

1 **12-13-06-Final Draft PI**
2 **Product Information**
3 **PegIntron™**
4 **(Peginterferon alfa-2b)**
5 **Powder For Injection**
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Alpha interferons, including PegIntron™, may cause or aggravate fatal or life-threatening neuropsychiatric, autoimmune, ischemic, and infectious disorders. Patients should be monitored closely with periodic clinical and laboratory evaluations. Patients with persistently severe or worsening signs or symptoms of these conditions should be withdrawn from therapy. In many but not all cases these disorders resolve after stopping PegIntron™ therapy. See WARNINGS, ADVERSE REACTIONS.

Use with Ribavirin. Ribavirin may cause birth defects and/or death of the unborn child. Extreme care must be taken to avoid pregnancy in female patients and in female partners of male patients. Ribavirin causes hemolytic anemia. The anemia associated with REBETOL therapy may result in a worsening of cardiac disease. Ribavirin is genotoxic and mutagenic and should be considered a potential carcinogen. (See REBETOL package insert for additional information and other warnings.)

7 **DESCRIPTION**

8 PegIntron™, peginterferon alfa-2b, Powder for Injection is a covalent conjugate of
9 recombinant alfa-2b interferon with monomethoxy polyethylene glycol (PEG). The
10 average molecular weight of the PEG portion of the molecule is 12,000 daltons. The
11 average molecular weight of the PegIntron™ molecule is approximately 31,000
12 daltons. The specific activity of peginterferon alfa-2b is approximately 0.7×10^8
13 IU/mg protein.

14 Interferon alfa-2b, is a water-soluble protein with a molecular weight of
15 19,271 daltons produced by recombinant DNA techniques. It is obtained from the



16 bacterial fermentation of a strain of *Escherichia coli* bearing a genetically engineered
17 plasmid containing an interferon gene from human leukocytes.

18 **PegIntron™ is supplied in both vials and the Redipen® for subcutaneous use.**

19 **Vials**

20 Each vial contains either 74 mcg, 118.4 mcg, 177.6 mcg, or 222 mcg of PegIntron™
21 as a white to off-white tablet-like solid, that is whole/in pieces or as a loose powder,
22 and 1.11 mg dibasic sodium phosphate anhydrous, 1.11 mg monobasic sodium
23 phosphate dihydrate, 59.2 mg sucrose, and 0.074 mg polysorbate 80. Following
24 reconstitution with 0.7 mL of the supplied Sterile Water for Injection, USP, each vial
25 contains PegIntron™ at strengths of either 50 mcg per 0.5 mL, 80 mcg per 0.5 mL,
26 120 mcg per 0.5 mL, or 150 mcg per 0.5 mL.

27 **Redipen®**

28 Redipen® is a dual-chamber glass cartridge containing lyophilized PegIntron™ as a
29 white to off-white tablet or powder that is whole or in pieces in the sterile active
30 chamber and a second chamber containing Sterile Water for Injection, USP. Each
31 PegIntron™ Redipen® contains either 67.5 mcg, 108 mcg, 162 mcg, or 202.5 mcg
32 of PegIntron™, and 1.013 mg dibasic sodium phosphate anhydrous, 1.013 mg
33 monobasic sodium phosphate dihydrate, 54 mg sucrose, and 0.0675 mg polysorbate
34 80. Each cartridge is reconstituted to allow for the administration of up to 0.5 mL of
35 solution. Following reconstitution, each Redipen® contains PegIntron™ at strengths
36 of either 50 mcg per 0.5 mL, 80 mcg per 0.5 mL, 120 mcg per 0.5 mL, or 150 mcg
37 per 0.5mL for a single use. Because a small volume of reconstituted solution is lost
38 during preparation of PegIntron™, each Redipen® contains an excess amount of
39 PegIntron™ powder and diluent to ensure delivery of the labeled dose.

40 **CLINICAL PHARMACOLOGY**

41 **General:** The biological activity of PegIntron™ is derived from its interferon alfa-2b
42 moiety. Interferons exert their cellular activities by binding to specific membrane
43 receptors on the cell surface and initiate a complex sequence of intracellular events.



44 These include the induction of certain enzymes, suppression of cell proliferation,
45 immunomodulating activities such as enhancement of the phagocytic activity of
46 macrophages and augmentation of the specific cytotoxicity of lymphocytes for target
47 cells, and inhibition of virus replication in virus-infected cells. Interferon alfa
48 upregulates the Th1 T-helper cell subset in *in vitro* studies. The clinical relevance of
49 these findings is not known.

50 **Pharmacodynamics:** PegIntron™ raises concentrations of effector proteins such
51 as serum neopterin and 2'5' oligoadenylate synthetase, raises body temperature,
52 and causes reversible decreases in leukocyte and platelet counts. The correlation
53 between the *in vitro* and *in vivo* pharmacologic and pharmacodynamic and clinical
54 effects is unknown.

55 **Pharmacokinetics:** Following a single subcutaneous (SC) dose of PegIntron™,
56 the mean absorption half-life ($t_{1/2 k_a}$) was 4.6 hours. Maximal serum concentrations
57 (C_{max}) occur between 15-44 hours post-dose, and are sustained for up to 48-72
58 hours. The C_{max} and AUC measurements of PegIntron™ increase in a dose-related
59 manner. After multiple dosing, there is an increase in bioavailability of PegIntron™.
60 Week 48 mean trough concentrations (320 pg/mL; range 0, 2960) are approximately
61 3-fold higher than Week 4 mean trough concentrations (94 pg/mL; range 0, 416).
62 The mean PegIntron™ elimination half-life is approximately 40 hours (range 22 to 60
63 hours) in patients with HCV infection. The apparent clearance of PegIntron™ is
64 estimated to be approximately 22.0 mL/hr·kg. Renal elimination accounts for 30% of
65 the clearance.

66 Pegylation of interferon alfa-2b produces a product (PegIntron™) whose clearance
67 is lower than that of non-pegylated interferon alfa-2b. When compared to INTRON A,
68 PegIntron™ (1 mcg/kg) has approximately a sevenfold lower mean apparent
69 clearance and a fivefold greater mean half-life permitting a reduced dosing
70 frequency. At effective therapeutic doses, PegIntron™ has approximately tenfold
71 greater C_{max} and 50-fold greater AUC than interferon alfa-2b.

72 **Special Populations**

73 **Renal Dysfunction**



74 Following multiple dosing of PegIntron™ (1 mcg/kg SC given every week for four
75 weeks) the clearance of PegIntron™ is reduced by a mean of 17% in patients with
76 moderate renal impairment (creatinine clearance 30-49 mL/min) and by a mean of
77 44% in patients with severe renal impairment (creatinine clearance 10-29 mL/min)
78 compared to subjects with normal renal function. Clearance was similar in patients
79 with severe renal impairment not on dialysis and patients who are receiving
80 hemodialysis. The dose of PegIntron™ for monotherapy should be reduced in
81 patients with moderate or severe renal impairment (see **DOSAGE AND**
82 **ADMINISTRATION: DOSE REDUCTION**). REBETOL should not be used in patients
83 with creatinine clearance < 50 mL/min (see **REBETOL Package Insert,**
84 **WARNINGS**).

85 **Gender**

86 During the 48-week treatment period with PegIntron™, no differences in the
87 pharmacokinetic profiles were observed between male and female patients with
88 chronic hepatitis C infection.

89 **Geriatric Patients**

90 The pharmacokinetics of geriatric subjects (> 65 years of age) treated with a single
91 subcutaneous dose of 1 mcg/kg of PegIntron™ were similar in C_{max} , AUC,
92 clearance, or elimination half-life as compared to younger subjects (28 to 44 years of
93 age).

94 **Effect of Food on Absorption of Ribavirin** Both AUC_{0-t} and C_{max} increased by
95 70% when REBETOL Capsules were administered with a high-fat meal (841 kcal,
96 53.8 g fat, 31.6 g protein, and 57.4 g carbohydrate) in a single-dose pharmacokinetic
97 study (see **DOSAGE AND ADMINISTRATION**).

