
1 **[Neulasta[®]] (pegfilgrastim)**

2

3 **DESCRIPTION**

4 Neulasta[™] (pegfilgrastim) is a covalent conjugate of recombinant methionyl human
5 G-CSF (Filgrastim) and monomethoxypolyethylene glycol. Filgrastim is a water-soluble
6 175 amino acid protein with a molecular weight of approximately 19 kilodaltons (kD).
7 Filgrastim is obtained from the bacterial fermentation of a strain of *Escherichia coli*
8 transformed with a genetically engineered plasmid containing the human G-CSF gene.
9 To produce pegfilgrastim, a 20 kD monomethoxypolyethylene glycol molecule is
10 covalently bound to the N-terminal methionyl residue of Filgrastim. The average
11 molecular weight of pegfilgrastim is approximately 39 kD.

12

13 Neulasta[™] is supplied in 0.6 mL prefilled syringes for subcutaneous (SC) injection.
14 Each syringe contains 6 mg pegfilgrastim (based on protein weight), in a sterile, clear,
15 colorless, preservative-free solution (pH 4.0) containing acetate (0.35 mg), sorbitol
16 (30.0 mg), polysorbate 20 (0.02 mg), and sodium (0.02 mg) in water for injection, USP.

17 **CLINICAL PHARMACOLOGY**

18 Both Filgrastim and pegfilgrastim are Colony Stimulating Factors that act on
19 hematopoietic cells by binding to specific cell surface receptors thereby stimulating
20 proliferation, differentiation, commitment, and end cell functional activation.^{1,2} Studies
21 on cellular proliferation, receptor binding, and neutrophil function demonstrate that

22 Filgrastim and pegfilgrastim have the same mechanism of action. Pegfilgrastim has
23 reduced renal clearance and prolonged persistence in vivo as compared to Filgrastim.

24 **Pharmacokinetics**

25 The pharmacokinetics and pharmacodynamics of Neulasta[™] were studied in 379 patients
26 with cancer. The pharmacokinetics of Neulasta[™] were nonlinear in cancer patients and
27 clearance decreased with increases in dose. Neutrophil receptor binding is an important
28 component of the clearance of Neulasta[™], and serum clearance is directly related to the
29 number of neutrophils. For example, the concentration of Neulasta[™] declined rapidly at
30 the onset of neutrophil recovery that followed myelosuppressive chemotherapy. In
31 addition to numbers of neutrophils, body weight appeared to be a factor. Patients with
32 higher body weights experienced higher systemic exposure to Neulasta[™] after receiving
33 a dose normalized for body weight. A large variability in the pharmacokinetics of
34 Neulasta[™] was observed in cancer patients. The half-life of Neulasta[™] ranged from 15
35 to 80 hours after SC injection.

36 **Special Populations**

37 No gender-related differences were observed in the pharmacokinetics of Neulasta[™], and
38 no differences were observed in the pharmacokinetics of geriatric patients (≥ 65 years of
39 age) compared to younger patients (< 65 years of age) (see PRECAUTIONS, Geriatric
40 Use). The pharmacokinetic profile in pediatric populations or in patients with hepatic or
41 renal insufficiency has not been assessed.

42 **CLINICAL STUDIES**

43 Neulasta[™] was evaluated in two randomized, double-blind, active control studies,
44 employing doxorubicin 60 mg/m² and docetaxel 75 mg/m² administered every 21 days
45 for up to 4 cycles for the treatment of metastatic breast cancer. Study 1 investigated the
46 utility of a fixed dose of Neulasta[™]. Study 2 employed a weight-adjusted dose. In the
47 absence of growth factor support, similar chemotherapy regimens have been reported to
48 result in a 100% incidence of severe neutropenia (absolute neutrophil count [ANC]
49 < 0.5 x 10⁹/L) with a mean duration of 5-7 days, and a 30-40% incidence of febrile
50 neutropenia. Based on the correlation between the duration of severe neutropenia and the
51 incidence of febrile neutropenia found in studies with Filgrastim, duration of severe
52 neutropenia was chosen as the primary endpoint in both studies, and the efficacy of
53 Neulasta[™] was demonstrated by establishing comparability to Filgrastim
54 (NEUPOGEN[®])-treated subjects in the mean days of severe neutropenia.

