[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 (SC) 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 SC 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). The pharmacokinetic profile in pediatric populations or in patients with hepatic or renal insufficiency has not been assessed.

CLINICAL STUDIES

Neulasta™ was evaluated in two randomized, double-blind, active control studies, employing 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] $< 0.5 \times 10^9$/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™ was demonstrated by establishing comparability to Filgrastim (NEUPOGEN®)-treated subjects in the mean days of severe neutropenia.

In study 1, 157 subjects were randomized to receive a single SC dose of 6 mg of Neulasta™ on day 2 of each chemotherapy cycle or Filgrastim at 5 mcg/kg/day SC beginning on day 2 of each cycle. In study 2, 310 subjects were randomized to receive a single SC injection of Neulasta™ at 100 mcg/kg on day 2 or Filgrastim at 5 mcg/kg/day SC beginning on day 2 of each cycle of chemotherapy.

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]	NEUPOGEN® (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

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.

CONTRAINDICATIONS

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

WARNINGS

Splenic Rupture

RARE CASES OF SPLENIC RUPTURE HAVE BEEN REPORTED FOLLOWING THE ADMINISTRATION OF THE PARENT COMPOUND OF NEULASTAÔ, FILGRASTIM, FOR PBPC MOBILIZATION IN BOTH HEALTHY DONORS AND PATIENTS WITH CANCER. SOME OF THESE CASES WERE FATAL. NEULASTAÔ HAS NOT BEEN EVALUATED IN THIS SETTING, THEREFORE, NEULASTAÔ SHOULD NOT BE USED FOR PBPC MOBILIZATION. PATIENTS RECEIVING NEULASTAÔ WHO REPORT LEFT UPPER ABDOMINAL 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-type reactions, including anaphylaxis, skin rash and urticaria, occurring on initial or subsequent treatment have been reported with the parent compound of Neulasta™, Filgrastim. In some cases, symptoms have recurred with rechallenge, suggesting a causal relationship. Allergic-type reactions to Neulasta™ have not been observed in clinical trials. If a serious allergic reaction or an anaphylactic reaction occurs, appropriate therapy should be administered and further use of Neulasta™ should be discontinued.

Sickle Cell Disease

Severe sickle cell crises have been reported in patients with sickle cell disease (specifically homozygous sickle cell anemia, sickle/hemoglobin C disease, and sickle/ß+ thalassemia) who received Filgrastim, the parent compound of pegfilgrastim, for PBPC mobilization or following chemotherapy. One of these cases was fatal. Pegfilgrastim should be used with caution in patients with sickle cell disease, and only after careful consideration of the potential risks and benefits. Patients with sickle cell disease who receive Neulasta™ should be kept well hydrated and monitored for the occurrence of sickle cell crises. In the event of severe sickle cell crisis supportive care should be administered, and interventions to ameliorate the underlying event, such as therapeutic red blood cell exchange transfusion, should be considered.

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.

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 SC 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 465 subjects with cancer who received Neulasta™ in clinical studies, 85 (18%) were age 65 and over, and 14 (3%) were age 75 and over. No overall differences in

safety or effectiveness were observed between these patients and younger patients; however, due to the small number of elderly subjects, small but clinically relevant differences cannot be excluded.

ADVERSE REACTIONS

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

Safety data are based upon 465 subjects with lymphoma and solid tumors (breast, lung, and thoracic tumors) enrolled in six randomized clinical studies. Subjects received Neulasta™ after nonmyeloablative cytotoxic chemotherapy. Most adverse experiences were attributed by the investigators to the underlying malignancy or cytotoxic chemotherapy and occurred at similar rates in subjects who received Neulasta™ (n = 465) or 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.

The most common adverse event attributed to Neulasta™ in clinical trials was medullary bone pain, reported in 26% of subjects, which was comparable to the incidence in Filgrastim-treated patients. This bone pain was generally reported to be of

mild-to-moderate severity. Approximately 12% 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.

In clinical studies, leukocytosis (WBC counts > 100 x 10^9/L) was observed in less than 1% of 465 subjects with non-myeloid malignancies receiving Neulasta™. Leukocytosis was not associated with any adverse effects.

In subjects receiving Neulasta™ in clinical trials, the only serious event that was not deemed attributable to underlying or concurrent disease, or to concurrent therapy was a case of hypoxia.

Reversible elevations in LDH, alkaline phosphatase, and uric acid, which did not require treatment intervention, were observed. The incidences of these changes, presented for Neulasta™ relative to Filgrastim, were: LDH (19% versus 29%), alkaline phosphatase (9% versus 16%), and uric acid (8% versus 9% [1% of reported cases for both treatment groups were classified as severe]).

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 doses of 300 mcg/kg have been administered SC to 8 normal volunteers and 3 patients with non-small cell lung cancer without serious adverse effects. These subjects 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 (SC) 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.

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

Neulasta™ is supplied in prefilled syringes with UltraSafe® Needle Guards. Following administration of Neulasta™ from the prefilled syringe, the UltraSafe® Needle Guard should be activated to prevent accidental needle sticks. To activate the UltraSafe® Needle Guard, place your hands behind the needle, grasp the guard with one hand, and slide 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. The prefilled syringe should be disposed of by placing the entire prefilled syringe with guard activated into an approved puncture-proof container.

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.

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

REFERENCES

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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.

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