

**CENTER FOR DRUG EVALUATION AND
RESEARCH AND CENTER FOR BIOLOGICS
EVALUATION AND RESEARCH**

APPLICATION NUMBER:

125031/0

APPROVED LABELING

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).

320 **REFERENCES**

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327 phase III study of Filgrastim in remission induction and consolidation therapy for
328 adults with de novo Acute Myeloid Leukemia. *Blood.* 1997;90:4710-4718.

329

330 [Amgen Logo]

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Neulasta™
(pegfilgrastim)

INFORMATION FOR PATIENTS AND CAREGIVERS

This patient package insert provides information and instructions for people who will be receiving Neulasta™ or their caregivers. This patient package insert does not tell you everything about Neulasta™. You should discuss any questions you have about treatment with Neulasta™ with your doctor.

What is Neulasta™?

Neulasta™ is a man-made form of granulocyte colony-stimulating factor (G-CSF), which is made using the bacteria *E coli*. G-CSF is a substance naturally produced by the body. It stimulates the growth of neutrophils (**nu-tro-fils**), a type of white blood cell important in the body's fight against infection.

What is Neulasta™ used for?

Neulasta™ is used to treat neutropenia (**nu-tro-peen-ee-ah**), a condition where the body makes too few white blood cells. Neutropenia can be caused by drugs used to treat cancer.

How does Neulasta™ work?

Neulasta™ works by stimulating the growth of neutrophils, a type of white blood cell. To make sure Neulasta™ is working, the doctor will ask that the patient have blood tests to count the number of white blood cells. It is important to follow the doctor's instructions about these tests.

Who should not take Neulasta™?

- People who have had an allergic reaction to other products made using the bacteria *E coli* should not take Neulasta™.

Talk to your doctor if you have any questions about this information.

What important information do I need to know about receiving Neulasta™?

Neulasta™ can reduce the risk of infection, but it may not prevent all infections. An infection can still happen during the time when your white blood cell levels are low. You must be alert and look for some of the common signs of infection, such as fever, chills, rash, sore throat, diarrhea, or redness, swelling, or pain around a cut or sore. If you notice any of these symptoms during treatment with Neulasta™, tell your doctor or nurse immediately.

Occasionally a reaction may develop at the injection site. If there is a lump, swelling, or bruising at the injection site that does not go away, talk to the doctor.

If you have sickle cell disease, make sure that your doctor knows about it before using Neulasta™. It is important that you drink plenty of fluids if you receive Neulasta™. If you have a sickle cell crisis after getting Neulasta™, you need to tell your doctor right away.

Make sure your doctor knows about all medications you are taking before starting Neulasta™ injections. If you are taking lithium, you may need more frequent blood tests.

The doctor, nurse, or caregiver will usually inject the dose of Neulasta™ a day after the last dose of chemotherapy in each cycle. Neulasta™ should only be injected on the day the doctor has determined and should not be injected until approximately 24 hours after receiving chemotherapy.

More information about Neulasta™ is available in the Physician Package Insert. If you have any questions, talk to your doctor.

What are possible or reasonably likely side effects of Neulasta™?

The most common side effect you may experience is aching in the bones and muscles. If this happens, it can usually be relieved with a non-aspirin pain reliever, such as acetaminophen.

Some people experience redness, swelling, or itching at the site of injection. This may be an allergy to the ingredients in Neulasta™, or it may be a local reaction. If you notice signs of a local reaction, call your doctor.

It is possible that serious allergic reactions could also happen. These reactions can cause a rash over the whole body, shortness of breath, wheezing, a drop in blood pressure, swelling around the mouth or eyes, fast pulse, or sweating. If at any time a serious allergic reaction happens, **call a doctor or emergency medical personnel immediately (for example, call 911)**. If you experience an allergic reaction during the injection of Neulasta™, the injection should be stopped immediately.

What about pregnancy or breastfeeding?

Neulasta™ has not been studied in pregnant women, and its effects on unborn babies are not known. If you take Neulasta™ while you are pregnant, it is possible that small amounts of it may get into your baby's blood. It is not known if Neulasta™ can get into human breast milk. If you are pregnant, plan to become pregnant, think you may be pregnant, or are breast feeding, you should tell your doctor before using Neulasta™.