55

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

61

62 Both studies met the primary objective of demonstrating that the mean days of severe
63 neutropenia of Neulasta[™]-treated patients did not exceed that of Filgrastim-treated

64 patients by more than one day in cycle 1 of chemotherapy (see Table 1). The rates of
65 febrile neutropenia in the two studies were comparable for Neulasta[™] and Filgrastim (in
66 the range of 10 to 20%). Other secondary endpoints included days of severe neutropenia
67 in cycles 2-4, the depth of ANC nadir in cycles 1-4, and the time to ANC recovery after
68 nadir. In both studies, the results for the secondary endpoints were similar between the
69 two treatment groups.

70 **Table 1. Mean Days of Severe Neutropenia (in Cycle 1)**

Study	Mean days of severe neutropenia		Difference in means (95% CI)
	Neulasta [®] ^a	NEUPOGEN [®] (5 mcg/kg/day)	
Study 1 n = 157	1.8	1.6	0.2 (-0.2, 0.6)
Study 2 n = 310	1.7	1.6	0.1 (-0.2, 0.4)

71 a. Study 1 dose = 6 mg x 1; study 2 dose = 100 mcg/kg x 1

72 INDICATIONS AND USAGE

73 Neulasta[™] is indicated to decrease the incidence of infection, as manifested by febrile
74 neutropenia, in patients with non-myeloid malignancies receiving myelosuppressive
75 anti-cancer drugs associated with a clinically significant incidence of febrile neutropenia.

76 CONTRAINDICATIONS

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

79 **WARNINGS**

80 **Splenic Rupture**

81 **RARE CASES OF SPLENIC RUPTURE HAVE BEEN REPORTED**
82 **FOLLOWING THE ADMINISTRATION OF THE PARENT COMPOUND OF**
83 **NEULASTA[®], FILGRASTIM, FOR PBPC MOBILIZATION IN BOTH**
84 **HEALTHY DONORS AND PATIENTS WITH CANCER. SOME OF THESE**
85 **CASES WERE FATAL. NEULASTA[®] HAS NOT BEEN EVALUATED IN THIS**
86 **SETTING, THEREFORE, NEULASTA[®] SHOULD NOT BE USED FOR PBPC**
87 **MOBILIZATION. PATIENTS RECEIVING NEULASTA[®] WHO REPORT**
88 **LEFT UPPER ABDOMINAL OR SHOULDER TIP PAIN SHOULD BE**
89 **EVALUATED FOR AN ENLARGED SPLEEN OR SPLENIC RUPTURE.**

90 **Adult Respiratory Distress Syndrome (ARDS)**

91 Adult respiratory distress syndrome (ARDS) has been reported in neutropenic patients
92 with sepsis receiving Filgrastim, the parent compound of Neulasta[™], and is postulated to
93 be secondary to an influx of neutrophils to sites of inflammation in the lungs.
94 Neutropenic patients receiving Neulasta[™] who develop fever, lung infiltrates, or
95 respiratory distress should be evaluated for the possibility of ARDS. In the event that
96 ARDS occurs, Neulasta[™] should be discontinued and/or withheld until resolution of
97 ARDS and patients should receive appropriate medical management for this condition.

98 **Allergic Reactions**

99 Allergic-type reactions, including anaphylaxis, skin rash and urticaria, occurring on
100 initial or subsequent treatment have been reported with the parent compound of
101 Neulasta[™], Filgrastim. In some cases, symptoms have recurred with rechallenge,
102 suggesting a causal relationship. Allergic-type reactions to Neulasta[™] have not been
103 observed in clinical trials. If a serious allergic reaction or an anaphylactic reaction
104 occurs, appropriate therapy should be administered and further use of Neulasta[™] should
105 be discontinued.