98 **Drug Interactions**

99 **Drugs Metabolized by Cytochrome P-450**

100 The pharmacokinetics of representative drugs metabolized by CYP1A2 (caffeine),
101 CYP2C8/9 (tolbutamide), CYP2D6 (dextromethorphan), CYP3A4 (midazolam), and

102 N-acetyltransferase (dapson) were studied in 22 patients with chronic hepatitis C
103 who received PegIntron™ (1.5mcg/kg) once weekly for 4 weeks. PegIntron™
104 treatment resulted in a 28% (mean) increase in a measure of CYP2C8/9 activity.
105 PegIntron™ treatment also resulted in a 66% (mean) increase in a measure of
106 CYP2D6 activity; however, the effect was variable as 13 patients had an increase, 5
107 patients had a decrease, and 4 patients had no significant change (see
108 **PRECAUTIONS: Drug Interactions**).

109 No significant effect was observed on the pharmacokinetics of representative drugs
110 metabolized by CYP1A2, CYP3A4, or N-acetyltransferase. The effects of
111 PegIntron™ on CYP2C19 activity were not assessed.

112 **Methadone**

113 The pharmacokinetics of concomitant administration of methadone and PegIntron™
114 were evaluated in 18 PegIntron™ naïve chronic hepatitis C patients receiving 1.5
115 mcg/kg/week PegIntron™ SC weekly. All patients were on stable methadone
116 maintenance therapy receiving ≥ 40 mg/day prior to initiating PegIntron™. Mean
117 methadone AUC was approximately 16% higher after 4 weeks of PegIntron™
118 treatment as compared to baseline. In 2 patients, methadone AUC was
119 approximately double after 4 weeks of PegIntron™ treatment as compared to
120 baseline (see **PRECAUTIONS: Drug Interactions**).

121 **Use with Ribavirin:**

122 Ribavirin has been shown *in vitro* to inhibit phosphorylation of zidovudine,
123 lamivudine and stavudine. However, in a study with another pegylated interferon in
124 combination with ribavirin, no pharmacokinetic (eg, plasma concentrations or
125 intracellular triphosphorylated active metabolite concentrations) or
126 pharmacodynamic (eg, loss of HIV/HCV virologic suppression) interaction was
127 observed when ribavirin and lamivudine (n=18), stavudine (n=10), or zidovudine
128 (n=6) were co-administered as part of a multi-drug regimen to HIV/HCV co-infected
129 patients. Exposure to didanosine or its active metabolite (dideoxyadenosine 5'-



130 triphosphate) is increased when didanosine is co-administered with ribavirin, which
131 could cause or worsen clinical toxicities (see **PRECAUTIONS: Drug Interactions**).

132 **CLINICAL STUDIES**

133 **PegIntron™ Monotherapy-Study 1**

134 A randomized study compared treatment with PegIntron™ (0.5, 1, or 1.5 mcg/kg
135 once weekly SC) to treatment with INTRON A (3 million units three times weekly SC)
136 in 1219 adults with chronic hepatitis from HCV infection. The patients were not
137 previously treated with interferon alfa, had compensated liver disease, detectable
138 HCV RNA, elevated ALT, and liver histopathology consistent with chronic hepatitis.
139 Patients were treated for 48 weeks and were followed for 24 weeks posttreatment.

140 Seventy percent of all patients were infected with HCV genotype 1, and 74 percent
141 of all patients had high baseline levels of HCV RNA (more than 2 million copies per
142 mL of serum), two factors known to predict poor response to treatment.

143 Response to treatment was defined as undetectable HCV RNA and normalization of
144 ALT at 24 weeks posttreatment. The response rates to the 1 and 1.5 mcg/kg
145 PegIntron™ doses were similar (approximately 24%) to each other and were both
146 higher than the response rate to INTRON A (12%). (See **Table 1.**)



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Table 1. Rates of Response to Treatment-Study 1

	A PegIntron™ 0.5 mcg/kg (N=315)	B PegIntron™ 1 mcg/kg (N=298)	C INTRON A 3 MIU TIW (N=307)	B - C (95% CI) Difference between PegIntron™ 1 mcg/kg and INTRON A
Treatment Response (Combined Virologic Response and ALT Normalization)	17%	24%	12%	11 (5, 18)
Virologic Response ^a	18%	25%	12%	12 (6,19)
ALT Normalization	24%	29%	18%	11 (5,18)

148 Serum HCV is measured by a research-based quantitative polymerase chain reaction assay by a central
149 laboratory.

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Patients with both viral genotype 1 and high serum levels of HCV RNA at baseline were less likely to respond to treatment with PegIntron™. Among patients with the two unfavorable prognostic variables, 8% (12/157) responded to PegIntron™ treatment and 2% (4/169) responded to INTRON A. Doses of PegIntron™ higher than the recommended dose did not result in higher response rates in these patients.

Patients receiving PegIntron™ with viral genotype 1 had a response rate of 14% (28/199) while patients with other viral genotypes had a 45% (43/96) response rate.

Ninety-six percent of the responders in the PegIntron™ groups and 100% of responders in the INTRON A group first cleared their viral RNA by week-24 of treatment (see **DOSAGE AND ADMINISTRATION**).

The treatment response rates were similar in men and women. Response rates were lower in African American and Hispanic patients and higher in Asians compared to Caucasians. Although African Americans had a higher proportion of poor prognostic factors compared to Caucasians, the number of non-Caucasians studied (9% of the total) was insufficient to allow meaningful conclusions about differences in response rates after adjusting for prognostic factors.



170 Liver biopsies were obtained before and after treatment in 60% of patients. A
 171 modest reduction in inflammation compared to baseline that was similar in all four
 172 treatment groups was observed.

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174 **PegIntron™/REBETOL Combination Therapy-Study 2**

175 A randomized study compared treatment with two PegIntron™/REBETOL regimens
 176 [PegIntron™ 1.5 mcg/kg SC once weekly (QW)/REBETOL 800 mg PO daily (in
 177 divided doses) ; PegIntron™ 1.5 mcg/kg SC QW for 4 weeks then 0.5 mcg/kg SC
 178 QW for 44 weeks/REBETOL 1000/1200 mg PO daily (in divided doses)] with
 179 INTRON A [3 MIU SC thrice weekly (TIW)/REBETOL 1000/1200 mg PO daily (in
 180 divided doses)] in 1530 adults with chronic hepatitis C. Interferon naïve patients
 181 were treated for 48 weeks and followed for 24 weeks posttreatment. Eligible
 182 patients had compensated liver disease, detectable HCV RNA, elevated ALT, and
 183 liver histopathology consistent with chronic hepatitis.

184 Response to treatment was defined as undetectable HCV RNA at 24 weeks
 185 posttreatment. The response rate to the PegIntron™ 1.5 mcg/kg plus ribavirin 800
 186 mg dose was higher than the response rate to Intron A/REBETOL (see **Table 2**).
 187 The response rate to PegIntron™ 1.5→0.5 mcg/kg/REBETOL was essentially the
 188 same as the response to INTRON A/REBETOL (data not shown).

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Table 2. Rates of Response to Treatment - Study 2

	PegIntron™ 1.5 mcg/kg QW REBETOL 800 mg QD	INTRON A 3 MIU TIW REBETOL 1000/1200 mg QD
Overall response ^{1,2}	52% (264/511)	46% (231/505)
Genotype 1	41% (141/348)	33% (112/343)
Genotype 2-6	75%(123/163)	73% (119/162)

190 ¹Serum HCV RNA is measured with a research-based quantitative polymerase chain reaction assay by a central
 191 laboratory.

192 ² Difference in overall treatment response (PegIntron™/REBETOL vs. INTRON A/REBETOL) is 6% with 95%
 193 confidence interval of (0.18, 11.63) adjusted for viral genotype and presence of cirrhosis at baseline.

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195 Patients with viral genotype 1, regardless of viral load, had a lower response
196 rate to PegIntron™ (1.5 mcg/kg)/REBETOL compared to patients with other viral
197 genotypes. Patients with both poor prognostic factors (genotype 1 and high viral
198 load) had a response rate of 30% (78/256) compared to a response rate of 29%
199 (71/247) with INTRON A/REBETOL.

