BOXED WARNING

Allergic Reactions Including Anaphylaxis

Neumega has caused allergic or hypersensitivity reactions, including anaphylaxis. Administration of Neumega should be permanently discontinued in any patient who develops an allergic or hypersensitivity reaction (see WARNINGS, CONTRAINDICATIONS, ADVERSE REACTIONS and ADVERSE REACTIONS, Immunogenicity).

DESCRIPTION

Interleukin eleven (IL-11) is a thrombopoietic growth factor that directly stimulates the proliferation of hematopoietic stem cells and megakaryocyte progenitor cells and induces megakaryocyte maturation resulting in increased platelet production. IL-11 is a member of a family of human growth factors which includes human growth hormone, granulocyte colony-stimulating factor (G-CSF), and other growth factors.

Oprelvekin, the active ingredient in Neumega, is produced in Escherichia coli (E. coli) by recombinant DNA technology. The protein has a molecular mass of approximately 19,000 daltons, and is non-glycosylated. The polypeptide is 177 amino acids in length and differs from the 178 amino acid length of native IL-11 only in lacking the amino-terminal proline residue. This alteration has not resulted in measurable differences in bioactivity either in vitro or in vivo.

Neumega is formulated in single-use vials containing 5 mg of oprelvekin (specific activity approximately $8 \times 10^6$ Units/mg) as a sterile, lyophilized powder with 23 mg Glycine, USP, 1.6 mg Dibasic Sodium Phosphate Heptahydrate, USP, and 0.55 mg Monobasic Sodium Phosphate Monohydrate, USP. When reconstituted with 1 mL of Sterile Water for Injection, USP, the resulting solution has a pH of 7.0 and a concentration of 5 mg/mL.

CLINICAL PHARMACOLOGY

The primary hematopoietic activity of Neumega is stimulation of megakaryocytopoiesis and thrombopoiesis. Neumega has shown potent thrombopoietic activity in animal models of compromised hematopoiesis, including moderately to severely myelosuppressed mice and nonhuman primates. In these models, Neumega improved platelet nadirs and accelerated platelet recoveries compared to controls.

Preclinical trials have shown that mature megakaryocytes which develop during in vivo treatment with Neumega are ultrastructurally normal. Platelets produced in response to Neumega were morphologically and functionally normal and possessed a normal life span.
IL-11 has also been shown to have non-hematopoietic activities in animals including the regulation of intestinal epithelium growth (enhanced healing of gastrointestinal lesions), the inhibition of adipogenesis, the induction of acute phase protein synthesis, inhibition of pro-inflammatory cytokine production by macrophages, and the stimulation of osteoclastogenesis and neurogenesis. Non-hematopoietic pathologic changes observed in animals include fibrosis of tendons and joint capsules, periosteal thickening, papilledema, and embryotoxicity (see PRECAUTIONS, Pediatric Use and PRECAUTIONS, Pregnancy Category C).

IL-11 is produced by bone marrow stromal cells and is part of the cytokine family that shares the gp130 signal transducer. Primary osteoblasts and mature osteoclasts express mRNAs for both IL-11 receptor (IL-11R alpha) and gp130. Both bone-forming and bone-resorbing cells are potential targets of IL-11. (1)

Pharmacokinetics

The pharmacokinetics of Neumega have been evaluated in studies of healthy, adult subjects and cancer patients receiving chemotherapy. In a study in which a single 50 µg/kg subcutaneous dose was administered to eighteen healthy men, the peak serum concentration (Cmax) of 17.4 ± 5.4 ng/mL (mean ± S.D.) was reached at 3.2 ± 2.4 hrs (Tmax) following dosing. The terminal half-life was 6.9 ± 1.7 hrs. In a second study in which single 75 µg/kg subcutaneous and intravenous doses were administered to twenty-four healthy subjects, the pharmacokinetic profiles were similar between men and women. The absolute bioavailability of Neumega was >80%. In a study in which multiple, subcutaneous doses of both 25 and 50 µg/kg were administered to cancer patients receiving chemotherapy, Neumega did not accumulate and clearance of Neumega was not impaired following multiple doses.

In a dose escalation Phase 1 study, Neumega was also administered to 43 pediatric (ages 8 months to 18 years) and 1 adult patient receiving ICE (ifosfamide, carboplatin, etoposide) chemotherapy. Administered doses ranged from 25 to 125 µg/kg. Analysis of data from 40 pediatric patients showed that Cmax and Tmax, and terminal half-life were comparable to that in adults. The mean area under the concentration-time curve (AUC) for pediatric patients (8 months to 12 years), receiving 50 µg/kg was approximately half that achieved in healthy adults receiving 50 µg/kg. Available data suggest that clearance of IL-11 decreases with increasing age.