106 **Sickle Cell Disease**

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

117 **PRECAUTIONS**

118 **General**

119 Use With Chemotherapy and/or Radiation Therapy

120 Neulasta[™] should not be administered in the period between 14 days before and 24 hours
121 after administration of cytotoxic chemotherapy (see DOSAGE AND
122 ADMINISTRATION) because of the potential for an increase in sensitivity of rapidly
123 dividing myeloid cells to cytotoxic chemotherapy.

124

125 The use of Neulasta[™] has not been studied in patients receiving chemotherapy associated
126 with delayed myelosuppression (eg, nitrosoureas, mitomycin C).

127

128 The administration of Neulasta[™] concomitantly with 5-fluorouracil or other
129 antimetabolites has not been evaluated in patients. Administration of pegfilgrastim at 0,
130 1 and 3 days before 5-fluorouracil resulted in increased mortality in mice; administration
131 of pegfilgrastim 24 hours after 5-fluorouracil did not adversely affect survival.

132

133 The use of Neulasta[™] has not been studied in patients receiving radiation therapy.

134 **Potential Effect on Malignant Cells**

135 Pegfilgrastim is a growth factor that primarily stimulates neutrophils and neutrophil
136 precursors; however, the G-CSF receptor through which pegfilgrastim and Filgrastim act

137 has been found on tumor cell lines, including some myeloid, T-lymphoid, lung, head and
138 neck, and bladder tumor cell lines. The possibility that pegfilgrastim can act as a growth
139 factor for any tumor type cannot be excluded. Use of Neulasta[™] in myeloid
140 malignancies and myelodysplasia (MDS) has not been studied. In a randomized study
141 comparing the effects of the parent compound of Neulasta[™], Filgrastim, to placebo in
142 patients undergoing remission induction and consolidation chemotherapy for acute
143 myeloid leukemia, important differences in remission rate between the two arms were
144 excluded. Disease-free survival and overall survival were comparable; however, the
145 study was not designed to detect important differences in these endpoints.³

146 **Information for Patients**

147 Patients should be informed of the possible side effects of Neulasta[™], and be instructed
148 to report them to the prescribing physician. Patients should be informed of the signs and
149 symptoms of allergic drug reactions and be advised of appropriate actions. Patients
150 should be counseled on the importance of compliance with their Neulasta[™] treatment,
151 including regular monitoring of blood counts.

152

153 If it is determined that a patient or caregiver can safely and effectively administer
154 Neulasta[™] (pegfilgrastim) at home, appropriate instruction on the proper use of
155 Neulasta[™] (pegfilgrastim) should be provided for patients and their caregivers, including
156 careful review of the “Information for Patients and Caregivers” insert. Patients and
157 caregivers should be cautioned against the reuse of needles, syringes, or drug product,

158 and be thoroughly instructed in their proper disposal. A puncture-resistant container for
159 the disposal of used syringes and needles should be available.

160 **Laboratory Monitoring**

161 To assess a patient's hematologic status and ability to tolerate myelosuppressive
162 chemotherapy, a complete blood count and platelet count should be obtained before
163 chemotherapy is administered. Regular monitoring of hematocrit value and platelet count
164 is recommended.

165 **Drug Interaction**

166 No formal drug interaction studies between Neulasta[™] and other drugs have been
167 performed. Drugs such as lithium may potentiate the release of neutrophils; patients
168 receiving lithium and Neulasta[™] should have more frequent monitoring of neutrophil
169 counts.

170 **Carcinogenesis, Mutagenesis, Impairment of Fertility**

171 No mutagenesis studies were conducted with pegfilgrastim. The carcinogenic potential
172 of pegfilgrastim has not been evaluated in long-term animal studies. In a toxicity study
173 of 6 months duration in rats given once weekly subcutaneous injections of up to
174 1000 mcg/kg of pegfilgrastim (approximately 23-fold higher than the recommended
175 human dose), no precancerous or cancerous lesions were noted.