HOW TO PREPARE AND GIVE A NEULASTA™ INJECTION

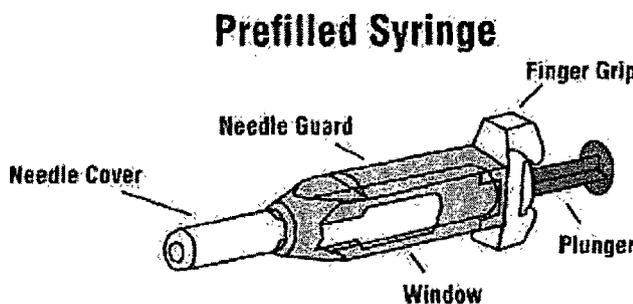
Neulasta™ is provided in a prefilled syringe. **Neulasta™ should be stored in its carton to protect from light until use.** If you are giving someone else Neulasta™ injections, it is important that you know how to inject Neulasta™. Before getting your Neulasta™ injection, always check to see that:

- The name Neulasta™ appears on the carton and prefilled syringe label.
- The expiration date on the prefilled syringe has not passed. **You should not use a prefilled syringe after the date on the label.**
- The Neulasta™ liquid should always be clear and colorless. Do not use Neulasta™ if the contents of the prefilled syringe appear discolored or cloudy, or if the prefilled syringe appears to contain lumps, flakes, or particles.

IMPORTANT: TO HELP AVOID POSSIBLE INFECTION, YOU SHOULD FOLLOW THESE INSTRUCTIONS.

Setting up for an injection

1. Find a clean, flat working surface, such as a table.
2. Remove the carton containing the prefilled syringe of Neulasta™ from the refrigerator. Allow Neulasta™ to reach room temperature (this takes about 30 minutes). Remove the syringe from the carton before injection. Each prefilled syringe should be used only once. **DO NOT SHAKE THE PREFILLED SYRINGE.** Shaking may damage Neulasta™. If the prefilled syringe has been shaken vigorously, the solution may appear foamy and it should not be used.
3. Assemble the supplies you will need for an injection:
 - Neulasta™ prefilled syringe with transparent (clear) plastic blue needle guard attached



- An alcohol swab and a cotton ball or gauze

Alcohol Swab



Cotton Ball



- puncture-proof disposal container
4. Wash your hands with soap and warm water.

