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**BRIEF SUMMARY OF PRESCRIBING INFORMATION**

**INDICATIONS AND USAGE**

Neulasta<sup>®</sup> is indicated to decrease the incidence of infection, as manifested by febrile neutropenia, in patients with nonmyeloid malignancies receiving myelosuppressive antineoplastic drugs associated with a clinically significant incidence of febrile neutropenia.

**CONTRAINDICATIONS**

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

**WARNINGS**

**Splenic Rupture**

**RARE CASES OF SPLENIC RUPTURE HAVE BEEN REPORTED FOLLOWING THE ADMINISTRATION OF THE PARENT COMPOUND OF NEULASTA<sup>®</sup>, FILGRASTIM, FOR PBPC MOBILIZATION IN BOTH HEALTHY DONORS AND PATIENTS WITH CANCER. SOME OF THESE CASES WERE FATAL. NEULASTA<sup>®</sup> HAS NOT BEEN EVALUATED IN THIS SETTING; THEREFORE, NEULASTA<sup>®</sup> SHOULD NOT BE USED FOR PBPC MOBILIZATION. PATIENTS RECEIVING NEULASTA<sup>®</sup> 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<sup>®</sup>, and is postulated to be secondary to an influx of neutrophils to sites of inflammation in the lungs. Neutropenic patients receiving Neulasta<sup>®</sup> who develop fever, lung infiltrates, or respiratory distress should be evaluated for the possibility of ARDS. In the event that ARDS occurs, Neulasta<sup>®</sup> should be discontinued and/or withheld until resolution of ARDS, and patients should receive appropriate medical management for this condition.

**Allergic Reactions**

Allergic-type reactions, including anaphylaxis, skin rash, and arthralgia, occurring on initial or subsequent treatment, have been reported with the parent compound of Neulasta<sup>®</sup>, Filgrastim. In some cases, symptoms have recurred with rechallenge, suggesting a causal relationship. Allergic-type reactions to Neulasta<sup>®</sup> 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<sup>®</sup> 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/β<sup>0</sup>-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<sup>®</sup> 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<sup>®</sup> should not be administered in the period between 14 days before and 24 hours after administration of cytotoxic chemotherapy (see **DOSEAGE AND ADMINISTRATION**) because of the potential for an increase in sensitivity of rapidly dividing myeloid cells to cytotoxic chemotherapy.

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

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

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

**Potential Effect on Malignant Cells**

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

**Information for Patients**

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

If it is determined that a patient or caregiver can safely and effectively administer Neulasta<sup>®</sup> at home, appropriate instruction on the proper use of Neulasta<sup>®</sup> 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 hemoglobin value and platelet count is recommended.

**Drug Interaction**

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

**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 at 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 preneoplastic 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.

**Neulasta<sup>®</sup> (pegfilgrastim)**

**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 (about 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 at 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 at lactation of doses up to 1000 mcg/kg/dose did not result in any adverse maternal effects. There were no deleterious effects on the growth and development of the offspring, and no adverse effects were found upon assessment of fertility indices.

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

**Nursing Mothers**

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

**Pediatric Use**

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

**Geriatric Use**

Of the 465 subjects with cancer who received Neulasta<sup>®</sup> in clinical studies, 65 (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<sup>®</sup> after nonmyeloblastic 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<sup>®</sup> (n = 400) or Filgrastim (n = 331). These adverse experiences occurred at rates between 72% and 75% 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, glossocytopenia, stomatitis, mucositis, and neutropenic fever.

The most common adverse event attributed to Neulasta<sup>®</sup> in clinical trials was mediastinal 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 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<sup>9</sup>/L) was observed in less than 1% of 465 subjects with nonmyeloid malignancies receiving Neulasta<sup>®</sup>. Leukocytosis was not associated with any adverse effects.

In subjects receiving Neulasta<sup>®</sup> 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 hypotension.

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<sup>®</sup> relative to Filgrastim, were as follows: LDH (18% vs 29%), alkaline phosphatase (25% vs 16%), and uric acid (8% vs 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<sup>®</sup> has not been adequately determined. While available data suggest that a small proportion of patients developed binding antibodies to Filgrastim or pegfilgrastim, the nature and specificity of these antibodies have not been adequately studied. No neutralizing antibodies have been detected using a cell-based bioassay in 46 patients who apparently developed binding antibodies. The detection of antibody formation is highly dependent on the sensitivity and specificity of the assay, and the observed incidence of antibody positivity in an assay may be influenced by several factors, including sample handling, concomitant medications, and underlying disease. Therefore, comparison of the incidence of antibodies to Neulasta<sup>®</sup> with the incidence of antibodies to other products may be misleading.

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

**OVERDOSAGE**

The maximum amount of Neulasta<sup>®</sup> that can be safely administered in single or multiple doses has not been determined. Single doses of 300 mcg/kg have been administered SC to 6 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<sup>9</sup>/L with a corresponding mean maximum WBC of 67 x 10<sup>9</sup>/L. The absolute maximum ANC observed was 96 x 10<sup>9</sup>/L, with a corresponding absolute maximum WBC observed of 120 x 10<sup>9</sup>/L. The duration of leukocytosis ranged from 6 to 13 days. Leukopenias should be considered in the management of symptomatic individuals.

**DOSEAGE AND ADMINISTRATION**

The recommended dosage of Neulasta<sup>®</sup> is a single SC injection of 6 mg administered once per chemotherapy cycle. Neulasta<sup>®</sup> should not be administered in the period between 14 days before and 24 hours after administration of cytotoxic chemotherapy (see **PRECAUTIONS**). The 6 mg fixed-dose formulation should not be used in infants, children, and smaller adolescents weighing less than 45 kg.

**REFERENCE**

\*Hill G, Hoelzer D, Sazci 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;90:4710-4716.



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