200 Patients with lower body weight tended to have higher adverse event rates
201 (see **ADVERSE REACTIONS**) and higher response rates than patients with higher
202 body weights. Differences in response rates between treatment arms did not
203 substantially vary with body weight.

204 Treatment response rates with PegIntron™/REBETOL were 49% in men and
205 56% in women. Response rates were lower in African American and Hispanic
206 patients and higher in Asians compared to Caucasians. Although African Americans
207 had a higher proportion of poor prognostic factors compared to Caucasians, the
208 number of non-Caucasians studied (11% of the total) was insufficient to allow
209 meaningful conclusions about differences in response rates after adjusting for
210 prognostic factors.

211 Liver biopsies were obtained before and after treatment in 68% of patients.
212 Compared to baseline approximately 2/3 of patients in all treatment groups were
213 observed to have a modest reduction in inflammation.

214 **INDICATIONS AND USAGE**

215 PegIntron™, peginterferon alfa-2b, is indicated for use alone or in combination with
216 REBETOL (ribavirin, USP) for the treatment of chronic hepatitis C in patients with
217 compensated liver disease who have not been previously treated with interferon
218 alpha and are at least 18 years of age.

219 **CONTRAINDICATIONS**

221 **PegIntron™ is contraindicated in patients with:**

- 222 • hypersensitivity to PegIntron™ or any other component of the product
- 223 • autoimmune hepatitis



- 224 • hepatic decompensation (Child-Pugh score >6 [class B and C]) in cirrhotic CHC
225 patients before or during treatment.

226 PegIntron™/REBETOL combination therapy is additionally contraindicated in:

- 227 • patients with hypersensitivity to ribavirin or any other component of the
228 product
- 229 • women who are pregnant
- 230 • men whose female partners are pregnant
- 231 • patients with hemoglobinopathies (eg, thalassemia major, sickle-cell anemia)
- 232 • patients with creatinine clearance < 50 mL/min

233 **WARNINGS**

234 Patients should be monitored for the following serious conditions, some of which
235 may become life threatening. Patients with persistently severe or worsening signs or
236 symptoms should be withdrawn from therapy.

237 **Neuropsychiatric events**

238 Life-threatening or fatal neuropsychiatric events, including suicide, suicidal and
239 homicidal ideation, depression, relapse of drug addiction/overdose, and aggressive
240 behavior have occurred in patients with and without a previous psychiatric disorder
241 during PegIntron™ treatment and follow-up. Psychoses, hallucinations, bipolar
242 disorders, and mania have been observed in patients treated with alpha interferons.
243 PegIntron™ should be used with extreme caution in patients with a history of
244 psychiatric disorders. Patients should be advised to report immediately any
245 symptoms of depression and/or suicidal ideation to their prescribing physicians.
246 Physicians should monitor all patients for evidence of depression and other
247 psychiatric symptoms. If patients develop psychiatric problems, including clinical
248 depression, it is recommended that the patients be carefully monitored during
249 treatment and in the 6 month-follow-up period. If psychiatric symptoms persist or
250 worsen, or suicidal ideation or aggressive behavior towards others is identified, it is
251 recommended that treatment with PegIntron™ be discontinued, and the patient
252 followed, with psychiatric intervention as appropriate. In severe cases, PegIntron™



253 should be stopped immediately and psychiatric intervention instituted. (See
254 **DOSAGE AND ADMINISTRATION: Dose Reduction.**) Cases of encephalopathy
255 have been observed in some patients, usually elderly, treated with higher doses of
256 PegIntron™.

257 **Bone marrow toxicity**

258 PegIntron™ suppresses bone marrow function, sometimes resulting in severe
259 cytopenias. PegIntron™ should be discontinued in patients who develop severe
260 decreases in neutrophil or platelet counts (see **DOSAGE AND ADMINISTRATION:**
261 **Dose Reduction**). Ribavirin may potentiate the neutropenia induced by interferon
262 alpha. Very rarely alpha interferons may be associated with aplastic anemia.

263 **Hepatic Failure**

264 Chronic hepatitis C (CHC) patients with cirrhosis may be at risk of hepatic
265 decompensation and death when treated with alpha interferons, including
266 PegIntron™. Cirrhotic CHC patients co-infected with HIV receiving highly active
267 antiretroviral therapy (HAART) and alpha interferons with or without ribavirin appear
268 to be at increased risk for the development of hepatic decompensation compared to
269 patients not receiving HAART. During treatment, patients' clinical status and hepatic
270 function should be closely monitored, and PegIntron™ treatment should be
271 immediately discontinued if decompensation (Child-Pugh score >6) is observed (see
272 **CONTRAINDICATIONS**).

273 **Endocrine disorders**

274 PegIntron™ causes or aggravates hypothyroidism and hyperthyroidism.
275 Hyperglycemia has been observed in patients treated with PegIntron™. Diabetes
276 mellitus has been observed in patients treated with alpha interferons. Patients with
277 these conditions who cannot be effectively treated by medication should not begin
278 PegIntron™ therapy. Patients who develop these conditions during treatment and
279 cannot be controlled with medication should not continue PegIntron™ therapy.

280 **Cardiovascular events**

281 Cardiovascular events, which include hypotension, arrhythmia, tachycardia,
282 cardiomyopathy, angina pectoris, and myocardial infarction, have been observed in
283 patients treated with PegIntron™. PegIntron™ should be used cautiously in patients
284 with cardiovascular disease. Patients with a history of myocardial infarction and
285 arrhythmic disorder who require PegIntron™ therapy should be closely monitored
286 (see **Laboratory Tests**). Patients with a history of significant or unstable cardiac
287 disease should not be treated with PegIntron™/REBETOL combination therapy.
288 (See **REBETOL package insert**.)

289 **Cerebrovascular disorders**

290 Ischemic and hemorrhagic cerebrovascular events have been observed in patients
291 treated with Interferon alfa-based therapies, including PegIntron™. Events occurred
292 in patients with few or no reported risk factors for stroke, including patients less than
293 45 years of age. Because these are spontaneous reports, estimates of frequency
294 cannot be made and a causal relationship between Interferon alfa-based therapies
295 and these events is difficult to establish.

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298 **Pulmonary disorders**

299 Dyspnea, pulmonary infiltrates, pneumonia, bronchiolitis obliterans, interstitial
300 pneumonitis, and sarcoidosis, some resulting in respiratory failure and/or patient
301 deaths, may be induced or aggravated by PegIntron™ or alpha interferon therapy.
302 Recurrence of respiratory failure has been observed with interferon rechallenge.
303 PegIntron™ combination treatment should be suspended in patients who develop
304 pulmonary infiltrates or pulmonary function impairment. Patients who resume
305 interferon treatment should be closely monitored.



306 Colitis

307 Fatal and nonfatal ulcerative or hemorrhagic/ischemic colitis have been observed
308 within 12 weeks of the start of alpha interferon treatment. Abdominal pain, bloody
309 diarrhea, and fever are the typical manifestations. PegIntron™ treatment should be
310 discontinued immediately in patients who develop these symptoms and signs. The
311 colitis usually resolves within 1-3 weeks of discontinuation of alpha interferons.

312 Pancreatitis

313 Fatal and nonfatal pancreatitis have been observed in patients treated with alpha
314 interferon. PegIntron™ therapy should be suspended in patients with signs and
315 symptoms suggestive of pancreatitis and discontinued in patients diagnosed with
316 pancreatitis.

317 Autoimmune disorders

318 Development or exacerbation of autoimmune disorders (eg, thyroiditis, thrombotic
319 thrombocytopenic purpura, idiopathic thrombocytopenic purpura, rheumatoid
320 arthritis, interstitial nephritis, systemic lupus erythematosus, psoriasis) have been
321 observed in patients receiving PegIntron™. PegIntron™ should be used with caution
322 in patients with autoimmune disorders.

323 Ophthalmologic disorders

324 Decrease or loss of vision, retinopathy including macular edema, retinal artery or
325 vein thrombosis, retinal hemorrhages and cotton wool spots, optic neuritis, and
326 papilledema may be induced or aggravated by treatment with peginterferon alfa-2b
327 or other alpha interferons. All patients should receive an eye examination at
328 baseline. Patients with preexisting ophthalmologic disorders (eg, diabetic or
329 hypertensive retinopathy) should receive periodic ophthalmologic exams during
330 interferon alpha treatment. Any patient who develops ocular symptoms should
331 receive a prompt and complete eye examination. Peginterferon alfa-2b treatment
332 should be discontinued in patients who develop new or worsening ophthalmologic
333 disorders.



