence of febrile neutropenia when administered in first and all subsequent cycles of a moderately myelosuppressive chemotherapy regimen, docetaxel administered at 100 mg/m² Q3W for 4 cycles, which has been reported to be associated with a febrile neutropenia rate of 10% to 20%.⁷

In this study, 928 patients with metastatic or non-metastatic breast cancer were treated with docetaxel. On day 2 of cycle 1, patients were randomized to receive either a single SC dose of 6 mg of Neulasta[®] or placebo. Patients who received Neulasta[®] in cycle 1 were scheduled to receive Neulasta[®] in all subsequent cycles. Patients who received placebo in cycle 1 were scheduled to receive placebo in all subsequent cycles; however, patients who experienced febrile neutropenia would receive open-label Neulasta[®].

The incidence of febrile neutropenia was statistically significantly lower for patients randomized to receive Neulasta[®] versus placebo (1% versus 17%, $p \leq 0.001$). The incidence of hospitalizations and IV anti-infective use associated with a clinical diagnosis of febrile neutropenia was significantly lower in the Neulasta[®] group compared with placebo [1% versus 14%, $p \leq 0.001$; and 2% versus 10%, $p \leq 0.001$, respectively (see Figure 1)].

Figure 1. Percentage of Subjects With Febrile Neutropenia (FN), Who Were Hospitalized, and Who Received IV Anti-infectives for FN

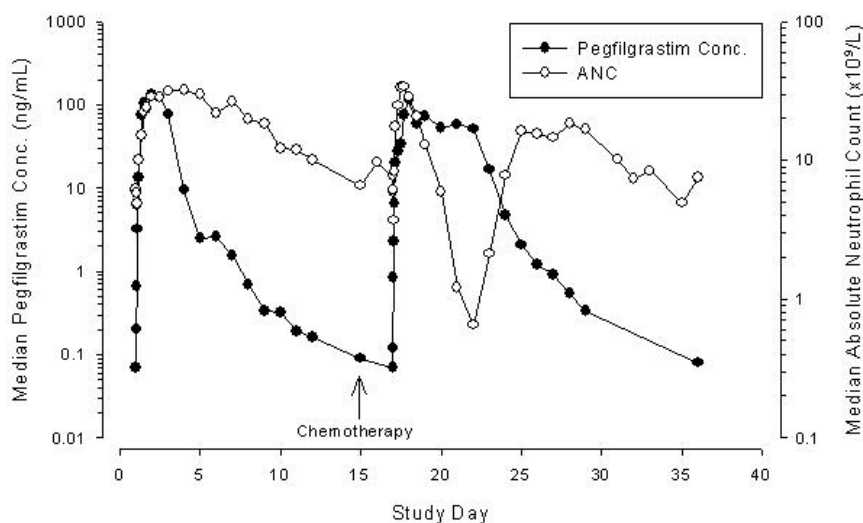


Data from phase II studies in patients with various malignancies undergoing a variety of chemotherapy regimens further support the safety and efficacy of Neulasta[®]. Dose-finding studies in patients with breast cancer (n = 152),⁸ thoracic tumours (n = 92), and non-Hodgkin's lymphoma (NHL) (n = 49) demonstrated that the efficacy of a single injection of Neulasta[®] 100 mcg/kg was similar to daily injections of filgrastim 5 mcg/kg/day, and superior to Neulasta[®] doses of 30 or 60 mcg/kg, at reducing the duration of severe neutropenia and the rate of febrile neutropenia. A randomized phase II study of patients with NHL or Hodgkin's lymphoma (n = 60) further supports the safety and efficacy of Neulasta[®].

DETAILED PHARMACOLOGY

The pharmacokinetics and pharmacodynamics of Neulasta[®] (pegfilgrastim) were studied in patients with cancer. The pharmacokinetics of pegfilgrastim were nonlinear in cancer patients and clearance decreased with increases in dose. Neutrophil-mediated clearance is an important component of the clearance of pegfilgrastim, and serum clearance is related to the number of neutrophils (neutrophil-mediated, self-regulating clearance). Consistent with a self-regulating clearance mechanism, the serum concentration of pegfilgrastim declined rapidly at the onset of neutrophil recovery, following myelosuppressive chemotherapy (see Figure 1).⁴ 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 in cancer patients. The half-life of pegfilgrastim ranged from 25 to 49 hours after SC injection.