In preclinical trials in rats, radiolabeled Neumega was rapidly cleared from the serum and distributed to highly perfused organs. The kidney was the primary route of elimination. The amount of intact Neumega in urine was low, indicating that the molecule was metabolized before excretion. In a clinical study, a single dose of Neumega was administered to subjects with severely impaired renal function (creatinine clearance <15 mL/min). The mean ± S.D. values for Cmax and AUC were 30.8 ± 8.6 ng/mL and 373 ± 106 ng·hr/mL, respectively. When compared with control subjects in this study with normal renal function, the mean Cmax was 2.2 fold higher and the mean AUC was 2.6 fold (95% confidence interval, 1.7%-3.8%) higher in the subjects with severe renal impairment. In the subjects with severe renal impairment,
clearance was approximately 40% of the value seen in subjects with normal renal function. The average terminal half-life was similar in subjects with severe renal impairment and those with normal renal function.

**Pharmacodynamics**

In a study in which Neumega was administered to non-myelosuppressed cancer patients, daily subcutaneous dosing for 14 days with Neumega increased the platelet count in a dose-dependent manner. Platelet counts began to increase relative to baseline between 5 and 9 days after the start of dosing with Neumega. After cessation of treatment, platelet counts continued to increase for up to 7 days then returned toward baseline within 14 days. No change in platelet reactivity as measured by platelet activation in response to ADP, and platelet aggregation in response to ADP, epinephrine, collagen, ristocetin and arachidonic acid has been observed in association with Neumega treatment.

In a randomized, double-blind, placebo-controlled study in normal volunteers, subjects receiving Neumega had a mean increase in plasma volume of >20%, and all subjects receiving Neumega had at least a 10% increase in plasma volume. Red blood cell volume decreased similarly (due to repeated phlebotomy) in the Neumega and placebo groups. As a result, whole blood volume increased approximately 10% and hemoglobin concentration decreased approximately 10% in subjects receiving Neumega compared with subjects receiving placebo. Mean 24 hour sodium excretion decreased, and potassium excretion did not increase, in subjects receiving Neumega compared with subjects receiving placebo.

**CLINICAL STUDIES**

Two randomized, double-blind, placebo-controlled trials in adults studied Neumega for the prevention of severe thrombocytopenia following single or repeated sequential cycles of various myelosuppressive chemotherapy regimens.

One study evaluated the effectiveness of Neumega in eliminating the need for platelet transfusions in patients who had recovered from an episode of severe chemotherapy-induced thrombocytopenia (defined as a platelet count =20,000/µL), and were to receive one additional cycle of the same chemotherapy without dose reduction. Patients had various underlying non-myeloid malignancies, and were undergoing dose-intensive chemotherapy with a variety of regimens. Patients were randomized to receive Neumega at a dose of 25 µg/kg or 50 µg/kg, or placebo. The primary endpoint was whether the patient required one or more platelet transfusions in the subsequent chemotherapy cycle. Ninety-three patients were randomized. Five patients withdrew from the study prior to receiving study drug. As a result, eighty-eight patients were included in a modified intent-to-treat analysis. The results for the Neumega 50 µg/kg and placebo groups are summarized in Table 1. The placebo group includes one patient who underwent chemotherapy dose reduction and who avoided platelet transfusions.

**TABLE 1**
In the primary efficacy analysis, more patients avoided platelet transfusion in the Neumega 50 µg/kg arm than in the placebo arm (p = 0.04, Fisher’s Exact test, 2-tailed). The difference in the proportion of patients avoiding platelet transfusions in the Neumega 50 µg/kg and placebo groups was 21% (95% confidence interval, 2%-40%). The results observed in patients receiving 25 µg/kg of Neumega were intermediate between those of the placebo and the 50 µg/kg groups.

A second study evaluated the effectiveness of Neumega in eliminating platelet transfusions over two dose-intensive chemotherapy cycles in breast cancer patients who had not previously experienced severe chemotherapy-induced thrombocytopenia. All patients received the same chemotherapy regimen (cyclophosphamide 3,200 mg/m² and doxorubicin 75 mg/m²). All patients received concomitant filgrastim (G-CSF) in all cycles. The patients were stratified by whether or not they had received prior chemotherapy, and randomized to receive Neumega 50 µg/kg or placebo. The primary endpoint was whether or not a patient required one or more platelet transfusions in the two study cycles. Seventy-seven patients were randomized. Thirteen patients failed to complete both study cycles—eight of these had insufficient data to be evaluated for the primary endpoint. The results of this trial are summarized in Table 2.