334 **Hypersensitivity**

335 Serious, acute hypersensitivity reactions (eg, urticaria, angioedema,
336 bronchoconstriction, anaphylaxis) and cutaneous eruptions (Stevens Johnson
337 syndrome, toxic epidermal necrolysis) have been rarely observed during alpha
338 interferon therapy. If such a reaction develops during treatment with PegIntron™,
339 discontinue treatment and institute appropriate medical therapy immediately.
340 Transient rashes do not necessitate interruption of treatment.

341 **Use with Ribavirin—(see also REBETOL Package Insert)**

342 **REBETOL may cause birth defects and/or death of the unborn child.**
343 **REBETOL therapy should not be started until a report of a negative pregnancy**
344 **test has been obtained immediately prior to planned initiation of therapy.**
345 **Patients should use at least two forms of contraception and have monthly**
346 **pregnancy tests (see BOXED WARNING, CONTRAINDICATIONS, and**
347 **PRECAUTIONS: Information for Patients and REBETOL package insert).**

348 **Anemia**

349 Ribavirin caused hemolytic anemia in 10% of PegIntron™/REBETOL-treated
350 patients within 1-4 weeks of initiation of therapy. Complete blood counts should be
351 obtained pretreatment and at week 2 and week 4 of therapy or more frequently if
352 clinically indicated. Anemia associated with REBETOL therapy may result in a
353 worsening of cardiac disease. Decrease in dosage or discontinuation of REBETOL
354 may be necessary. (See **DOSAGE AND ADMINISTRATION: Dose Reduction.**)

355 **PRECAUTIONS**

- 356 • PegIntron™ alone or in combination with REBETOL has not been studied in
357 patients who have failed other alpha interferon treatments.
- 358 • The safety and efficacy of PegIntron™ alone or in combination with REBETOL
359 for the treatment of hepatitis C in liver or other organ transplant recipients have
360 not been studied. In a small (n=16) single-center, uncontrolled case experience,
361 renal failure in renal allograft recipients receiving interferon alpha and ribavirin



362 combination therapy was more frequent than expected from the center's previous
363 experience with renal allograft recipients not receiving combination therapy. The
364 relationship of the renal failure to renal allograft rejection is not clear.

- 365 • The safety and efficacy of PegIntron™/REBETOL for the treatment of patients
366 with HCV co-infected with HIV or HBV have not been established.

367 **Triglycerides:**

368 Elevated triglyceride levels have been observed in patients treated with interferon
369 alfa including PegIntron™ therapy. Hypertriglyceridemia may result in pancreatitis
370 (see **WARNINGS: Pancreatitis**). Elevated triglyceride levels should be managed as
371 clinically appropriate. Discontinuation of PegIntron™ therapy should be considered
372 for patients with symptoms of potential pancreatitis, such as abdominal pain,
373 nausea, or vomiting and persistently elevated triglycerides (eg, triglycerides >1000
374 mg/dL).

375 **Patients with Renal Insufficiency**

376 Increases in serum creatinine levels have been observed in patients with renal
377 insufficiency receiving interferon alfa products, including PegIntron™. Patients with
378 impaired renal function should be closely monitored for signs and symptoms of
379 interferon toxicity, including increases in serum creatinine, and PegIntron™ dosing
380 should be adjusted accordingly or discontinued (see **CLINICAL PHARMACOLOGY:**
381 **Pharmacokinetics and DOSAGE AND ADMINISTRATION: Dose Reduction**).
382 PegIntron™ monotherapy should be used with caution in patients with creatinine
383 clearance < 50 mL/min; the potential risks should be weighed against the potential
384 benefits in these patients. Combination therapy with REBETOL must not be used in
385 patients with creatinine clearance < 50 mL/min (see **REBETOL Package Insert**
386 **WARNINGS**).

387 **Information for Patients:** Patients receiving PegIntron™ alone or in combination
388 with REBETOL should be directed in its appropriate use, informed of the benefits



389 and risks associated with treatment, and referred to the MEDICATION GUIDES for
390 PegIntron™ and, if applicable, REBETOL (ribavirin, USP).

391 Patients must be informed that REBETOL may cause birth defects and/or
392 death of the unborn child. Extreme care must be taken to avoid pregnancy in female
393 patients and in female partners of male patients during treatment with combination
394 PegIntron™/REBETOL therapy and for 6 months posttherapy. Combination
395 PegIntron™/REBETOL therapy should not be initiated until a report of a negative
396 pregnancy test has been obtained immediately prior to initiation of therapy. It is
397 recommended that patients undergo monthly pregnancy tests during therapy and for
398 6 months posttherapy (see **CONTRAINIDICATIONS and REBETOL package**
399 **insert**).

400 Patients should be informed that there are no data regarding whether
401 PegIntron™ therapy will prevent transmission of HCV infection to others. Also, it is
402 not known if treatment with PegIntron™ will cure hepatitis C or prevent cirrhosis,
403 liver failure, or liver cancer that may be the result of infection with the hepatitis C
404 virus.

405 Patients should be advised that laboratory evaluations are required before
406 starting therapy and periodically thereafter (see **Laboratory Tests**). It is advised
407 that patients be well hydrated, especially during the initial stages of treatment. “Flu-
408 like” symptoms associated with administration of PegIntron™ may be minimized by
409 bedtime administration of PegIntron™ or by use of antipyretics.

410 Patients should be advised to use a puncture-resistant container for the
411 disposal of used syringes, needles, and the Redipen®. The full container should be
412 disposed of in accordance with state and local laws. Patients should be thoroughly
413 instructed in the importance of proper disposal. Patients should also be cautioned
414 against reusing or sharing needles, syringes, or the Redipen®.

415 **Dental and periodontal disorders:**

416 Dental and periodontal disorders have been reported in patients receiving
417 PegIntron™/REBETOL combination therapy. In addition, dry mouth could have a
418 damaging effect on teeth and mucous membranes of the mouth during long-term



419 treatment with the combination of REBETOL and PegIntron™. Patients should
420 brush their teeth thoroughly twice daily and have regular dental examinations. If
421 vomiting occurs, patients should be advised to rinse out their mouth thoroughly
422 afterwards.

423 **Laboratory Tests:** PegIntron™ alone or in combination with ribavirin may cause
424 severe decreases in neutrophil and platelet counts, and hematologic, endocrine
425 (eg, TSH) and hepatic abnormalities. Transient elevations in ALT (2- to 5-fold above
426 baseline) were observed in 10% of patients treated with PegIntron™, and was not
427 associated with deterioration of other liver functions. Triglyceride levels are
428 frequently elevated in patients receiving alpha interferon therapy including
429 PegIntron™ and should be periodically monitored.

430 Patients on PegIntron™ or PegIntron™/REBETOL combination therapy
431 should have hematology and blood chemistry testing before the start of treatment
432 and then periodically thereafter. In the clinical trial CBC (including hemoglobin,
433 neutrophil, and platelet counts) and chemistries (including AST, ALT, bilirubin, and
434 uric acid) were measured during the treatment period at weeks 2, 4, 8, 12, and then
435 at 6-week intervals or more frequently if abnormalities developed. TSH levels were
436 measured every 12 weeks during the treatment period. HCV RNA should be
437 measured at 6 months of treatment. PegIntron™ or PegIntron™/REBETOL
438 combination therapy should be discontinued in patients with persistent high viral
439 levels.

440 Patients who have pre-existing cardiac abnormalities should have
441 electrocardiograms administered before treatment with PegIntron™/REBETOL.

442 **Drug Interactions**

443 Caution should be used when administering PegIntron™ with medications
444 metabolized by CYP2C8/9 (eg, warfarin and phenytoin) or CYP2D6 (eg, flecainide)
445 (see **CLINICAL PHARMACOLOGY; Drug Interactions**).

