[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.[1,2] 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®, and no differences were observed in the pharmacokinetics of geriatric patients (≥ 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® was evaluated in three randomized, double-blind, controlled studies. Studies 1 and 2 were active-controlled studies that employed doxorubicin 60 mg/m^2 and docetaxel 75 mg/m^2 administered every 21 days for up to 4 cycles for the treatment of metastatic breast cancer. Study 1 investigated the utility of a fixed dose of Neulasta®. Study 2 employed a weight-adjusted dose. In the absence of growth factor support, similar chemotherapy regimens have been reported to result in a 100% incidence of severe neutropenia (absolute neutrophil count [ANC] < 0.5 x 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® was demonstrated by establishing comparability to Filgrastim-treated patients in the mean days of severe neutropenia.

In Study 1, 157 patients were randomized to receive a single subcutaneous injection of Neulasta® 6 mg on day 2 of each chemotherapy cycle or daily subcutaneous Filgrastim 5 mcg/kg/day beginning on day 2 of each chemotherapy cycle. In Study 2, 310 patients were randomized to receive a single subcutaneous injection of Neulasta® 100 mcg/kg on day 2 or daily subcutaneous Filgrastim 5 mcg/kg/day beginning on day 2 of each chemotherapy cycle.

Both studies met the primary objective of demonstrating that the mean days of severe neutropenia of Neulasta®-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® 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®[a]	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)**

[a] 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^2 administered every 21 days for up to 4 cycles for the treatment of metastatic or non-metastatic breast cancer. In this study, 928 patients were randomized to receive a single subcutaneous injection of Neulasta® 6 mg or placebo on day 2 of each chemotherapy cycle. Study 3 met the primary objective of demonstrating that the incidence of febrile neutropenia (defined as temperature ≥ 38.2°C and ANC ≤ 0.5 x10^9/L) was lower for Neulasta®-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®-treated patients compared with the placebo-treated patients.

INDICATIONS AND USAGE

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

CONTRAINDICATIONS

Neulasta® 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® for peripheral blood progenitor cell (PBPC) mobilization has not been evaluated in adequate and well-controlled studies. Neulasta® should not be used for PBPC mobilization.

Splenic Rupture

RARE CASES OF SPLENIC RUPTURE HAVE BEEN REPORTED FOLLOWING THE ADMINISTRATION OF NEULASTA®. SPLENIC RUPTURE, IN SOME CASES RESULTING IN DEATH, HAS ALSO BEEN ASSOCIATED WITH FILGRASTIM, THE PARENT COMPOUND OF NEULASTA®. PATIENTS RECEIVING NEULASTA® 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®, 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.

Allergic Reactions

Allergic reactions to Neulasta®, 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® 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® 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® for such patients, and only after careful consideration of the potential risks and benefits.

PRECAUTIONS

General

Use With Chemotherapy and/or Radiation Therapy

Neulasta® 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® has not been studied in patients receiving chemotherapy associated with delayed myelosuppression (eg, nitrosoureas, mitomycin C).

The administration of Neulasta® 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® 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® in myeloid malignancies and myelodysplasia (MDS) has not been studied. In a randomized study comparing the effects of the parent compound of Neulasta®, 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.[3]

Information for Patients

Patients should be informed of the possible side effects of Neulasta®, 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® treatment, including regular monitoring of blood counts.

If it is determined that a patient or caregiver can safely and effectively administer Neulasta® (pegfilgrastim) at home, appropriate instruction on the proper use of Neulasta® (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® and other drugs have been performed. Drugs such as lithium may potentiate the release of neutrophils; patients receiving lithium and Neulasta® should have more frequent monitoring of neutrophil counts.

Increased hematopoetic 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® 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® is administered to a nursing woman.

Pediatric Use

The safety and effectiveness of Neulasta® 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® 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® 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® use and for approximating rates.

The data described below reflect exposure to Neulasta® in 932 patients. Neulasta® 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® 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®-treated patients as compared to placebo-treated patients. The incidence of other commonly reported adverse events were similar in the Neulasta®- 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® in the placebo-controlled study.

Table 2. Adverse Events Occurring in ≥ 10%[a] of Patients in the Placebo-Controlled Study.

Event	Neulasta® (n = 467)	Placebo (n = 461)
Alopecia	48%	47%
Bone Pain[b]	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%

[a] *Events occurring in ≥ 10% of Neulasta®-treated patients and at a higher incidence as compared to placebo-treated patients.*

[b] *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®, 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®-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®- and 31% of placebo-treated patients utilized non-narcotic analgesics and 10% of Neulasta®- 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®- and Filgrastim-treated patients. No patient withdrew from study due to bone pain.

Laboratory Abnormalities

In clinical studies, leukocytosis (WBC counts > 100 x 10^9/L) was observed in less than 1% of 932 patients with non-myeloid malignancies receiving Neulasta®. 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®- 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® 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® 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® 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 x 10^9/L, with a corresponding mean maximum WBC of 67 x 10^9/L. The absolute maximum ANC observed was 96 x 10^9/L with a corresponding absolute maximum WBC observed of 120 x 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® is a single subcutaneous injection of 6 mg administered once per chemotherapy cycle. Neulasta® 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® should be visually inspected for discoloration and particulate matter before administration. Neulasta® should not be administered if discoloration or particulates are observed.

For method of administration please see patient package insert.

Storage

Neulasta® 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® may be allowed to reach room temperature for a maximum of 48 hours but should be protected from light. Neulasta® left at room temperature for more than 48 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.

HOW SUPPLIED

Neulasta® 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® Needle Guard.

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

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

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

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