Figure 1. Median Neulasta[®] (pegfilgrastim) Serum Concentration and Absolute Neutrophil Count Profiles in Patients With Non-Small Cell Lung Cancer (n = 3) After a Single Injection of Neulasta[®] 100 mcg/kg Administered Before and After Chemotherapy



Pharmacologic Effects of Pegfilgrastim in Animals

Pegfilgrastim has been shown to elevate neutrophil counts in mice, rats, and primates after a single dose, similar to daily doses of filgrastim. The increase in circulating neutrophil levels in response to pegfilgrastim is dose dependent regardless of route of administration (IV or SC). Despite lower bioavailability with SC administration, the pharmacological effect is similar to comparable doses given IV. Pegfilgrastim has been shown to accelerate neutrophil recovery after exposure to various chemotherapeutic agents in animal models, and has been shown to mobilize significant numbers of progenitor cells to the peripheral blood. Dosing with pegfilgrastim either on the same day, or 24 hours after chemotherapy, has been shown to be effective in elevating neutrophil counts in animal models. Compared to filgrastim, daily fluctuations in neutrophil counts in mice are minimized by pegfilgrastim.

TOXICOLOGY

Preclinical Studies

The preclinical toxicology of Neulasta[®] (pegfilgrastim) was studied in Sprague-Dawley[®] rats and cynomolgus monkeys. A single-dose IV study was conducted in rats. Pegfilgrastim caused no clinical signs or mortality at single IV doses up to 10,000 mcg/kg in rats.

Repeat-dose studies included 2-week SC (every-other-day dosing) and 6-month SC/IV (weekly dosing) studies in rats and a 1-month SC (weekly dosing) study in monkeys. Dosing was intermittent to mimic intended human use of Neulasta[®] (pegfilgrastim). Pegfilgrastim was well tolerated for 6 months at once-weekly doses up to 1000 mcg/kg SC or 300 mcg/kg IV in rats, and for 1 month at once-weekly doses up to 750 mcg/kg SC in cynomolgus monkeys. No effects on

body weight, food consumption, or survival were observed. Pegfilgrastim caused an increase in leukocyte counts, primarily segmented neutrophils, but also some increases in band neutrophils, monocytes, and lymphocytes. Pegfilgrastim also modestly decreased erythrocyte counts, hemoglobin and hematocrit levels, decreased serum cholesterol, slightly decreased serum potassium, and increased serum alkaline phosphatase. Splenomegaly was the principal gross pathological finding. Histopathological examination revealed increased neutrophilic granulopoiesis in bone marrow and extramedullary hematopoiesis in spleen, liver, and/or lymph nodes. Leukocytosis in spleen, liver, and lymph nodes, and mild inflammation and mononuclear cell infiltrate at the injection site were additionally observed in monkeys treated with pegfilgrastim. Observed changes tended to reverse upon cessation of treatment. Changes specific to every-other-day dosing in rats (≥ 500 mcg/kg only) included slightly increased serum ALT and/or AST, mild myelofibrosis in bone marrow, and increased osteoblastic/osteoclastic activity in bone. Little or no seroreactivity to pegfilgrastim was evident in rats, whereas a dose- and time-dependent increase in seroreactivity was observed in monkeys; however, pegfilgrastim-induced neutrophil increases were maintained.

Pegfilgrastim has been shown to have adverse effects in pregnant rabbits when given every-other-day at doses as low as 50 mcg/kg. Nonclinical data in pregnant rats indicate that very low levels of pegfilgrastim may cross the placenta.

