

1 NEUMEGA®
2 [nu-meg<a]
3 (oprelvekin)
4 Rx ONLY

5

6 **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**).

7

8 **DESCRIPTION**

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

14

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

20

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

26

27 **CLINICAL PHARMACOLOGY**

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

33

34 Preclinical trials have shown that mature megakaryocytes which develop during *in vivo* treatment
35 with Neumega are ultrastructurally normal. Platelets produced in response to Neumega were
36 morphologically and functionally normal and possessed a normal life span.

37

38 IL-11 has also been shown to have non-hematopoietic activities in animals including the
39 regulation of intestinal epithelium growth (enhanced healing of gastrointestinal lesions), the
40 inhibition of adipogenesis, the induction of acute phase protein synthesis, inhibition of pro-
41 inflammatory cytokine production by macrophages, and the stimulation of osteoclastogenesis
42 and neurogenesis. Non-hematopoietic pathologic changes observed in animals include fibrosis
43 of tendons and joint capsules, periosteal thickening, papilledema, and embryotoxicity (see
44 **PRECAUTIONS, Pediatric Use** and **PRECAUTIONS, Pregnancy Category C**).

45
46 IL-11 is produced by bone marrow stromal cells and is part of the cytokine family that shares
47 the gp130 signal transducer. Primary osteoblasts and mature osteoclasts express mRNAs for
48 both IL-11 receptor (IL-11R alpha) and gp130. Both bone-forming and bone-resorbing cells
49 are potential targets of IL-11. (1)

50

51 **Pharmacokinetics**

52 The pharmacokinetics of Neumega have been evaluated in studies of healthy, adult subjects and
53 cancer patients receiving chemotherapy. In a study in which a single 50 µg/kg subcutaneous
54 dose was administered to eighteen healthy men, the peak serum concentration (C_{max}) of 17.4
55 ± 5.4 ng/mL (mean ± S.D.) was reached at 3.2 ± 2.4 hrs (T_{max}) following dosing. The terminal
56 half-life was 6.9 ± 1.7 hrs. In a second study in which single 75 µg/kg subcutaneous and
57 intravenous doses were administered to twenty-four healthy subjects, the pharmacokinetic
58 profiles were similar between men and women. The absolute bioavailability of Neumega was
59 >80%. In a study in which multiple, subcutaneous doses of both 25 and 50 µg/kg were
60 administered to cancer patients receiving chemotherapy, Neumega did not accumulate and
61 clearance of Neumega was not impaired following multiple doses.

62

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

71

72 In preclinical trials in rats, radiolabeled Neumega was rapidly cleared from the serum and
73 distributed to highly perfused organs. The kidney was the primary route of elimination. The
74 amount of intact Neumega in urine was low, indicating that the molecule was metabolized before
75 excretion. In a clinical study, a single dose of Neumega was administered to subjects with
76 severely impaired renal function (creatinine clearance <15 mL/min). The mean ± S.D. values for
77 C_{max} and AUC were 30.8 ± 8.6 ng/mL and 373 ± 106 ng*hr/mL, respectively. When
78 compared with control subjects in this study with normal renal function, the mean C_{max} was 2.2
79 fold higher and the mean AUC was 2.6 fold (95% confidence interval, 1.7%-3.8%) higher in
80 the subjects with severe renal impairment. In the subjects with severe renal impairment,

81 clearance was approximately 40% of the value seen in subjects with normal renal function. The
82 average terminal half-life was similar in subjects with severe renal impairment and those with
83 normal renal function.

84 85 **Pharmacodynamics**

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

94
95 In a randomized, double-blind, placebo-controlled study in normal volunteers, subjects
96 receiving Neumega had a mean increase in plasma volume of >20%, and all subjects receiving
97 Neumega had at least a 10% increase in plasma volume. Red blood cell volume decreased
98 similarly (due to repeated phlebotomy) in the Neumega and placebo groups. As a result, whole
99 blood volume increased approximately 10% and hemoglobin concentration decreased
100 approximately 10% in subjects receiving Neumega compared with subjects receiving placebo.
101 Mean 24 hour sodium excretion decreased, and potassium excretion did not increase, in
102 subjects receiving Neumega compared with subjects receiving placebo.