446 **Methadone**



447 In a pharmacokinetic study of 18 chronic hepatitis C patients concomitantly
448 receiving methadone, treatment with PegIntron™ once weekly for 4 weeks was
449 associated with a mean increase of 16% in methadone AUC; in 2 out of 18 patients,
450 methadone AUC doubled (see **CLINICAL PHARMACOLOGY: Drug Interactions**).
451 The clinical significance of this finding is unknown; however, patients should be
452 monitored for the signs and symptoms of increased narcotic effect.

453 **Use with Ribavirin:**

454 **Nucleoside Analogues**

455 Hepatic decompensation (some fatal) has occurred in cirrhotic HIV/HCV co-infected
456 patients receiving combination antiretroviral therapy for HIV and interferon alfa and
457 ribavirin. Adding treatment with alfa interferons alone or in combination with ribavirin
458 may increase the risk in this patient subset. Patients receiving interferon with
459 ribavirin and Nucleoside Reverse Transcriptase Inhibitors (NRTIs) should be closely
460 monitored for treatment-associated toxicities, especially hepatic decompensation
461 and anemia. Discontinuation of NRTIs should be considered as medically
462 appropriate (see **Individual NRTI Product Information**). Dose reduction or
463 discontinuation of interferon, ribavirin, or both should also be considered if
464 worsening clinical toxicities are observed, including hepatic decompensation (eg,
465 Child-Pugh > 6).

466 **Stavudine, Lamivudine, and Zidovudine:** *In vitro* studies have shown ribavirin can
467 reduce the phosphorylation of pyrimidine nucleoside analogues such as stavudine,
468 lamivudine, and zidovudine. In a study with another pegylated interferon alfa, no
469 evidence of a pharmacokinetic or pharmacodynamic (eg, loss of HIV/HCV virologic
470 suppression) interaction was seen when ribavirin was co-administered with
471 zidovudine, lamivudine, or stavudine in HIV/HCV co-infected patients (see
472 **CLINICAL PHARMACOLOGY: Drug Interactions**).

473 Although there was no evidence of loss of HIV/HCV virologic suppression
474 when ribavirin was co-administered with zidovudine, HIV/HCV co-infected patients
475 who were administered zidovudine in combination with pegylated interferon alfa and



476 ribavirin developed severe neutropenia (ANC <500) and severe anemia (hemoglobin
477 <8 g/dL) more frequently than similar patients not receiving zidovudine.

478 **Didanosine:** Co-administration of REBETOL Capsules or Oral Solution and
479 didanosine is not recommended. Reports of fatal hepatic failure, as well as
480 peripheral neuropathy, pancreatitis, and symptomatic hyperlactatemia/lactic
481 acidosis have been reported in clinical trials (see **CLINICAL PHARMACOLOGY:**
482 **Drug Interactions**).

483 **Carcinogenesis, Mutagenesis, and Impairment of Fertility**

484 **Carcinogenesis and Mutagenesis:** PegIntron™ has not been tested for its
485 carcinogenic potential. Neither PegIntron™, nor its components interferon or
486 methoxypolyethylene glycol caused damage to DNA when tested in the standard
487 battery of mutagenesis assays, in the presence and absence of metabolic activation.

488 **Use with Ribavirin:** Ribavirin is genotoxic and mutagenic and should be
489 considered a potential carcinogen. See REBETOL package insert for additional
490 warnings relevant to PegIntron™ therapy in combination with ribavirin.

491 **Impairment of Fertility:** PegIntron™ may impair human fertility. Irregular
492 menstrual cycles were observed in female cynomolgus monkeys given
493 subcutaneous injections of 4239 mcg/m² PegIntron™ alone every other day for one
494 month (approximately 345 times the recommended weekly human dose based upon
495 body surface area). These effects included transiently decreased serum levels of
496 estradiol and progesterone, suggestive of anovulation. Normal menstrual cycles and
497 serum hormone levels resumed in these animals 2 to 3 months following cessation
498 of PegIntron™ treatment. Every other day dosing with 262 mcg/m² (approximately
499 21 times the weekly human dose) had no effects on cycle duration or reproductive
500 hormone status. The effects of PegIntron™ on male fertility have not been studied.

501 **Pregnancy Category C: PegIntron™ monotherapy:** Non-pegylated Interferon
502 alfa-2b, has been shown to have abortifacient effects in *Macaca mulatta* (rhesus
503 monkeys) at 15 and 30 million IU/kg (estimated human equivalent of 5 and 10 million



504 IU/kg, based on body surface area adjustment for a 60 kg adult). PegIntron™
505 should be assumed to also have abortifacient potential. There are no adequate and
506 well-controlled studies in pregnant women. PegIntron™ therapy is to be used during
507 pregnancy only if the potential benefit justifies the potential risk to the fetus.
508 Therefore, PegIntron™ is recommended for use in fertile women only when they are
509 using effective contraception during the treatment period.

510 **Pregnancy Category X : Use with Ribavirin**

511 **Significant teratogenic and/or embryocidal effects have been demonstrated in**
512 **all animal species exposed to ribavirin. REBETOL therapy is contraindicated**
513 **in women who are pregnant and in the male partners of women who are**
514 **pregnant. See CONTRAINDICATIONS and the REBETOL Package Insert.**

515 **Ribavirin Pregnancy Registry: A Ribavirin Pregnancy Registry has been**
516 **established to monitor maternal-fetal outcomes of pregnancies in female**
517 **patients and female partners of male patients exposed to ribavirin during**
518 **treatment and for 6 months following cessation of treatment. Physicians and**
519 **patients are encouraged to report such cases by calling 1-800-593-2214.**

520 **Nursing Mothers:** It is not known whether the components of PegIntron™ and/or
521 REBETOL are excreted in human milk. Studies in mice have shown that mouse
522 interferons are excreted in breast milk. Because of the potential for adverse
523 reactions from the drug in nursing infants, a decision must be made whether to
524 discontinue nursing or discontinue the PegIntron™ and REBETOL treatment, taking
525 into account the importance of the therapy to the mother.

526 **Pediatric:** Safety and effectiveness in pediatric patients below the age of 18 years
527 have not been established.

528 **Geriatric:** In general, younger patients tend to respond better than older patients to
529 interferon-based therapies. Clinical studies of PegIntron™ alone or in combination
530 with REBETOL did not include sufficient numbers of subjects aged 65 and over;
531 however, to determine whether they respond differently than younger subjects.



532 Treatment with alpha interferons, including PegIntron™, is associated with
533 neuropsychiatric, cardiac, pulmonary, GI, and systemic (flu-like) adverse effects.
534 Because these adverse reactions may be more severe in the elderly, caution should
535 be exercised in the use of PegIntron™ in this population. This drug is known to be
536 substantially excreted by the kidney. Because elderly patients are more likely to
537 have decreased renal function, the risk of toxic reactions to this drug may be greater
538 in patients with impaired renal function (see **CLINICAL PHARMACOLOGY: Special**
539 **Populations: Renal Dysfunction**). REBETOL should not be used in patients with
540 creatinine clearance <50 mL/min. When using PegIntron™/REBETOL therapy, refer
541 also to the REBETOL Package Insert.

542 **ADVERSE REACTIONS**

543 Nearly all study patients in clinical trials experienced one or more adverse events. In
544 the PEG monotherapy trial the incidence of serious adverse events was similar
545 (about 12%) in all treatment groups. In the PegIntron™/REBETOL combination trial,
546 the incidence of serious adverse events was 17% in the PegIntron™/REBETOL
547 groups compared to 14% in the INTRON A/REBETOL group.

548 In many but not all cases, adverse events resolved after dose reduction or
549 discontinuation of therapy. Some patients experienced ongoing or new serious
550 adverse events during the 6-month follow-up period. In the PegIntron™/REBETOL
551 trial, 13 patients experienced life-threatening psychiatric events (suicidal ideation or
552 attempt) and one patient accomplished suicide.

553 There have been five patient deaths which occurred in clinical trials: one
554 suicide in a patient receiving PegIntron™ monotherapy and one suicide in a patient
555 receiving PegIntron™/REBETOL combination therapy; two deaths among patients
556 receiving INTRON A monotherapy (1 murder/suicide and 1 sudden death) and one
557 patient death in the INTRON A/REBETOL group (motor vehicle accident).