<table>
<thead>
<tr>
<th>STUDY RESULTS</th>
<th>Placebo n=30</th>
<th>Neumega 50 µg/kg n=29</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number (%) of patients avoiding platelet transfusion</td>
<td>2 (7%)</td>
<td>8 (28%)</td>
</tr>
<tr>
<td>Number (%) of patients requiring platelet transfusion</td>
<td>28 (93%)</td>
<td>21 (72%)</td>
</tr>
<tr>
<td>Median (mean) number of platelet transfusion events</td>
<td>2.5 (3.3)</td>
<td>1 (2.2)</td>
</tr>
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</table>

### TABLE 2

<table>
<thead>
<tr>
<th>STUDY RESULTS</th>
<th>Overall n=77</th>
<th>No Prior Chemotherapy n=54</th>
<th>Prior Chemotherapy n=23</th>
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<tbody>
<tr>
<td>Placebo n=37</td>
<td>Neumega n=40</td>
<td>Placebo n=27</td>
<td>Neumega n=27</td>
</tr>
<tr>
<td>Number (%) of patients avoiding platelet transfusion</td>
<td>15 (41%)</td>
<td>26 (65%)</td>
<td>14 (52%)</td>
</tr>
<tr>
<td>Number (%) of patients requiring platelet transfusion</td>
<td>16 (43%)</td>
<td>12 (30%)</td>
<td>9 (33%)</td>
</tr>
<tr>
<td>Number (%) of patients not evaluable</td>
<td>6 (16%)</td>
<td>2 (5%)</td>
<td>4 (15%)</td>
</tr>
</tbody>
</table>
This study showed a trend in favor of Neumega, particularly in the subgroup of patients with prior chemotherapy. Open-label treatment with Neumega has been continued for up to four consecutive chemotherapy cycles without evidence of any adverse effect on the rate of neutrophil recovery or red blood cell transfusion requirements. Some patients continued to maintain platelet nadirs >20,000/µL for at least four sequential cycles of chemotherapy without the need for transfusions, chemotherapy dose reduction, or changes in treatment schedules.

Platelet activation trials done on a limited number of patients showed no evidence of abnormal spontaneous platelet activation, or an abnormal response to ADP. In an unblinded, retrospective analysis of the two placebo-controlled studies, 19 of 69 patients (28%) receiving Neumega 50 µg/kg and 34 of 67 patients (51%) receiving placebo reported at least one hemorrhagic adverse event which involved bleeding.

In a randomized, double-blind, placebo-controlled, Phase 2 study conducted in patients who received autologous bone marrow transplantation following myeloablative chemotherapy, the incidence of platelet transfusions and time to neutrophil and platelet engraftment were similar in the Neumega and placebo-treated arms.

In long term follow-up of patients, the distribution of survival and progression-free survival times was similar between patients randomized to Neumega therapy and those randomized to receive placebo.

**INDICATIONS AND USAGE**

Neumega is indicated for the prevention of severe thrombocytopenia and the reduction of the need for platelet transfusions following myelosuppressive chemotherapy in adult patients with nonmyeloid malignancies who are at high risk of severe thrombocytopenia. Efficacy was demonstrated in patients who had experienced severe thrombocytopenia following the previous chemotherapy cycle. Neumega is not indicated following myeloablative chemotherapy. The safety and effectiveness of Neumega have not been established in pediatric patients.

**CONTRAINDICATIONS**

Neumega is contraindicated in patients with a history of hypersensitivity to Neumega or any component of the product (see **WARNINGS, Allergic Reactions Including Anaphylaxis**).

**WARNINGS**

**Allergic Reactions Including Anaphylaxis**

In the post-marketing setting, Neumega has caused allergic or hypersensitivity reactions, including anaphylaxis. The administration of Neumega should be attended by appropriate precautions in case allergic reactions occur. In addition, patients should be counseled about the symptoms for which they should seek medical attention. (see **PRECAUTIONS, Information for Patients**). Signs and symptoms reported included fever, rash, urticaria, shortness of breath, hypotension, flushing, facial edema, edema of the tongue, laryngeal edema, and mental status changes. Reactions occurred after the first dose or subsequent doses of Neumega.
Administration of Neumega should be permanently discontinued in any patient who develops an allergic or hypersensitivity reaction (see BOXED WARNING, CONTRAINDICATIONS, ADVERSE REACTIONS, and ADVERSE REACTIONS, Immunogenicity).