103 104 **CLINICAL STUDIES**

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

108
109 One study evaluated the effectiveness of Neumega in eliminating the need for platelet
110 transfusions in patients who had recovered from an episode of severe chemotherapy-induced
111 thrombocytopenia (defined as a platelet count =20,000/ μ L), and were to receive one additional
112 cycle of the same chemotherapy without dose reduction. Patients had various underlying non-
113 myeloid malignancies, and were undergoing dose-intensive chemotherapy with a variety of
114 regimens. Patients were randomized to receive Neumega at a dose of 25 μ g/kg or 50 μ g/kg, or
115 placebo. The primary endpoint was whether the patient required one or more platelet
116 transfusions in the subsequent chemotherapy cycle. Ninety-three patients were randomized.
117 Five patients withdrew from the study prior to receiving study drug. As a result, eighty-eight
118 patients were included in a modified intent-to-treat analysis. The results for the Neumega 50
119 μ g/kg and placebo groups are summarized in Table 1. The placebo group includes one patient
120 who underwent chemotherapy dose reduction and who avoided platelet transfusions.

121
122

TABLE 1

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

123

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

130

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

141

TABLE 2 STUDY RESULTS						
	Overall n=77		No Prior Chemotherapy n=54		Prior Chemotherapy n=23	
	Placebo n=37	Neumega n=40	Placebo n=27	Neumega n=27	Placebo n=10	Neumega n=13
Number (%) of patients avoiding platelet transfusion	15 (41%)	26 (65%)	14 (52%)	19 (70%)	1 (10%)	7 (54%)
Number (%) of patients requiring platelet transfusion	16 (43%)	12 (30%)	9 (33%)	7 (26%)	7 (70%)	5 (38%)
Number (%) of patients not evaluable	6 (16%)	2 (5%)	4 (15%)	1 (4%)	2 (20%)	1 (8%)

142

143 This study showed a trend in favor of Neumega, particularly in the subgroup of patients with
144 prior chemotherapy. Open-label treatment with Neumega has been continued for up to four
145 consecutive chemotherapy cycles without evidence of any adverse effect on the rate of
146 neutrophil recovery or red blood cell transfusion requirements. Some patients continued to
147 maintain platelet nadirs >20,000/ μ L for at least four sequential cycles of chemotherapy without
148 the need for transfusions, chemotherapy dose reduction, or changes in treatment schedules.

149
150 Platelet activation trials done on a limited number of patients showed no evidence of abnormal
151 spontaneous platelet activation, or an abnormal response to ADP. In an unblinded,
152 retrospective analysis of the two placebo-controlled studies, 19 of 69 patients (28%) receiving
153 Neumega 50 μ g/kg and 34 of 67 patients (51%) receiving placebo reported at least one
154 hemorrhagic adverse event which involved bleeding.

155
156 In a randomized, double-blind, placebo-controlled, Phase 2 study conducted in patients who
157 received autologous bone marrow transplantation following myeloablative chemotherapy, the
158 incidence of platelet transfusions and time to neutrophil and platelet engraftment were similar in
159 the Neumega and placebo-treated arms.

160
161 In long term follow-up of patients, the distribution of survival and progression-free survival times
162 was similar between patients randomized to Neumega therapy and those randomized to receive
163 placebo.

164

165 **INDICATIONS AND USAGE**

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

172

173 **CONTRAINDICATIONS**

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

176

177 **WARNINGS**

178 **Allergic Reactions Including Anaphylaxis**

179 In the post-marketing setting, Neumega has caused allergic or hypersensitivity reactions,
180 including anaphylaxis. The administration of Neumega should be attended by appropriate
181 precautions in case allergic reactions occur. In addition, patients should be counseled about the
182 symptoms for which they should seek medical attention. (see **PRECAUTIONS, Information**
183 **for Patients**). Signs and symptoms reported included fever, rash, urticaria, shortness of breath,
184 hypotension, flushing, facial edema, edema of the tongue, laryngeal edema, and mental status
185 changes. Reactions occurred after the first dose or subsequent doses of Neumega.