Pegfilgrastim administered SC to pregnant rabbits at doses of 200 and 250 mcg/kg every-other-day during the period of organogenesis was associated with an increased incidence of abortions. Increased postimplantation loss due to early resorptions and decreased numbers of live fetuses were observed at pegfilgrastim doses of 200 to 1000 mcg/kg every other day. Decreased maternal food consumption and/or weight gain and decreased fetal weight were observed at doses of 50 to 1000 mcg/kg every other day. Pegfilgrastim did not cause visceral or skeletal malformations in rabbit fetuses at doses as high as 200 mcg/kg every-other-day and did not cause external malformations in rabbit fetuses at doses as high as 1000 mcg/kg every other day.

Pegfilgrastim was not associated with an increase in external, visceral, or skeletal malformations in fetuses when administered by SC injection to pregnant rats during the period of organogenesis at dose levels up to 1000 mcg/kg every other day. However, an increased incidence of wavy ribs, generally regarded as a reversible pathological finding, was observed in rat fetuses at dose levels of 300 and 1000 mcg/kg every other day. No maternal or neonatal toxicities were observed in female rats administered once-weekly SC injections of pegfilgrastim up to 1000 mcg/kg in a pre- and postnatal developmental study.

Filgrastim is known to be negative in bacterial mutagenesis assays (Ames assay). Pegfilgrastim did not cause precancerous or cancerous lesions in Sprague-Dawley[®] rats after once-weekly SC injections of up to 1000 mcg/kg for 6 months. Given the similar biochemical activity to filgrastim, the chemical nature of the PEG moiety, and extensive clinical experience with filgrastim, it is considered unlikely that pegfilgrastim would be carcinogenic when used as directed.

Pegfilgrastim is a growth factor that primarily stimulates production of neutrophils and neutrophil precursors; however, the G-CSF receptor through which pegfilgrastim and filgrastim act has been found on tumour cell lines, including some myeloid, T-lymphoid, lung, head and

neck, and bladder tumour cell lines. *In vitro* proliferation has been observed in response to filgrastim in some of these cell lines, particularly acute myeloid leukemia (AML) cell lines.

Indices of mating or fertility in male and female Sprague-Dawley[®] rats were not adversely affected by once-weekly SC injections of pegfilgrastim of up to 1000 mcg/kg for 2 to 4 weeks before and during cohabitation.

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PART III: CONSUMER INFORMATION

Neulasta[®]
(pegfilgrastim)

This leaflet is part III of a three-part "Product Monograph" published when Neulasta[®] was approved for sale in Canada and is designed specifically for Consumers. It provides you (or your caregiver) with information and instructions on how Neulasta[®] injections should be given. It does not tell you everything about Neulasta[®]. Questions about treatment with Neulasta[®] should be discussed with your doctor.

ABOUT THIS MEDICATION**Why have I been prescribed Neulasta[®]?**

Neulasta[®] is used to treat neutropenia (nu-tro-peen-ee-ah). Neutropenia is a condition where the body makes too few white blood cells and which may be caused by drugs used to treat cancer. Neutropenia is the most serious common side-effect of chemotherapy. Neutropenia predisposes your body to infections and prevents you from fighting them. Your doctor has decided to prescribe Neulasta[®] for you to increase the number of neutrophils, which will fight infections.

How does Neulasta[®] work?

Neulasta[®] works by stimulating the bone marrow to make white blood cells. To make sure Neulasta[®] is working, your doctor may ask that you have regular 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[®]?

- People who are allergic to pegfilgrastim (Neulasta[®]), filgrastim (NEUPOGEN[®]), any of the ingredients of Neulasta[®], or to other products made using the bacteria *Escherichia coli* should not take Neulasta[®].
- Make sure your doctor knows about all medications you are taking before starting Neulasta[®] injections. Patients taking lithium may need more frequent blood tests.
- Talk to your doctor if you have any questions about this information.

What is Neulasta[®]?

Neulasta[®], the brandname for pegfilgrastim, is a man-made, long-acting form of granulocyte colony-stimulating factor (G-CSF), a substance naturally produced by the body. It stimulates the growth of a type of white blood cell important in the body's fight against infection, called a neutrophil (**nu**-tro-fil).