558 Overall, 10-14% of patients receiving PegIntron™, alone or in combination
559 with REBETOL, discontinued therapy compared with 6% treated with INTRON A
560 alone and 13% treated with INTRON A in combination with REBETOL. The most



561 common reasons for discontinuation of therapy were related to psychiatric, systemic
562 (eg, fatigue, headache), or gastrointestinal adverse events.

563 In the combination therapy trial, dose reductions due to adverse reactions
564 occurred in 42% of patients receiving PegIntron™ (1.5 mcg/kg)/REBETOL and in
565 34% of those receiving INTRON A/REBETOL. The majority of patients (57%)
566 weighing 60 kg or less receiving PegIntron™ (1.5 mcg/kg)/REBETOL required dose
567 reduction. Reduction of interferon was dose related (PegIntron™ 1.5 mcg/kg >
568 PegIntron™ 0.5 mcg/kg or INTRON A), 40%, 27%, 28%, respectively. Dose
569 reduction for REBETOL was similar across all three groups, 33-35%. The most
570 common reasons for dose modifications were neutropenia (18%), or anemia (9%)
571 (see **Laboratory Values**). Other common reasons included depression, fatigue,
572 nausea, and thrombocytopenia.

573 In the PegIntron™/REBETOL combination trial the most common adverse
574 events were psychiatric which occurred among 77% of patients and included most
575 commonly depression, irritability, and insomnia, each reported by approximately 30-
576 40% of subjects in all treatment groups. Suicidal behavior (ideation, attempts, and
577 suicides) occurred in 2% of all patients during treatment or during follow-up after
578 treatment cessation (see **WARNINGS**).

579 PegIntron™ induced fatigue or headache in approximately two-thirds of
580 patients, and induced fever or rigors in approximately half of the patients. The
581 severity of some of these systemic symptoms (eg, fever and headache) tended to
582 decrease as treatment continues. The incidence tends to be higher with
583 PegIntron™ than with INTRON A therapy alone or in combination with REBETOL.

584 Application site inflammation and reaction (eg, bruise, itchiness, irritation)
585 occurred at approximately twice the incidence with PegIntron™ therapies (in up to
586 75% of patients) compared with INTRON A. However, injection site pain was
587 infrequent (2-3%) in all groups.

588 Other common adverse events in the PegIntron™/REBETOL group included
589 myalgia (56%), arthralgia (34%), nausea (43%), anorexia (32%), weight loss (29%),
590 alopecia (36%), and pruritus (29%).



591 In the PegIntron™ monotherapy trial the incidence of severe adverse events
 592 was 13% in the INTRON A group and 17% in the PegIntron™ groups. In the
 593 PegIntron™/REBETOL combination therapy trial, the incidence of severe adverse
 594 events was 23% in the INTRON A/REBETOL group and 31-34% in the
 595 PegIntron™/REBETOL groups. The incidence of life-threatening adverse events
 596 was $\leq 1\%$ across all groups in the monotherapy and combination therapy trials.
 597 Adverse events that occurred in the clinical trial at $>5\%$ incidence are provided in
 598 **Table 3** by treatment group. Due to potential differences in ascertainment
 599 procedures, adverse event rate comparisons across studies should not be made.

600 **Table 3. Adverse Events Occurring in $> 5\%$ of Patients**

Adverse Events	Percentage of Patients Reporting Adverse Events*			
	Study 1		Study 2	
	PegIntron™ 1 mcg/kg (n=297)	INTRON A 3 MIU (n=303)	PegIntron™ 1.5 mcg/kg/ REBETOL (n=511)	INTRON A/ REBETOL (n=505)
Application Site				
Injection Site Inflammation/Reaction	47	20	75	49
Autonomic Nervous Sys.				
Mouth Dry	6	7	12	8
Sweating Increased	6	7	11	7
Flushing	6	3	4	3
Body as a Whole				
Fatigue/Asthenia	52	54	66	63
Headache	56	52	62	58
Rigors	23	19	48	41
Fever	22	12	46	33
Weight Decrease	11	13	29	20
RUQ Pain	8	8	12	6
Chest Pain	6	4	8	7
Malaise	7	6	4	6
Central/Periph. Nerv. Sys.				



Adverse Events	Percentage of Patients Reporting Adverse Events*			
	Study 1		Study 2	
	PegIntron™ 1 mcg/kg (n=297)	INTRON A 3 MIU (n=303)	PegIntron™ 1.5 mcg/kg/ REBETOL (n=511)	INTRON A/ REBETOL (n=505)
Dizziness	12	10	21	17
Endocrine				
Hypothyroidism	5	3	5	4
Gastrointestinal				
Nausea	26	20	43	33
Anorexia	20	17	32	27
Diarrhea	18	16	22	17
Vomiting	7	6	14	12
Abdominal Pain	15	11	13	13
Dyspepsia	6	7	9	8
Constipation	1	3	5	5
Hematologic Disorders				
Neutropenia	6	2	26	14
Anemia	0	0	12	17
Leukopenia	<1	0	6	5
Thrombocytopenia	7	<1	5	2
Liver and Biliary System				
Hepatomegaly	6	5	4	4
Musculoskeletal				
Myalgia	54	53	56	50
Arthralgia	23	27	34	28
Musculoskeletal Pain	28	22	21	19
Psychiatric				
Insomnia	23	23	40	41
Depression	29	25	31	34
Anxiety/Emotional Lability/Irritability	28	34	47	47
Concentration Impaired	10	8	17	21
Agitation	2	2	8	5
Nervousness	4	3	6	6
Reproductive, Female				
Menstrual Disorder	4	3	7	6
Resistance Mechanism				
Infection Viral	11	10	12	12
Infection Fungal	<1	3	6	1
Respiratory System				
Dyspnea	4	2	26	24



Percentage of Patients Reporting Adverse Events*				
Adverse Events	Study 1		Study 2	
	PegIntron™ 1 mcg/kg (n=297)	INTRON A 3 MIU (n=303)	PegIntron™ 1.5 mcg/kg/ REBETOL (n=511)	INTRON A/ REBETOL (n=505)
Coughing	8	5	23	16
Pharyngitis	10	7	12	13
Rhinitis	2	2	8	6
Sinusitis	7	7	6	5
Skin and Appendages				
Alopecia	22	22	36	32
Pruritus	12	8	29	28
Rash	6	7	24	23
Skin Dry	11	9	24	23
Special Senses Other,				
Taste Perversion	<1	2	9	4
Vision Disorders				
Vision blurred	2	3	5	6
Conjunctivitis	4	2	4	5

601 *Patients reporting one or more adverse events. A patient may have reported more than one
602 adverse event within a body system/organ class category.

603 Many patients continued to experience adverse events several months after
604 discontinuation of therapy. By the end of the 6-month follow-up period, the
605 incidence of ongoing adverse events by body class in the PegIntron™
606 1.5/REBETOL group was 33% (psychiatric), 20% (musculoskeletal), and 10% (for
607 endocrine and for GI). In approximately 10-15% of patients weight loss, fatigue, and
608 headache had not resolved.

609 Individual serious adverse events occurred at a frequency $\leq 1\%$ and included
610 suicide attempt, suicidal ideation, severe depression; psychosis, aggressive
611 reaction, relapse of drug addiction/overdose; nerve palsy (facial, oculomotor);
612 cardiomyopathy, myocardial infarction, angina, pericardial effusion, retinal ischemia,
613 retinal artery or vein thrombosis, blindness, decreased visual acuity, optic neuritis,
614 transient ischemic attack, supraventricular arrhythmias, loss of consciousness;
615 neutropenia, infection (sepsis, pneumonia, abscess, cellulitis); emphysema,
616 bronchiolitis obliterans, pleural effusion, gastroenteritis, pancreatitis, gout,
617 hyperglycemia, hyperthyroidism and hypothyroidism, autoimmune thrombocytopenia
618 with or without purpura, rheumatoid arthritis, interstitial nephritis, lupus-like



619 syndrome, sarcoidosis, aggravated psoriasis; urticaria, injection-site necrosis,
620 vasculitis, phototoxicity.