186 Administration of Neumega should be permanently discontinued in any patient who develops an
187 allergic or hypersensitivity reaction (see **BOXED WARNING, CONTRAINDICATIONS,**
188 **ADVERSE REACTIONS,** and **ADVERSE REACTIONS, Immunogenicity**).

189

190 **Fluid Retention**

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

200

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

204

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

209

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

212

213 **Dilutional Anemia**

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

220

221 **Cardiovascular Events**

222 Neumega use is associated with cardiovascular events including arrhythmias and pulmonary
223 edema. Cardiac arrest has been reported, but the causal relationship to Neumega is uncertain.
224 Use with caution in patients with a history of atrial arrhythmias, and only after consideration of
225 the potential risks in relation to anticipated benefit. In clinical trials, cardiac events including atrial
226 arrhythmias (atrial fibrillation or atrial flutter) occurred in 15% (23/157) of patients treated with
227 Neumega at doses of 50 µg/kg. Arrhythmias were usually brief in duration; conversion to sinus
228 rhythm typically occurred spontaneously or after rate-control drug therapy. Approximately one-

229 half (11/24) of the patients who were rechallenged had recurrent atrial arrhythmias. Clinical
230 sequelae, including stroke, have been reported in patients who experienced atrial arrhythmias
231 while receiving Neumega.
232

233 The mechanism for induction of arrhythmias is not known. Neumega was not directly
234 arrhythmogenic in animal models. In some patients, development of atrial arrhythmias may be
235 due to increased plasma volume associated with fluid retention (see **WARNINGS, Fluid**
236 **Retention**).
237

238 **Nervous System Events**

239 Stroke has been reported in the setting of patients who develop atrial fibrillation/flutter while
240 receiving Neumega (see **WARNINGS, Cardiovascular Events**). Patients with a history of
241 stroke or transient ischemic attack may also be at increased risk for these events.
242

243 **Papilledema**

244 Papilledema has been reported in 2% (10/405) of patients receiving Neumega in clinical trials
245 following repeated cycles of exposure. The incidence was higher 16% (7/43) in children than in
246 adults, 1% (3/362). Nonhuman primates treated with Neumega at a dose of 1,000 µg/kg SC
247 once daily for 4 to 13 weeks developed papilledema that was not associated with inflammation
248 or any other histologic abnormality and was reversible after dosing was discontinued. Neumega
249 should be used with caution in patients with pre-existing papilledema, or with tumors involving
250 the central nervous system since it is possible that papilledema could worsen or develop during
251 treatment (see **ADVERSE REACTIONS**).
252

253 **PRECAUTIONS**

254 **General**

255 Dosing with Neumega should begin 6 to 24 hours following the completion of chemotherapy
256 dosing. The safety and efficacy of Neumega given immediately prior to or concurrently with
257 cytotoxic chemotherapy or initiated at the time of expected nadir have not been established (see
258 **DOSAGE AND ADMINISTRATION**).
259

260 The effectiveness of Neumega has not been evaluated in patients receiving chemotherapy
261 regimens of greater than 5 days duration or regimens associated with delayed myelosuppression
262 (eg, nitrosoureas, mitomycin-C).
263

264 **Chronic Administration**

265 Neumega has been administered safely using the recommended dosage schedule (see
266 **DOSAGE AND ADMINISTRATION**) for up to 6 cycles following chemotherapy. The
267 safety and efficacy of chronic administration of Neumega have not been established. Continuous
268 dosage (2 to 13 weeks) in nonhuman primates produced joint capsule and tendon fibrosis and
269 periosteal hyperostosis (see **PRECAUTIONS, Pediatric Use**). The relevance of these
270 findings to humans is unclear.
271

272 **Information for Patients**

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

280

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

291

292 **Laboratory Monitoring**

293 A complete blood count should be obtained prior to chemotherapy and at regular intervals
294 during Neumega therapy (see **DOSAGE AND ADMINISTRATION**). Platelet counts
295 should be monitored during the time of the expected nadir and until adequate recovery has
296 occurred (post-nadir counts $\geq 50,000/\mu\text{L}$).