176

177 When administered once weekly via subcutaneous injections to male and female rats at
178 doses up to 1000 mcg/kg prior to, and during mating, reproductive performance, fertility
179 and sperm assessment parameters were not affected.

180 **Pregnancy Category C**

181 Pegfilgrastim has been shown to have adverse effects in pregnant rabbits when
182 administered SC every other day during gestation at doses as low as 50 mcg/kg/dose
183 (approximately 4-fold higher than the recommended human dose). Decreased maternal
184 food consumption, accompanied by a decreased maternal body weight gain and decreased
185 fetal body weights were observed at 50 to 1000 mcg/kg/dose. Pegfilgrastim doses of 200
186 and 250 mcg/kg/dose resulted in an increased incidence of abortions. Increased
187 post-implantation loss due to early resorptions, was observed at doses of 200 to
188 1000 mcg/kg/dose and decreased numbers of live rabbit fetuses were observed at
189 pegfilgrastim doses of 200 to 1000 mcg/kg/dose, given every other day.

190

191 Subcutaneous injections of pegfilgrastim of up to 1000 mcg/kg/dose every other day
192 during the period of organogenesis in rats were not associated with an embryotoxic or
193 fetotoxic outcome. However, an increased incidence (compared to historical controls) of
194 wavy ribs was observed in rat fetuses at 1000 mcg/kg/dose every other day. Very low
195 levels (< 0.5%) of pegfilgrastim crossed the placenta when administered subcutaneously
196 to pregnant rats every other day during gestation.

197

198 Once weekly subcutaneous injections of pegfilgrastim to female rats from day 6 of
199 gestation through day 18 of lactation at doses up to 1000 mcg/kg/dose did not result in
200 any adverse maternal effects. There were no deleterious effects on the growth and
201 development of the offspring and no adverse effects were found upon assessment of
202 fertility indices.

203

204 There are no adequate and well-controlled studies in pregnant women. Neulasta[™] should
205 be used during pregnancy only if the potential benefit to the mother justifies the potential
206 risk to the fetus.

207 **Nursing Mothers**

208 It is not known whether pegfilgrastim is excreted in human milk. Because many drugs
209 are excreted in human milk, caution should be exercised when Neulasta[™] is administered
210 to a nursing woman.

211 **Pediatric Use**

212 The safety and effectiveness of Neulasta[™] in pediatric patients have not been established.
213 The 6 mg fixed dose single-use syringe formulation should not be used in infants,
214 children and smaller adolescents weighing less than 45 kg.

215 **Geriatric Use**

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

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

221 **ADVERSE REACTIONS**

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

224

225 Safety data are based upon 465 subjects with lymphoma and solid tumors (breast, lung,
226 and thoracic tumors) enrolled in six randomized clinical studies. Subjects received
227 Neulasta[™] after nonmyeloablative cytotoxic chemotherapy. Most adverse experiences
228 were attributed by the investigators to the underlying malignancy or cytotoxic
229 chemotherapy and occurred at similar rates in subjects who received Neulasta[™] (n = 465)
230 or Filgrastim (n = 331). These adverse experiences occurred at rates between 72% and
231 15% and included: nausea, fatigue, alopecia, diarrhea, vomiting, constipation, fever,
232 anorexia, skeletal pain, headache, taste perversion, dyspepsia, myalgia, insomnia,
233 abdominal pain, arthralgia, generalized weakness, peripheral edema, dizziness,
234 granulocytopenia, stomatitis, mucositis, and neutropenic fever.

235

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

239 mild-to-moderate severity. Approximately 12% of all subjects utilized non-narcotic
240 analgesics and less than 6% utilized narcotic analgesics in association with bone pain.
241 No patient withdrew from study due to bone pain.

242

243 In clinical studies, leukocytosis (WBC counts $> 100 \times 10^9/L$) was observed in less than
244 1% of 465 subjects with non-myeloid malignancies receiving Neulasta[™]. Leukocytosis
245 was not associated with any adverse effects.