Content of Neulasta[®]

Neulasta[®] comes in prefilled syringes containing 6 mg of pegfilgrastim, the active substance. Neulasta[®] also contains sodium acetate, sorbitol, polysorbate 20 and water for injection.

The needle cover on the prefilled syringe contains a derivative of

latex (dry natural rubber). If you know you are allergic to latex, talk to your healthcare provider before using Neulasta[®].

WARNINGS AND PRECAUTIONS**What important information do I need to know about taking Neulasta[®]?**

Your doctor will decide if you are able to give yourself a subcutaneous (i.e., under the skin) injection. Neulasta[®] should only be injected on the day the doctor has determined for you, and should not be injected until 24 hours after receiving your last dose of chemotherapy in each cycle.

(If you are injecting someone else with Neulasta[®], it is important that you inform yourself about Neulasta[®] to know how and when to give the Neulasta[®] injection.)

Neulasta[®] can reduce the risk of infection, but it may not prevent all infections. An infection can still happen during the short time when your white blood cell levels are low. You and your caregivers 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[®], tell your doctor or nurse immediately.

Occasionally a problem 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 your doctor.

Serious allergic reactions can also occur. These reactions may cause a rash over the whole body, shortness of breath, wheezing, a drop in blood pressure (usually causing dizziness or lightheadedness), swelling around the mouth or eyes, fast pulse, or sweating. **If at any time a serious allergic reaction occurs, immediately call a doctor or emergency services (for example, call 911).**

If you have sickle cell anemia, tell your doctor prior to treatment. If you develop left upper abdominal pain or pain at the tip of your shoulder, tell your doctor or nurse immediately.

More information about Neulasta[®] is available in the Product Monograph. Any questions should be discussed with your doctor.

Pregnancy or breast feeding and Neulasta[®]

Neulasta[®] has not been studied in pregnant women, and its effects on developing babies are not known. It is possible that Neulasta[®] 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 consult your doctor before using Neulasta[®].

INTERACTIONS WITH THIS MEDICATION

Drug interactions between Neulasta[®] and other drugs have not been studied. Drugs such as lithium may affect the release of neutrophils into the blood stream. You should discuss your

treatment with your doctor before using Neulasta®.

PROPER USE OF THIS MEDICATION

Usual dose:

The recommended dosage of Neulasta® is a single subcutaneous injection, just under the skin, of 6 mg (the contents of one prefilled syringe), administered once per cycle of chemotherapy. You must wait at least 24 hours after your course of cancer chemotherapy before injecting Neulasta®.

Missed dose:

As there should be a two-week period between Neulasta® and your next course of cancer chemotherapy, if you miss a planned dose, consult your doctor before taking the missed dose.

HOW TO PREPARE AND GIVE A Neulasta® INJECTION

Neulasta® is available in a prefilled syringe. Neulasta® should be stored in its carton to protect it from light until use. If you are giving someone else Neulasta® injections, it is important that you know how to inject Neulasta®.

Before a Neulasta® injection is given, always check to see that:

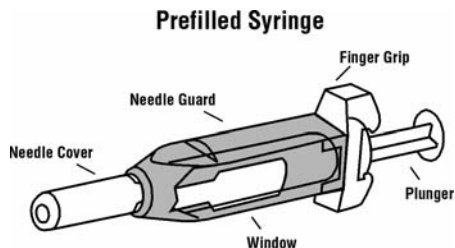
- The name Neulasta® appears on the dispensing pack and prefilled syringe label.
- The expiration date on the prefilled syringe has not passed. You should not use a prefilled syringe after the expiry date on the label.
- The Neulasta® liquid should always be clear and colourless. Do not use Neulasta® if the contents of the prefilled syringe appear discoloured or cloudy, or if the prefilled syringe appears to contain lumps, flakes, or particles.