**Fluid Retention**

Neumega is known to cause serious fluid retention that can result in peripheral edema, dyspnea on exertion, pulmonary edema, capillary leak syndrome, atrial arrhythmias, and exacerbation of pre-existing pleural effusions. (see CLINICAL PHARMACOLOGY; Pharmacodynamics, WARNINGS, Cardiovascular Events; and WARNINGS, Dilutional Anemia). It should be used with caution in patients with clinically evident congestive heart failure, patients who may be susceptible to developing congestive heart failure, patients receiving aggressive hydration, patients with a history of heart failure who are well-compensated and receiving appropriate medical therapy, and patients who may develop fluid retention as a result of associated medical conditions or whose medical condition may be exacerbated by fluid retention.

Fluid retention is reversible within several days following discontinuation of Neumega. During dosing with Neumega, fluid balance should be monitored and appropriate medical management is advised.

Close monitoring of fluid and electrolyte status should be performed in patients receiving chronic diuretic therapy. Sudden deaths have occurred in oprelvekin-treated patients receiving chronic diuretic therapy and ifosfamide who developed severe hypokalemia (see ADVERSE REACTIONS).

Pre-existing fluid collections, including pericardial effusions or ascites, should be monitored. Drainage should be considered if medically indicated.

**Dilutional Anemia**

Moderate decreases in hemoglobin concentration, hematocrit, and red blood cell count (~10% to 15%) without a decrease in red blood cell mass have been observed. These changes are predominantly due to an increase in plasma volume (dilutional anemia) that is primarily related to renal sodium and water retention. The decrease in hemoglobin concentration typically begins within 3 to 5 days of the initiation of Neumega, and is reversible over approximately a week following discontinuation of Neumega (see WARNINGS, Fluid Retention).

**Cardiovascular Events**

Neumega use is associated with cardiovascular events including arrhythmias and pulmonary edema. Cardiac arrest has been reported, but the causal relationship to Neumega is uncertain. Use with caution in patients with a history of atrial arrhythmias, and only after consideration of the potential risks in relation to anticipated benefit. In clinical trials, cardiac events including atrial arrhythmias (atrial fibrillation or atrial flutter) occurred in 15% (23/157) of patients treated with Neumega at doses of 50 µg/kg. Arrhythmias were usually brief in duration; conversion to sinus rhythm typically occurred spontaneously or after rate-control drug therapy. Approximately one-
half (11/24) of the patients who were rechallenged had recurrent atrial arrhythmias. Clinical sequelae, including stroke, have been reported in patients who experienced atrial arrhythmias while receiving Neumega.

The mechanism for induction of arrhythmias is not known. Neumega was not directly arrhythmogenic in animal models. In some patients, development of atrial arrhythmias may be due to increased plasma volume associated with fluid retention (see WARNINGS, Fluid Retention).

Nervous System Events
Stroke has been reported in the setting of patients who develop atrial fibrillation/flutter while receiving Neumega (see WARNINGS, Cardiovascular Events). Patients with a history of stroke or transient ischemic attack may also be at increased risk for these events.

Papilledema
Papilledema has been reported in 2% (10/405) of patients receiving Neumega in clinical trials following repeated cycles of exposure. The incidence was higher 16% (7/43) in children than in adults, 1% (3/362). Nonhuman primates treated with Neumega at a dose of 1,000 µg/kg SC once daily for 4 to 13 weeks developed papilledema that was not associated with inflammation or any other histologic abnormality and was reversible after dosing was discontinued. Neumega should be used with caution in patients with pre-existing papilledema, or with tumors involving the central nervous system since it is possible that papilledema could worsen or develop during treatment (see ADVERSE REACTIONS).

PRECAUTIONS
General
Dosing with Neumega should begin 6 to 24 hours following the completion of chemotherapy dosing. The safety and efficacy of Neumega given immediately prior to or concurrently with cytotoxic chemotherapy or initiated at the time of expected nadir have not been established (see DOSAGE AND ADMINISTRATION).

The effectiveness of Neumega has not been evaluated in patients receiving chemotherapy regimens of greater than 5 days duration or regimens associated with delayed myelosuppression (eg, nitrosoureas, mitomycin-C).