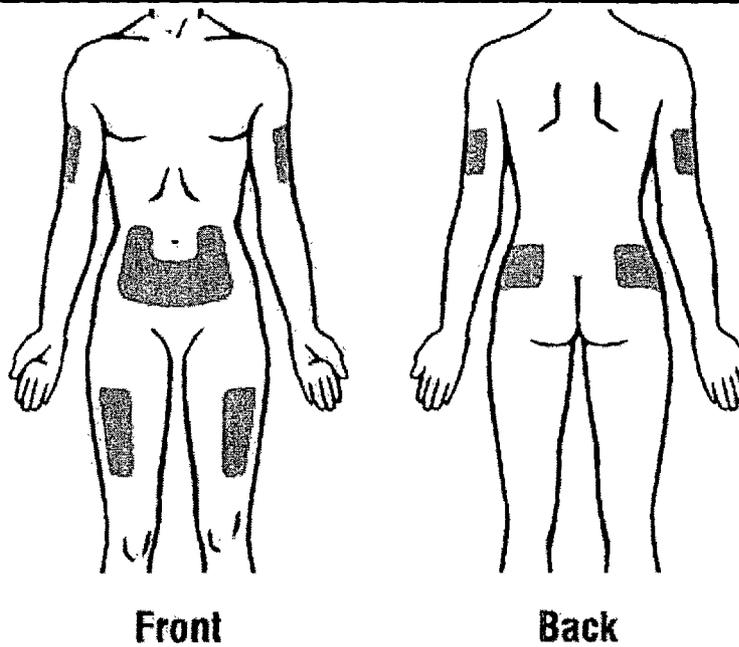


HOW TO PREPARE FOR INJECTION OF NEULASTA™

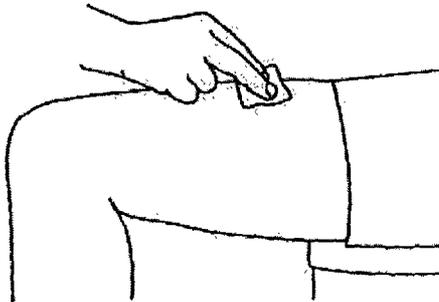
5. Remove the syringe from the package and the tray. Check to see that the plastic blue needle guard is covering the barrel of the glass syringe. **DO NOT** push the blue needle guard over the needle cover before injection. This may activate or lock the needle guard. If the blue needle guard is covering the needle that means it has been activated. **Do NOT** use that syringe. Dispose of that syringe in the puncture-proof disposal container. Use a new syringe. **Do not activate the needle guard prior to injection.**
6. Hold the syringe barrel through the needle guard windows with the needle pointing up. Holding the syringe with the needle pointing up helps to prevent medicine from leaking out of the needle. Carefully pull the needle cover straight off.
7. Check the syringe for air bubbles. If there are air bubbles, gently tap the syringe with your fingers until the air bubbles rise to the top of the syringe. Slowly push the plunger up to force the air bubbles out of the syringe.
8. Gently place the prefilled syringe with the window flat on your clean working surface so that the needle does not touch anything.

Selecting and preparing the injection site

9. Choose an injection site. Four recommended injection sites for Neulasta™ are:
 - The outer area of the upper arms
 - The abdomen, except for the two inch area around the navel
 - The front of the middle thighs
 - The upper outer areas of the buttocks



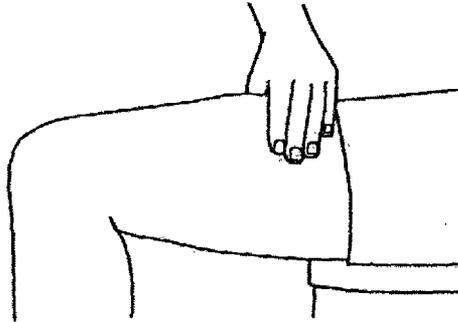
10. Clean the injection site with an alcohol swab.



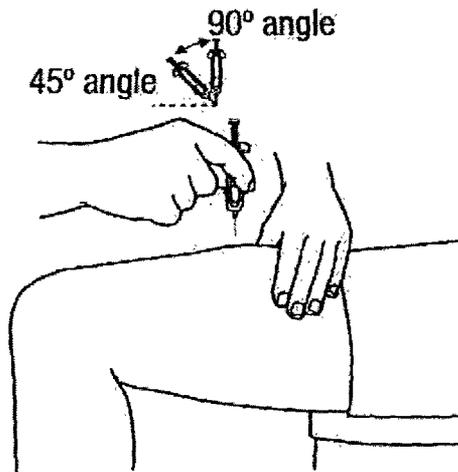
Injecting the dose of Neulasta™

11. Pick up the prefilled syringe from your clean flat working surface by grabbing the sides of the needle guard with your thumb and forefinger.

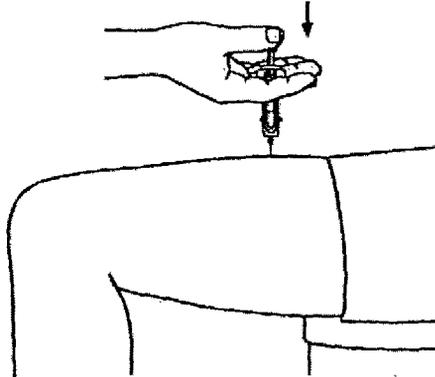
12. Hold the syringe in the hand you will use to inject Neulasta™. Use the other hand to pinch a fold of skin at the cleaned injection site. Note: Hold the syringe barrel through the needle guard windows when giving the injection.