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

Setting up for an injection

1. Find a comfortable, well-lit working place for injecting Neulasta®.
2. Remove the prefilled syringe of Neulasta® from the refrigerator and check the date on the prefilled syringe to be sure that the Neulasta® has not expired. **Do not use a prefilled syringe of Neulasta® after the date on the label.**
3. Allow Neulasta® to reach room temperature (this takes about 30 minutes). Neulasta® should not be left at room temperature for more than 72 hours. Each prefilled syringe is designed to be used only once. **DO NOT SHAKE THE PREFILLED SYRINGE.** Shaking too hard or for too long may damage the Neulasta®.
4. Assemble the supplies needed for an injection:

- Neulasta® prefilled syringe with transparent (clear) blue plastic needle guard attached.



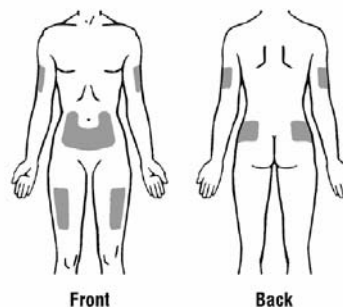
- alcohol swab and a cotton ball or gauze
- puncture-proof disposal container

5. Clean the work area.
6. Wash your hands thoroughly with soap and water before preparing for the injection.

Selecting and preparing the injection site

7. Find a site for injection prior to preparing the prefilled syringe. Alternate the injection site each time you inject Neulasta®. The usual sites for injections are:

- Back of the upper arms
- Abdomen, except for the navel and waist
- Upper thighs



8. Clean the injection site with an alcohol swab. Use a circular motion from the inside to the outside of the injection site.

Preparing the Neulasta® prefilled syringe for injection

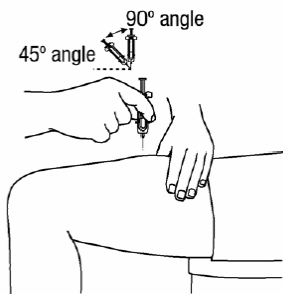
9. Remove the syringe from the package and the tray. Check to see that the plastic blue needle guard is covering the barrel of the syringe. **DO NOT** push the blue needle guard over the needle cover before injection. This may activate or lock the needle guard. If the blue needle guard is covering the needle that means it has been activated. **DO NOT** use that syringe and discard it in the puncture-proof disposal container. Use a new syringe.
10. Hold the syringe with the needle pointing up. Carefully pull the needle cover straight off. Put the syringe needle

cover into the disposal container. Take care not to touch the needle. Holding the syringe with the needle pointing up helps reduce the amount of medicine that may leak out of the needle.

11. Check the syringe for air bubbles. If there are bubbles, hold the syringe with the needle pointing upward and pull back on the plunger slightly to remove any Neulasta[®] that may be inside the needle. Gently tap the syringe until the bubbles rise to the top of the syringe barrel. Then slowly push the plunger, forcing the bubbles but not the liquid out of the syringe.
12. Do not lay the syringe down or allow the needle to touch anything.

Injecting the dose from a Neulasta[®] prefilled syringe

13. Holding the syringe in one hand, use the other hand to pinch a fold of skin at the previously prepared injection site.
NOTE: Hold the syringe barrel through the two needle guard windows when giving the injection.
14. Holding the syringe like a pencil, insert the needle either straight up and down (90 degree angle) or at a slight angle (45 degrees) to the skin.
15. After the needle is in, let go of the skin. Pull the plunger back slightly.



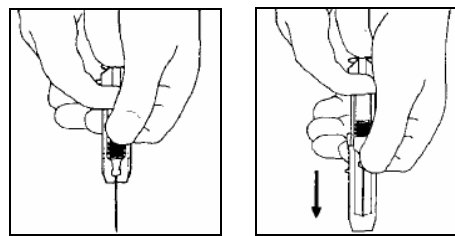
If blood comes into the syringe, do not inject Neulasta[®], because the needle has entered a blood vessel. Withdraw the syringe and discard it. Get a new prefilled syringe and choose a new injection site. Remember to check again for blood before injecting Neulasta[®].

16. If no blood appears, slowly push down on the plunger all the way, until all the medication is gone from the syringe.
17. Pull the needle out of the skin, place the cotton ball or gauze over the injection site, and press for several seconds.