Chronic Administration
Neumega has been administered safely using the recommended dosage schedule (see DOSAGE AND ADMINISTRATION) for up to 6 cycles following chemotherapy. The safety and efficacy of chronic administration of Neumega have not been established. Continuous dosage (2 to 13 weeks) in nonhuman primates produced joint capsule and tendon fibrosis and periosteal hyperostosis (see PRECAUTIONS, Pediatric Use). The relevance of these findings to humans is unclear.
Information for Patients

In situations when the physician determines that Neumega may be used outside of the hospital or office setting, persons who will be administering Neumega should be instructed as to the proper dose, and the method for reconstituting and administering Neumega (see DOSAGE AND ADMINISTRATION). If home use is prescribed, patients should be instructed in the importance of proper disposal and cautioned against the reuse of needles, syringes, drug product, and diluent. A puncture resistant container should be used by the patient for the disposal of used needles.

Patients should be informed of the most common adverse reactions associated with Neumega administration, including those symptoms related to fluid retention (see ADVERSE REACTIONS and WARNINGS). Mild to moderate peripheral edema and shortness of breath on exertion can occur within the first week of treatment and may continue for the duration of administration of Neumega. Patients who have preexisting pleural or other effusions or a history of congestive heart failure should be advised to contact their physician for worsening of dyspnea. Most patients who receive Neumega develop anemia. Patients should be advised to contact their physician if symptoms attributable to atrial arrhythmia develop. Female patients of childbearing potential should be advised of the possible risks to the fetus of Neumega (see PRECAUTIONS, Pregnancy Category C).

Laboratory Monitoring

A complete blood count should be obtained prior to chemotherapy and at regular intervals during Neumega therapy (see DOSAGE AND ADMINISTRATION). Platelet counts should be monitored during the time of the expected nadir and until adequate recovery has occurred (post-nadir counts =50,000/µL).

Drug Interactions

Most patients in trials evaluating Neumega were treated concomitantly with filgrastim (G-CSF) with no adverse effect of Neumega on the activity of G-CSF. No information is available on the clinical use of sargramostim (GM-CSF) with Neumega in human subjects. However, in a study in nonhuman primates in which Neumega and GM-CSF were coadministered, there were no adverse interactions between Neumega and GM-CSF and no apparent difference in the pharmacokinetic profile of Neumega.

Drug interactions between Neumega and other drugs have not been fully evaluated. Based on in vitro and nonclinical in vivo evaluations of Neumega, drug-drug interactions with known substrates of P450 enzymes would not be predicted.

Carcinogenesis, Mutagenesis, Impairment of Fertility

No trials have been performed to assess the carcinogenic potential of Neumega. In vitro, Neumega did not stimulate the growth of tumor colony-forming cells harvested from patients with a variety of human malignancies. Neumega has been shown to be non-genotoxic in in vitro trials. These data suggest that Neumega is not mutagenic. Although prolonged estrus cycles

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have been noted at 2 to 20 times the human dose, no effects on fertility have been observed in rats treated with Neumega at doses up to 1000 µg/kg/day.

**Pregnancy Category C**
Neumega has been shown to have embryocidal effects in pregnant rats and rabbits when given in doses of 0.2 to 20 times the human dose. There are no adequate and well-controlled studies of Neumega in pregnant women. Neumega should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Neumega has been tested in studies of fertility, early embryonic development, and pre and postnatal development in rats and in studies of organogenesis (teratogenicity) in rats and rabbits.

Parental toxicity has been observed when Neumega is given at doses of 2 to 20 times the human dose (=100 µg/kg/day) in the rat and at 0.02 to 2.0 times the human dose (=1 µg/kg/day) in the rabbit. Findings in pregnant rats consisted of transient hypoactivity and dyspnea after administration (maternal toxicity), as well as prolonged estrus cycle, increased early embryonic deaths and decreased numbers of live fetuses. In addition, low fetal body weights and a reduced number of ossified sacral and caudal vertebrae (ie, retarded fetal development) occurred in rats at 20 times the human dose. Findings in pregnant rabbits consisted of decreased fecal/urine eliminations (the only toxicity noted at 1 µg/kg/day in dams) as well as decreased food consumption, body weight loss, abortion, increased embryonic and fetal deaths, and decreased numbers of live fetuses. No teratogenic effects of Neumega were observed in rabbits at doses up to 0.6 times the human dose (30 µg/kg/day).

Adverse effects in the first generation offspring of rats given Neumega at maternally toxic doses =2 times the human dose (=100 µg/kg/day) during both gestation and lactation included increased newborn mortality, decreased viability index on day 4 of lactation, and decreased body weights during lactation. In rats given 20 times the human dose (1000 µg/kg/day) during both gestation and lactation, maternal toxicity and growth retardation of the first generation offspring resulted in an increased rate of fetal death of the second generation offspring.