621 **Laboratory Values**

622 Changes in selected laboratory values during treatment with PegIntron™ alone or in
623 combination with REBETOL treatment are described below. **Decreases in**
624 **hemoglobin, neutrophils, and platelets may require dose reduction or**
625 **permanent discontinuation from therapy. (See DOSAGE AND**
626 **ADMINISTRATION: Dose Reduction.)**

627 **Hemoglobin.** REBETOL induced a decrease in hemoglobin levels in approximately
628 two thirds of patients. Hemoglobin levels decreased to <11g/dL in about 30% of
629 patients. Severe anemia (<8 g/dL) occurred in <1% of patients. Dose modification
630 was required in 9% and 13% of patients in the PegIntron™/REBETOL and INTRON
631 A /REBETOL groups. Hemoglobin levels become stable by treatment week 4-6 on
632 average. Hemoglobin levels return to baseline between 4 and 12 weeks post-
633 treatment. In the PegIntron™ monotherapy trial, hemoglobin decreases were
634 generally mild and dose modifications were rarely necessary (see **DOSAGE AND**
635 **ADMINISTRATION: Dose Reduction**).

636 **Neutrophils.** Decreases in neutrophil counts were observed in a majority of patients
637 treated with PegIntron™ alone (70%) or as combination therapy with REBETOL
638 (85%) and INTRON A/REBETOL (60%). Severe potentially life-threatening
639 neutropenia (<0.5 x 10⁹/L) occurred in 1% of patients treated with PegIntron™
640 monotherapy, 2% of patients treated with INTRON A/REBETOL, and in 4% of
641 patients treated with PegIntron™/REBETOL. Two percent of patients receiving
642 PegIntron™ monotherapy and 18% of patients receiving PegIntron™ /REBETOL
643 required modification of interferon dosage. Few patients (< 1%) required permanent
644 discontinuation of treatment. Neutrophil counts generally return to pre-treatment
645 levels within 4 weeks of cessation of therapy. (See **DOSAGE AND**
646 **ADMINISTRATION: Dose Reduction**.)

647 **Platelets.** Platelet counts decrease in approximately 20% of patients treated with
648 PegIntron™ alone or with REBETOL and in 6% of patients treated with INTRON



649 A/REBETOL. Severe decreases in platelet counts ($<50,000/\text{mm}^3$) occur in $<1\%$ of
650 patients. Patients may require discontinuation or dose modification as a result of
651 platelet decreases. (See **DOSAGE AND ADMINISTRATION: Dose Reduction.**) In
652 the PegIntron™/REBETOL combination therapy trial, 1% or 3% of patients required
653 dose modification of INTRON A or PegIntron™, respectively. Platelet counts
654 generally returned to pre-treatment levels within 4 weeks of the cessation of therapy.

655 **Triglycerides.** Elevated triglyceride levels have been observed in patients treated
656 with interferon alphas including PegIntron™.

657 **Thyroid Function.** Development of TSH abnormalities, with and without clinical
658 manifestations, are associated with interferon therapies. Clinically apparent thyroid
659 disorders occur among patients treated with either INTRON A or PegIntron™ (with
660 or without REBETOL) at a similar incidence (5% for hypothyroidism and 3% for
661 hyperthyroidism). Subjects developed new onset TSH abnormalities while on
662 treatment and during the follow-up period. At the end of the follow-up period, 7% of
663 subjects still had abnormal TSH values.

664 **Bilirubin and uric acid.** In the PegIntron™/REBETOL trial, 10-14% of patients
665 developed hyperbilirubinemia and 33-38% developed hyperuricemia in association
666 with hemolysis. Six patients developed mild to moderate gout.

667 **Postmarketing Experience**

668 The following adverse reactions have been identified and reported during post-
669 approval use of PegIntron™ therapy: aphthous stomatitis, erythema multiforme,
670 hearing impairment, hearing loss, memory loss, migraine headache, myositis,
671 peripheral neuropathy, renal insufficiency, renal failure, rhabdomyolysis, seizures,
672 Stevens Johnson syndrome, thrombotic thrombocytopenic purpura, toxic epidermal
673 necrolysis, vertigo. Because the reports of these reactions are voluntary and the
674 population of uncertain size, it is not always possible to reliably estimate the
675 frequency of the reaction or establish a causal relationship to drug exposure.

676 **Immunogenicity:** Approximately 2% of patients receiving PegIntron™ (32/1759) or
677 INTRON A (11/728) with or without REBETOL developed low-titer (≤ 160)
678 neutralizing antibodies to PegIntron™ or INTRON A. The clinical and pathological



679 significance of the appearance of serum neutralizing antibodies is unknown. No
680 apparent correlation of antibody development to clinical response or adverse events
681 was observed. The incidence of posttreatment-binding antibody ranged from 8 to
682 15 percent. The data reflect the percentage of patients whose test results were
683 considered positive for antibodies to PegIntron™ in a Biacore assay that is used to
684 measure binding antibodies, and in an antiviral neutralization assay, which
685 measures serum-neutralizing antibodies. The percentage of patients whose test
686 results were considered positive for antibodies is highly dependent on the sensitivity
687 and specificity of the assays. Additionally, the observed incidence of antibody
688 positivity in these assays may be influenced by several factors including sample
689 timing and handling, concomitant medications, and underlying disease. For these
690 reasons, comparison of the incidence of antibodies to PegIntron™ with the incidence
691 of antibodies to other products may be misleading.

692 **OVERDOSAGE**

693 There is limited experience with overdosage. In the clinical studies, a few patients
694 accidentally received a dose greater than that prescribed. There were no instances
695 in which a participant in the monotherapy or combination therapy trials received
696 more than 10.5 times the intended dose of PegIntron™. The maximum dose
697 received by any patient was 3.45 mcg/kg weekly over a period of approximately 12
698 weeks. The maximum known overdosage of REBETOL was an intentional ingestion
699 of 10 g (fifty 200-mg capsules). There were no serious reactions attributed to these
700 overdosages. In cases of overdosing, symptomatic treatment and close observation
701 of the patient are recommended.

702 **DOSAGE AND ADMINISTRATION**

703 There are no safety and efficacy data on treatment for longer than one year. A
704 patient should self-inject PegIntron™ only if it has been determined that it is
705 appropriate and the patient agrees to medical follow-up as necessary and training in
706 proper injection technique has been given to him/her.



707 It is recommended that patients receiving PegIntron™, alone or in
 708 combination with ribavirin, be discontinued from therapy if HCV viral levels remain
 709 high after 6 months of therapy.

710 **PegIntron™ Monotherapy**

711 The recommended dose of PegIntron™ regimen is 1 mcg/kg/week subcutaneously
 712 for one year. The dose should be administered on the same day of the week.

713 The volume of PegIntron™ to be injected depends on patient weight (see **Table 4**
 714 below).

715 **Table 4 Recommended PegIntron™ Monotherapy Dosing**

Body weight kg	PegIntron™ Redipen® or Vial Strength to Use	Amount of PegIntron™ (mcg) To Administer	Volume (mL)* of PegIntron™ to Administer
≤45	50 mcg per 0.5 mL	40	0.4
46 - 56		50	0.5
57 - 72	80 mcg per 0.5 mL	64	0.4
73 – 88		80	0.5
89 – 106	120 mcg per 0.5 mL	96	0.4
107 - 136		120	0.5
137 - 160	150 mcg per 0.5 mL	150	0.5

716 * When reconstituted as directed.

717

718 **PegIntron™/REBETOL Combination Therapy**

719 When administered in combination with REBETOL, the recommended dose of
 720 PegIntron™ is 1.5 micrograms/kg/week. The volume of PegIntron™ to be injected
 721 depends on the strength of PegIntron™ and patient's body weight. (See **Table 5.**)



722 **TABLE 5. Recommended PegIntron™ Combination Therapy Dosing**

723

Body weight kg	PegIntron™ Redipen® or Vial Strength to Use	Amount of PegIntron™ (mcg) To Administer	Volume (mL)* of PegIntron™ to Administer
<40	50 mcg per 0.5 mL	50	0.5
40-50	80 mcg per 0.5 mL	64	0.4
51-60		80	0.5
61-75	120 mcg per 0.5 mL	96	0.4
76-85		120	0.5
>85	150 mcg per 0.5 mL	150	0.5

724

* When reconstituted as directed.