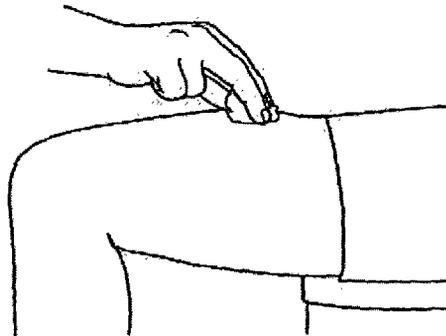
13. Holding the syringe like a pencil, use a quick “dart-like” motion to insert the needle either straight up and down (90 degree angle) or at a slight angle (45 degrees) into the skin.



14. After the needle is inserted, let go of the skin. Pull the plunger back slightly. If no blood appears, slowly push down on the plunger all the way, until all the Neulasta™ is injected. **If blood comes into the syringe, do not inject Neulasta™, because the needle has entered a blood vessel.** Withdraw the syringe and discard it in the puncture-proof container. Repeat the steps to prepare a new prefilled syringe and choose and clean a new injection site. Remember to check again for blood before injecting Neulasta™.



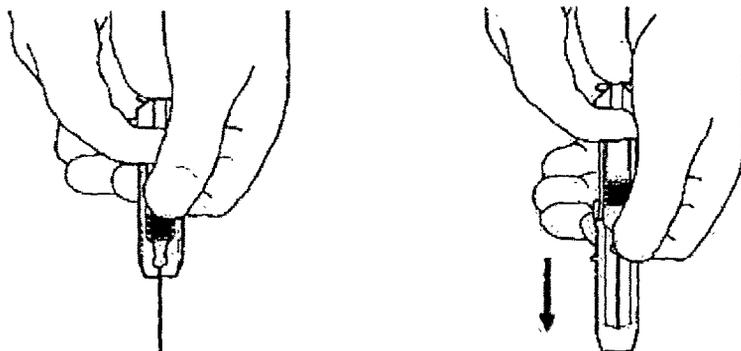
15. When the syringe is empty, pull the needle out of the skin and place a cotton ball or gauze over the injection site and press for several seconds.



16. Use a prefilled syringe with the needle guard only once.

Activating the Needle Guard after the injection has been given

17. After injecting Neulasta™ from the prefilled syringe, do not recap the needle. Keep your hands behind the needle at all times. While holding the clear plastic finger grip of the syringe with one hand, grasp the blue needle guard with your free hand and slide the blue needle guard over the needle until the needle is completely covered and the needle guard clicks into place. **NOTE: If an audible click is not heard, the needle guard may not be completely activated.**



18. Place the prefilled syringe with the activated needle guard into a puncture-proof container for proper disposal as described below.

Disposal of prefilled syringes and needle guards

You should always follow the instructions given by your doctor, nurse, or pharmacist on how to properly dispose of containers with used syringes and needle guards. There may be special state and local laws for disposal of used needles and syringes.

- Do not throw the container in the household trash. Do not recycle.
- DO NOT put the needle cover (the cap) back on the needle.
- Place all used needle covers and syringes in a hard-plastic container with a screw-on-cap, or a metal container with a plastic lid, such as a coffee can, labeled "used syringes". If a metal container is used, cut a small hole in the plastic lid and tape the lid to the metal container. If a hard-plastic container is used, always screw the cap on tightly after each use.
- Do not use glass or clear plastic containers.
- When the container is full, tape around the cap or lid to make sure the cap or lid does not come off.
- **Always** keep the container out of the reach of children.

How should Neulasta™ be stored?

Neulasta™ should be stored in the refrigerator at 2° to 8°C (36° to 46°F), but not in the freezer. Neulasta™ should be protected from light, so you should keep it in its carton until you are ready to use it. Avoid shaking Neulasta™. If Neulasta™ is accidentally frozen, allow it to thaw in the refrigerator before injecting. However, if it is frozen a second time, do not use. Neulasta™ can be left out at room temperature for up to 48 hours. Do not leave Neulasta™ in direct sunlight. For all questions about storage, contact your doctor, nurse, or pharmacist.

[Amgen Logo]

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