**Nursing Mothers**
It is not known if Neumega is excreted in human milk. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from Neumega, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

**Pediatric Use**
A safe and effective dose of Neumega has not been established in children. In a Phase 1, single arm, dose-escalation study, 43 pediatric patients were treated with Neumega at doses ranging from 25 to 125 µg/kg/day following ICE chemotherapy. All patients required platelet transfusions and the lack of a comparator arm made the study design inadequate to assess efficacy. The projected effective dose (based on comparable AUC observed for the effective dose in healthy adults) in children appears to exceed the maximum tolerated pediatric dose of...
50 µg/kg/day (see CLINICAL PHARMACOLOGY, Pharmacokinetics). Papilledema was dose-limiting and occurred in 16% of children (see WARNINGS, Papilledema).

The most common adverse events seen in pediatric studies included tachycardia (84%), conjunctival injection (58%), radiographic and echocardiographic evidence of cardiomegaly (21%) and periosteal changes (11%). These events occurred at a higher frequency in children than adults. The incidence of other adverse events were generally similar to those observed using Neumega at a dose of 50 µg/kg in the randomized studies in adults receiving chemotherapy (see ADVERSE REACTIONS).

Studies in animals were predictive of the effect of Neumega on developing bone in children. In growing rodents treated with 100, 300, or 1000 µg/kg/day for a minimum of 28 days, thickening of femoral and tibial growth plates was noted, which did not completely resolve after a 28-day non-treatment period. In a nonhuman primate toxicology study of Neumega, animals treated for 2 to 13 weeks at doses of 10 to 1000 µg/kg showed partially reversible joint capsule and tendon fibrosis and periosteal hyperostosis. An asymptomatic, laminated periosteal reaction in the diaphyses of the femur, tibia, and fibula has been observed in one patient during pediatric studies involving multiple courses of Neumega treatment. The relationship of these findings to treatment with Neumega is unclear. No studies have been performed to assess the long-term effects of Neumega on growth and development.

Use in Patients with Renal Impairment

Neumega is eliminated primarily by the kidneys. The pharmacokinetics of Neumega have not been studied in patients with mild or moderate renal impairment (creatinine clearance =15 mL/min). Fluid retention associated with Neumega treatment has not been studied in patients with renal impairment, but fluid balance should be carefully monitored in these patients (see WARNINGS, Fluid Retention).

ADVERSE REACTIONS

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical studies of a drug cannot be directly compared to rates in the clinical studies of another drug 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 drug use and for approximating rates.

Three hundred twenty-four subjects, with ages ranging from 8 months to 75 years, have been exposed to Neumega treatment in clinical studies. Subjects have received up to six (eight in pediatric patients) sequential courses of Neumega treatment, with each course lasting from 1 to 28 days. Apart from the sequelae of the underlying malignancy or cytotoxic chemotherapy, most adverse events were mild or moderate in severity and reversible after discontinuation of Neumega dosing.
In general, the incidence and type of adverse events were similar between Neumega 50 µg/kg and placebo groups. The most frequently reported serious adverse events were neutropenic fever, syncope, atrial fibrillation, fever and pneumonia. The most commonly reported adverse events were edema, dyspnea, tachycardia, conjunctival injection, palpitations, atrial arrhythmias, and pleural effusions. The most commonly reported adverse reactions resulting in clinical intervention (eg, discontinuation of Neumega, adjustment in dosage, or the need for concomitant medication to treat an adverse reaction symptom) were atrial arrhythmias, syncope, dyspnea, congestive heart failure, and pulmonary edema. Selected adverse events that occurred in ≥10% of Neumega-treated patients are listed in Table 3.