246

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

250

251 Reversible elevations in LDH, alkaline phosphatase, and uric acid, which did not require
252 treatment intervention, were observed. The incidences of these changes, presented for
253 Neulasta[™] relative to Filgrastim, were: LDH (19% versus 29%), alkaline phosphatase
254 (9% versus 16%), and uric acid (8% versus 9% [1% of reported cases for both treatment
255 groups were classified as severe]).

256 Immunogenicity

257 As with all therapeutic proteins, there is a potential for immunogenicity. The incidence
258 of antibody development in patients receiving Neulasta[™] has not been adequately
259 determined. While available data suggest that a small proportion of patients developed

260 binding antibodies to Filgrastim or pegfilgrastim, the nature and specificity of these
261 antibodies has not been adequately studied. No neutralizing antibodies have been
262 detected using a cell-based bioassay in 46 patients who apparently developed binding
263 antibodies. The detection of antibody formation is highly dependent on the sensitivity
264 and specificity of the assay, and the observed incidence of antibody positivity in an assay
265 may be influenced by several factors including sample handling, concomitant
266 medications, and underlying disease. Therefore, comparison of the incidence of
267 antibodies to Neulasta[™] with the incidence of antibodies to other products may be
268 misleading.

269

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

275 **OVERDOSAGE**

276 The maximum amount of Neulasta[™] that can be safely administered in single or multiple
277 doses has not been determined. Single doses of 300 mcg/kg have been administered SC
278 to 8 normal volunteers and 3 patients with non-small cell lung cancer without serious
279 adverse effects. These subjects experienced a mean maximum ANC of $55 \times 10^9/L$, with a
280 corresponding mean maximum WBC of $67 \times 10^9/L$. The absolute maximum ANC
281 observed was $96 \times 10^9/L$ with a corresponding absolute maximum WBC observed of

282 120 x 10⁹/L. The duration of leukocytosis ranged from 6 to 13 days. Leukapheresis
283 should be considered in the management of symptomatic individuals.

284 **DOSAGE AND ADMINISTRATION**

285 The recommended dosage of Neulasta[™] is a single subcutaneous (SC) injection of 6 mg
286 administered once per chemotherapy cycle. Neulasta[™] should not be administered in the
287 period between 14 days before and 24 hours after administration of cytotoxic
288 chemotherapy (see PRECAUTIONS).

289

290 The 6 mg fixed dose formulation should not be used in infants, children and smaller
291 adolescents weighing less than 45 kg.

292

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

296

297 Neulasta[™] is supplied in prefilled syringes with UltraSafe[®] Needle Guards. Following
298 administration of Neulasta[™] from the prefilled syringe, the UltraSafe[®] Needle Guard
299 should be activated to prevent accidental needle sticks. To activate the UltraSafe[®]
300 Needle Guard, place your hands behind the needle, grasp the guard with one hand, and
301 slide the guard forward until the needle is completely covered and the guard clicks into
302 place. NOTE: If an audible click is not heard, the needle guard may not be completely

303 activated. The prefilled syringe should be disposed of by placing the entire prefilled
304 syringe with guard activated into an approved puncture-proof container.

305

306 **Storage**

307 Neulasta[™] should be stored refrigerated at 2° to 8°C (36° to 46°F); syringes should be
308 kept in their carton to protect from light until time of use. Shaking should be avoided.
309 Before injection, Neulasta[™] may be allowed to reach room temperature for a maximum
310 of 48 hours but should be protected from light. Neulasta[™] left at room temperature for
311 more than 48 hours should be discarded. Freezing should be avoided; however, if
312 accidentally frozen, Neulasta[™] should be allowed to thaw in the refrigerator before
313 administration. If frozen a second time, Neulasta[™] should be discarded.

314 **HOW SUPPLIED**

315 Neulasta[™] is supplied as a preservative-free solution containing 6 mg (0.6 mL) of
316 pegfilgrastim (10 mg/mL) in a single-dose syringe with a 27 gauge, 1/2 inch needle with
317 an UltraSafe[®] Needle Guard.

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

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