297

298 **Drug Interactions**

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

305

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

309

310 **Carcinogenesis, Mutagenesis, Impairment of Fertility**

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

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

317

318 **Pregnancy Category C**

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

323

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

337

338 Adverse effects in the first generation offspring of rats given Neumega at maternally toxic doses
339 =2 times the human dose (=100 µg/kg/day) during both gestation and lactation included
340 increased newborn mortality, decreased viability index on day 4 of lactation, and decreased
341 body weights during lactation. In rats given 20 times the human dose (1000 µg/kg/day) during
342 both gestation and lactation, maternal toxicity and growth retardation of the first generation
343 offspring resulted in an increased rate of fetal death of the second generation offspring.

344

345 **Nursing Mothers**

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

350

351 **Pediatric Use**

352 A safe and effective dose of Neumega has not been established in children. In a Phase 1, single
353 arm, dose-escalation study, 43 pediatric patients were treated with Neumega at doses ranging
354 from 25 to 125 µg/kg/day following ICE chemotherapy. All patients required platelet
355 transfusions and the lack of a comparator arm made the study design inadequate to assess
356 efficacy. The projected effective dose (based on comparable AUC observed for the effective
357 dose in healthy adults) in children appears to exceed the maximum tolerated pediatric dose of

358 50 µg/kg/day (see **CLINICAL PHARMACOLOGY, Pharmacokinetics**). Papilledema was
359 dose-limiting and occurred in 16% of children (see **WARNINGS, Papilledema**).

360

361 The most common adverse events seen in pediatric studies included tachycardia (84%),
362 conjunctival injection (58%), radiographic and echocardiographic evidence of cardiomegaly
363 (21%) and periosteal changes (11%). These events occurred at a higher frequency in children
364 than adults. The incidence of other adverse events were generally similar to those observed
365 using Neumega at a dose of 50 µg/kg in the randomized studies in adults receiving
366 chemotherapy (see **ADVERSE REACTIONS**).

367

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

378

379 **Use in Patients with Renal Impairment**

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

385

386 **ADVERSE REACTIONS**

387 Because clinical trials are conducted under widely varying conditions, adverse reaction rates
388 observed in the clinical studies of a drug cannot be directly compared to rates in the clinical
389 studies of another drug and may not reflect the rates observed in practice. The adverse reaction
390 information from clinical trials does, however, provide a basis for identifying the adverse events
391 that appear to be related to drug use and for approximating rates.

392

393 Three hundred twenty-four subjects, with ages ranging from 8 months to 75 years, have been
394 exposed to Neumega treatment in clinical studies. Subjects have received up to six (eight in
395 pediatric patients) sequential courses of Neumega treatment, with each course lasting from 1 to
396 28 days. Apart from the sequelae of the underlying malignancy or cytotoxic chemotherapy, most
397 adverse events were mild or moderate in severity and reversible after discontinuation of
398 Neumega dosing.

399

400 In general, the incidence and type of adverse events were similar between Neumega 50 µg/kg
 401 and placebo groups. The most frequently reported serious adverse events were neutropenic
 402 fever, syncope, atrial fibrillation, fever and pneumonia. The most commonly reported adverse
 403 events were edema, dyspnea, tachycardia, conjunctival injection, palpitations, atrial arrhythmias,
 404 and pleural effusions. The most commonly reported adverse reactions resulting in clinical
 405 intervention (eg, discontinuation of Neumega, adjustment in dosage, or the need for concomitant
 406 medication to treat an adverse reaction symptom) were atrial arrhythmias, syncope, dyspnea,
 407 congestive heart failure, and pulmonary edema. Selected adverse events that occurred in =10%
 408 of Neumega-treated patients are listed in Table 3.
 409

TABLE 3
SELECTED ADVERSE EVENTS

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

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

410
 411 The following adverse events also occurred more frequently in cancer patients receiving
 412 Neumega than in those receiving placebo: amblyopia, paresthesia, dehydration, skin
 413 discoloration, exfoliative dermatitis, and eye hemorrhage; a statistically significant association of
 414 Neumega to these events has not been established. Other than a higher incidence of severe
 415 asthenia in Neumega treated patients (10 [14%] in Neumega patients versus 2 [3%] in placebo
 416 patients), the incidence of severe or life-threatening adverse events was comparable in the
 417 Neumega and placebo treatment groups.
 418