### TABLE 3
**SELECTED ADVERSE EVENTS**

<table>
<thead>
<tr>
<th>Body System</th>
<th>Adverse Event</th>
<th>Placebo n=67 (%)</th>
<th>50 µg/kg n=69 (%)</th>
<th>Body System</th>
<th>Adverse Event</th>
<th>Placebo n=67 (%)</th>
<th>50 µg/kg n=69 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Body as a Whole</td>
<td>Edema</td>
<td>10 (15)</td>
<td>41 (59)</td>
<td>Nervous System</td>
<td>Dizziness</td>
<td>19 (28)</td>
<td>26 (38)</td>
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<tr>
<td></td>
<td>Neutropenic fever</td>
<td>28 (42)</td>
<td>33 (48)</td>
<td>Insomnia</td>
<td>18 (27)</td>
<td>23 (33)</td>
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<tr>
<td></td>
<td>Headache</td>
<td>24 (36)</td>
<td>28 (41)</td>
<td>Respiratory System</td>
<td>Dyspnea*</td>
<td>15 (22)</td>
<td>33 (48)</td>
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<tr>
<td></td>
<td>Fever</td>
<td>19 (28)</td>
<td>25 (36)</td>
<td>Rhinitis</td>
<td>21 (31)</td>
<td>29 (42)</td>
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<tr>
<td>Cardiovascular System</td>
<td>Tachycardia*</td>
<td>2 (3)</td>
<td>14 (20)</td>
<td>Cough increased</td>
<td>15 (22)</td>
<td>20 (29)</td>
<td></td>
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<tr>
<td></td>
<td>Vasodilatation</td>
<td>6 (9)</td>
<td>13 (19)</td>
<td>Pharyngitis</td>
<td>11 (16)</td>
<td>17 (25)</td>
<td></td>
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<td></td>
<td>Palpitations*</td>
<td>2 (3)</td>
<td>10 (14)</td>
<td>Pleural effusions</td>
<td>0 (0)</td>
<td>7 (10)</td>
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<td></td>
<td>Syncope</td>
<td>4 (6)</td>
<td>9 (13)</td>
<td>Skin and Appendages</td>
<td>11 (16)</td>
<td>17 (25)</td>
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<tr>
<td></td>
<td>Atrial</td>
<td>1 (1)</td>
<td>8 (12)</td>
<td>Rash</td>
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<td></td>
<td></td>
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<td></td>
<td>Special Senses</td>
<td>2 (3)</td>
<td>13 (19)</td>
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<tr>
<td>Digestive System</td>
<td>Nausea/vomiting</td>
<td>47 (70)</td>
<td>53 (77)</td>
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<tr>
<td></td>
<td>Mucositis</td>
<td>25 (37)</td>
<td>30 (43)</td>
<td>Conjunctival injection</td>
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<tr>
<td></td>
<td>Diarrhea</td>
<td>22 (33)</td>
<td>30 (43)</td>
<td></td>
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<tr>
<td></td>
<td>Oral moniliasis*</td>
<td>1 (1)</td>
<td>10 (14)</td>
<td></td>
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<td></td>
</tr>
</tbody>
</table>

*Occurred in significantly more Neumega-treated patients than in placebo-treated patients.

The following adverse events also occurred more frequently in cancer patients receiving Neumega than in those receiving placebo: amblyopia, paresthesia, dehydration, skin discoloration, exfoliative dermatitis, and eye hemorrhage; a statistically significant association of Neumega to these events has not been established. Other than a higher incidence of severe asthenia in Neumega treated patients (10 [14%] in Neumega patients versus 2 [3%] in placebo patients), the incidence of severe or life-threatening adverse events was comparable in the Neumega and placebo treatment groups.

Two patients with cancer treated with Neumega experienced sudden death which the investigator considered possibly or probably related to Neumega. Both deaths occurred in patients with severe hypokalemia (<3.0 mEq/L) who had received high doses of ifosfamide and were receiving daily doses of a diuretic (see **WARNINGS, Cardiovascular Events**).
Other serious events associated with Neumega were cardiovascular events including atrial arrhythmias, stroke and papilledema. In addition, cardiomegaly was reported in children.

The following adverse events, occurring in \( \geq 10\% \) of patients, were observed at equal or greater frequency in placebo-treated patients: asthenia, pain, chills, abdominal pain, infection, anorexia, constipation, dyspepsia, ecchymosis, myalgia, bone pain, nervousness, and alopecia. The incidence of fever, neutropenic fever, flu-like symptoms, thrombocytosis, thrombotic events, the average number of units of red blood cells transfused per patient, and the duration of neutropenia \(<500 \text{ cells/µL} \) were similar in the Neumega 50 µg/kg and placebo groups.

**Immunogenicity**

In clinical studies that evaluated the immunogenicity of Neumega, two of 181 patients (1%) developed antibodies to Neumega. In one of these two patients, neutralizing antibodies to Neumega were detected in an unvalidated assay. The clinical relevance of the presence of these antibodies is unknown. In the post-marketing setting, cases of allergic reactions, including anaphylaxis have been reported (see **WARNINGS, Allergic Reactions Including Anaphylaxis**). The presence of antibodies to Neumega was not assessed in these patients.

The data reflect the percentage of patients whose test results were considered positive for antibodies to Neumega and are highly dependent on the sensitivity and specificity of the assay. Additionally the observed incidence of antibody positivity in an assay may be influenced by several factors including sample handling, concomitant medications, and underlying disease. For these reasons, comparisons of the incidence of antibodies to Neumega with incidence of antibodies to other products may be misleading.