Activating the needle guard on used prefilled syringes

18. After injecting Neulasta[®] from the prefilled syringe, do not recap the needle. Keep your hands behind the needle

at all times. To activate the needle guard, hold the finger grip of the syringe with one hand and grasp the needle guard with your free hand, sliding it completely over the needle until the needle guard clicks into place. **NOTE: If an audible click is not heard, the needle guard may not be completely activated.**



Disposing of syringes and needles

19. Dispose of the entire prefilled syringe as directed by your doctor, or by following these steps:
 - Do not put the needle cover back on the used needle.
 - Place all needle covers and used prefilled syringes in a labeled hard-plastic container with a screw-on cap, or a labeled metal container with a plastic lid, such as a coffee can. 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. When the container is full, tape around the cap or lid and dispose of the container according to your doctor's instructions.
 - Always store the container out of the reach of children.
 - Please check with your doctor, nurse, or pharmacist for instructions on how to properly dispose of the filled container.

Do not throw the container in household trash. Do not recycle.

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

What are possible or reasonably likely side effects of Neulasta[®]?

The most common side effect that you may experience is aching in the bones and muscles. If this occurs, it can usually be relieved with a non-aspirin over-the-counter pain reliever. Ask your doctor which is the most suitable one for you.

Some patients experience redness, swelling, or itching at the site of injection. This may be an allergy to the ingredients in Neulasta[®], or it may be a local reaction. If you notice any of these signs or symptoms, call your doctor.

Serious allergic reactions can also happen. These reactions may cause a rash over the whole body, shortness of breath, wheezing, a drop in blood pressure (usually causing dizziness or lightheadedness), swelling around the mouth or eyes, fast pulse, or sweating. If you experience an allergic reaction during the injection of Neulasta[®], the injection should be stopped immediately. **If at any time a serious allergic reaction occurs,**

immediately call a doctor or emergency services (for example, call 911).

Keep out of reach of children. For any questions about storage, contact your doctor or nurse.

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM

Symptom / effect		Talk with your doctor or pharmacist	
		Only if severe	In all cases
Very Common ≥ 10%	<ul style="list-style-type: none"> Bone Pain 		✓
Rare ≥ 0.01% and <0.1%	<ul style="list-style-type: none"> Allergic reactions (including the following symptoms: rash over the whole body, shortness of breath, a drop in blood pressure (usually causing dizziness or lightheadedness), swelling around the mouth or eyes, fast pulse, weakness, sweating; severe redness or swelling or itching at injection site) 		✓
Very Rare <0.01%	<ul style="list-style-type: none"> Splenic rupture (including the following symptoms: left upper abdominal pain or pain at the tip of your shoulder) 		✓
	<ul style="list-style-type: none"> Acute respiratory distress syndrome (including the following symptoms: fever, shortness of breath, cough, or congestion in your lungs) 		✓

This is not a complete list of side effects. For any unexpected effects while taking Neulasta®, contact your doctor or pharmacist.

HOW TO STORE IT

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. Avoid shaking Neulasta®. If Neulasta® is accidentally frozen, allow it to thaw in the refrigerator before giving the next dose. However, if it is frozen a second time, do not use it and contact your doctor or nurse for further instructions. Neulasta® can be left out at room temperature for up to 72 hours. Protect Neulasta® from light.

REPORTING SUSPECTED SIDE EFFECTS

To monitor drug safety, Health Canada collects information on serious and unexpected effects of drugs. If you suspect you have had a serious or unexpected reaction to this drug you may notify Health Canada by:

toll-free telephone: 866-234-2345
 toll-free fax: 866-678-6789
 By email: cadtmp@hc-sc.gc.ca

By regular mail:
 National AR Centre
 Marketed Health Products Safety and Effectiveness
 Information Division
 Marketed Health Products Directorate
 Tunney's Pasture, AL 0701C
 Ottawa ON K1A 0K9

NOTE: Before contacting Health Canada, you should contact your physician or pharmacist.

MORE INFORMATION

A copy of this document plus the full product monograph, prepared for health professionals, can be attained by contacting the sponsor, Amgen Canada Inc. at: 1-866-502-6436

This leaflet was prepared by Amgen Canada Inc.

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