419 Two patients with cancer treated with Neumega experienced sudden death which the
 420 investigator considered possibly or probably related to Neumega. Both deaths occurred in
 421 patients with severe hypokalemia (<3.0 mEq/L) who had received high doses of ifosfamide and
 422 were receiving daily doses of a diuretic (see **WARNINGS, Cardiovascular Events**).
 423

424 Other serious events associated with Neumega were cardiovascular events including atrial
425 arrhythmias, stroke and papilledema. In addition, cardiomegaly was reported in children.

426

427 The following adverse events, occurring in =10% of patients, were observed at equal or greater
428 frequency in placebo-treated patients: asthenia, pain, chills, abdominal pain, infection, anorexia,
429 constipation, dyspepsia, ecchymosis, myalgia, bone pain, nervousness, and alopecia. The
430 incidence of fever, neutropenic fever, flu-like symptoms, thrombocytosis, thrombotic events, the
431 average number of units of red blood cells transfused per patient, and the duration of
432 neutropenia <500 cells/ μ L were similar in the Neumega 50 μ g/kg and placebo groups.

433

434 **Immunogenicity**

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

441

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

448

449 **Abnormal Laboratory Values**

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

455

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

460

461 **Postmarketing Reports**

462 The following adverse reactions have been reported during the post-approval use of Neumega:
463 allergic reactions, anaphylaxis (see **BOXED WARNING, WARNINGS, Allergic**
464 **Reactions including Anaphylaxis** and **CONTRAINDICATIONS**).

465

466 Because these reactions are reported voluntarily from a population of uncertain size, it is not
467 always possible to reliably estimate their frequency or establish a causal relationship to drug
468 exposure. Decisions to include these reactions in labeling are typically based on one or more of
469 the following factors: (1) seriousness of the reactions, (2) frequency of reporting, or (3) strength
470 of causal connection to Neumega.

471

472 **OVERDOSAGE**

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

481

482 **DOSAGE AND ADMINISTRATION**

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

487

488 Dosing should be initiated 6 to 24 hours after the completion of chemotherapy. Platelet counts
489 should be monitored periodically to assess the optimal duration of therapy. Dosing should be
490 continued until the post-nadir platelet count is $\geq 50,000/\mu\text{L}$. In controlled clinical trials, doses
491 were administered in courses of 10 to 21 days. Dosing beyond 21 days per treatment course is
492 not recommended.

493

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

496

497 Preparation of Neumega

498

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

505

506 2. During reconstitution, the Sterile Water for Injection, USP should be directed at the side of
507 the vial and the contents gently swirled. **EXCESSIVE OR VIGOROUS AGITATION**
508 **SHOULD BE AVOIDED.**

509

510 3. Parenteral drug products should be inspected visually for particulate matter and discoloration
511 prior to administration, whenever solution and container permit. If particulate matter is
512 present or the solution is discolored, the vial should not be used.

513

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

519

520 **HOW SUPPLIED**

521 Neumega is supplied as a sterile, white, preservative-free, lyophilized powder in vials containing
522 5 mg Oprelvekin. Neumega is available in boxes containing one single-dose Neumega vial and
523 one 1-mL vial of diluent for Neumega (Sterile Water for Injection, USP) - NDC 58394-004-
524 01, and boxes containing seven single-dose Neumega vials and seven 1-mL vials of diluent for
525 Neumega (Sterile Water for Injection, USP) - NDC 58394-004-02.

526

527 **Storage**

528 Lyophilized Neumega and diluent should be stored in a refrigerator at 2°C to 8°C (36°F to
529 46°F). Protect from light. DO NOT FREEZE. Reconstituted Neumega must be used within 3
530 hours of reconstitution and can be stored in the vial either at 2°C to 8°C (36°F to 46°F) or at
531 room temperature up to 25°C (77°F).

532

533 **REFERENCES**

534

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537

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