**Abnormal Laboratory Values**

The most common laboratory abnormality reported in patients in clinical trials was a decrease in hemoglobin concentration predominantly as a result of expansion of the plasma volume (see **WARNINGS, Fluid Retention**). The increase in plasma volume is also associated with a decrease in the serum concentration of albumin and several other proteins (eg, transferrin and gamma globulins). A parallel decrease in calcium without clinical effects has been documented.

After daily SC injections, treatment with Neumega resulted in a two-fold increase in plasma fibrinogen. Other acute-phase proteins also increased. These protein levels returned to normal after dosing with Neumega was discontinued. Von Willebrand factor (vWF) concentrations increased with a normal multimer pattern in healthy subjects receiving Neumega.

**Postmarketing Reports**

The following adverse reactions have been reported during the post-approval use of Neumega: allergic reactions, anaphylaxis (see **BOXED WARNING, WARNINGS, Allergic Reactions including Anaphylaxis** and **CONTRAINDICATIONS**).
Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure. Decisions to include these reactions in labeling are typically based on one or more of the following factors: (1) seriousness of the reactions, (2) frequency of reporting, or (3) strength of causal connection to Neumega.

OVERDOSAGE

Doses of Neumega above 125 µg/kg have not been administered to humans. While clinical experience is limited, doses of Neumega greater than 50 µg/kg may be associated with an increased incidence of cardiovascular events in adult patients (see WARNINGS, Fluid Retention and Cardiovascular Events). If an overdose of Neumega is administered, Neumega should be discontinued, and the patient should be closely observed for signs of toxicity (see WARNINGS and ADVERSE REACTIONS). Reinstitution of Neumega therapy should be based upon individual patient factors (eg, evidence of toxicity, continued need for therapy).

DOSAGE AND ADMINISTRATION

The recommended dose of Neumega in adults is 50 µg/kg given once daily. Neumega should be administered subcutaneously as a single injection in either the abdomen, thigh, or hip (or upper arm if not self-injecting). A safe and effective dose has not been established in children (see PRECAUTIONS, Pediatric Use).

Dosing should be initiated 6 to 24 hours after the completion of chemotherapy. Platelet counts should be monitored periodically to assess the optimal duration of therapy. Dosing should be continued until the post-nadir platelet count is ≥50,000/µL. In controlled clinical trials, doses were administered in courses of 10 to 21 days. Dosing beyond 21 days per treatment course is not recommended.

Treatment with Neumega should be discontinued at least 2 days before starting the next planned cycle of chemotherapy.

Preparation of Neumega

1. Neumega is a sterile, white, preservative-free, lyophilized powder for subcutaneous injection upon reconstitution. Neumega (5 mg vials) should be reconstituted aseptically with 1.0 mL of Sterile Water for Injection, USP (without preservative). The reconstituted Neumega solution is clear, colorless, isotonic, with a pH of 7.0, and contains 5 mg/mL of Neumega. The single-use vial should not be re-entered or reused. Any unused portion of either reconstituted Neumega solution or Sterile Water for Injection, USP should be discarded.

2. During reconstitution, the Sterile Water for Injection, USP should be directed at the side of the vial and the contents gently swirled. EXCESSIVE OR VIGOROUS AGITATION SHOULD BE AVOIDED.
3. Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit. If particulate matter is present or the solution is discolored, the vial should not be used.

4. Because neither Neumega powder for injection nor its accompanying diluent, Sterile Water for Injection, USP contains a preservative, Neumega should be used within 3 hours following reconstitution. Reconstituted Neumega may be refrigerated [2°C to 8°C (36°F to 46°F)] or at room temperature [up to 25°C (77°F)]. DO NOT FREEZE OR SHAKE THE RECONSTITUTED SOLUTION.

HOW SUPPLIED

Neumega is supplied as a sterile, white, preservative-free, lyophilized powder in vials containing 5 mg Oprelvekin. Neumega is available in boxes containing one single-dose Neumega vial and one 1-mL vial of diluent for Neumega (Sterile Water for Injection, USP) - NDC 58394-004-01, and boxes containing seven single-dose Neumega vials and seven 1-mL vials of diluent for Neumega (Sterile Water for Injection, USP) - NDC 58394-004-02.

Storage

Lyophilized Neumega and diluent should be stored in a refrigerator at 2°C to 8°C (36°F to 46°F). Protect from light. DO NOT FREEZE. Reconstituted Neumega must be used within 3 hours of reconstitution and can be stored in the vial either at 2°C to 8°C (36°F to 46°F) or at room temperature up to 25°C (77°F).

REFERENCES


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