725

726

The recommended dose of REBETOL is 800 mg/day in 2 divided doses: two capsules (400 mg) with breakfast and two capsules (400 mg) with dinner. REBETOL should not be used in patients with creatinine clearance <50 mL/min.

727

728

729 **Dose Reduction**

730

If a serious adverse reaction develops during the course of treatment (see **WARNINGS**) discontinue or modify the dosage of PegIntron™ and/or REBETOL until the adverse event abates or decreases in severity. If persistent or recurrent serious adverse events develop despite adequate dosage adjustment, discontinue treatment. For guidelines for dose modifications and discontinuation based on laboratory parameters, see **Tables 6** and **7**. Dose reduction of PegIntron™ may be accomplished by utilizing a lower dose strength as shown in **Table 8** or **9**. For vials, 50% dose reduction may also be accomplished by reducing the volume administered by one-half without changing the dose strength.

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739 In the combination therapy trial, dose reductions occurred among 42% of patients
 740 receiving PegIntron™ 1.5 mcg/kg/REBETOL 800 mg daily including 57% of those
 741 patients weighing 60 kg or less (see **ADVERSE REACTIONS**).

742 **Table 6: Guidelines for Modification or Discontinuation of PegIntron™ or**
 743 **PegIntron™/REBETOL and for Scheduling Visits for Patients with Depression**

Depression Severity ¹	Initial Management (4-8 wks)			Depression	
	Dose modification	Visit schedule	Remains stable	Improves	Worsens
Mild	No change	Evaluate once weekly by visit and/or phone.	Continue weekly visit schedule.	Resume normal visit schedule.	(See moderate or severe depression)
Moderate	Decrease IFN dose 50%	Evaluate once weekly (office visit at least every other week).	Consider psychiatric consultation. Continue reduced dosing.	If symptoms improve and are stable for 4 wks, may resume normal visit schedule. Continue reduced dosing or return to normal dose.	(See severe depression)
Severe	Discontinue IFN/R permanently.	Obtain immediate psychiatric consultation.	Psychiatric therapy as necessary		

¹ See DSM-IV for definitions.

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Table 7. Guidelines for Dose Modification and Discontinuation of PegIntron™ or PegIntron™/REBETOL for Hematologic Toxicity

Laboratory Values		PegIntron™	REBETOL
Hgb*	<10.0 g/dL <8.5 g/dL	----- Permanently discontinue	Decrease by 200mg/day Permanently discontinue
WBC	<1.5 x10 ⁹ /L <1.0 x10 ⁹ /L	Reduce dose by 50% Permanently discontinue	----- Permanently discontinue
Neutrophil	<0.75 x10 ⁹ /L <0.5 x10 ⁹ /L	Reduce dose by 50% Permanently discontinue	----- Permanently discontinue
Platelets	<80 x10 ⁹ /L <50 x10 ⁹ /L	Reduce dose by 50% Permanently discontinue	----- Permanently discontinue



748 * For patients with a history of stable cardiac disease receiving PegIntron™ in combination with
 749 ribavirin, the PegIntron™ dose should be reduced by half and the ribavirin dose by 200 mg/day if a > 2g/dL
 750 decrease in hemoglobin is observed during any 4-week period. Both PegIntron™ and ribavirin should be
 751 permanently discontinued if patients have hemoglobin levels <12 g/dL after this ribavirin dose reduction.

752

753 **Table 8. Reduced PegIntron™ Dose (0.5mcg /kg) for (1mcg /kg) Monotherapy**

754

Body weight kg	PegIntron™ Redipen®/Vial Strength to Use	Amount of PegIntron™(mcg) To Administer	Volume (mL)** of PegIntron™ to Administer
≤45	50 mcg per 0.5 mL*	20	0.2
46 - 56		25	0.25
57 - 72	50 mcg per 0.5 mL	30	0.3
73 – 88		40	0.4
89-106	50 mcg per 0.5 mL	50	0.5
107-136	80 mcg per 0.5 mL	64	0.4
137-160		80	0.5

755 * Must use vial. Minimum delivery for Redipen® 0.3 mL.

756 ** When reconstituted as directed.



757 **TABLE 9. Reduced PegIntron™ Dose (0.75 mcg /kg) for (1.5 mcg/kg) Combination**
 758 **Therapy**

759

Body weight (kg)	PegIntron™ Redipen®/Vial Strength to Use	Amount of PegIntron™(mcg) to Administer	Volume (mL)** of PegIntron™ to Administer
<40	50 mcg per 0.5 ml*	25	0.25
40-50	50 mcg per 0.5 ml	30	0.3
51-60		40	0.4
61-75	50 mcg per 0.5 ml	50	0.5
76-85	80 mcg per 0.5 ml	64	0.4
>85		80	0.5

760 * Must use vial. Minimum delivery for Redipen® 0.3 mL

761 ** When reconstituted as directed

762 **Renal Function**

763 In patients with moderate renal dysfunction (creatinine clearance 30-50 mL/min), the
 764 PegIntron™ dose should be reduced by 25%. Patients with severe renal
 765 dysfunction (creatinine clearance 10-29 mL/min) including those on hemodialysis,
 766 should have the PegIntron™ dose reduced by 50%. If renal function decreases
 767 during treatment, PegIntron™ therapy should be discontinued.

768 **Preparation and Administration**769 **PegIntron™ Redipen®**

770 PegIntron™ Redipen® consists of a dual-chamber glass cartridge with sterile,
 771 lyophilized peginterferon alfa-2b in the active chamber and Sterile Water for
 772 Injection, USP in the diluent chamber. The PegIntron™ in the glass cartridge should
 773 appear as a white to off-white tablet shaped solid that is whole or in pieces, or
 774 powder. To reconstitute the lyophilized peginterferon alfa-2b in the Redipen®, hold



775 the Redipen® upright (dose button down) and press the two halves of the pen
776 together until there is an audible click. Gently invert the pen to mix the solution. **DO**
777 **NOT SHAKE.** The reconstituted solution has a concentration of either 50 mcg per
778 0.5 mL, 80 mcg per 0.5 mL, 120 mcg per 0.5 mL, or 150 mcg per 0.5 mL for a single
779 subcutaneous injection. Visually inspect the solution for particulate matter and
780 discoloration prior to administration. The reconstituted solution should be clear and
781 colorless. Do not use if the solution is discolored or cloudy, or if particulates are
782 present.

783 Keeping the pen upright, attach the supplied needle and select the
784 appropriate PegIntron™ dose by pulling back on the dosing button until the dark
785 bands are visible and turning the button until the dark band is aligned with the
786 correct dose. The prepared PegIntron™ solution is to be injected subcutaneously.

787 The PegIntron™ Redipen® is a single-use pen and does not contain a
788 preservative. The reconstituted solution should be used immediately and cannot be
789 stored for more than 24 hours at 2°-8° C (see **Storage**). **DO NOT REUSE THE**
790 **REDIPEN®.** The sterility of any remaining product can no longer be guaranteed.
791 **DISCARD THE UNUSED PORTION.** Pooling of unused portions of some
792 medications has been linked to bacterial contamination and morbidity.

793 **PegIntron™ Vials**

794 Two B-D® Safety Lok™ syringes are provided in the package; one syringe is for the
795 reconstitution steps and one for the patient injection. There is a plastic safety sleeve
796 to be pulled over the needle after use. The syringe locks with an audible click when
797 the green stripe on the safety sleeve covers the red stripe on the needle.
798 Instructions for the preparation and administration of PegIntron™ Powder for
799 Injection are provided below.

800 **Reconstitute the PegIntron™ lyophilized product with only 0.7 mL of**
801 **1.25 mL of supplied diluent (Sterile Water for Injection, USP). The diluent vial**
802 **is for single use only. The remaining diluent should be discarded.** No other
803 medications should be added to solutions containing PegIntron™, and PegIntron™
804 should not be reconstituted with other diluents. Swirl gently to hasten complete



805 dissolution of the powder. The reconstituted solution should be clear and colorless.
806 Visually inspect the solution for particulate matter and discoloration prior to
807 administration. The solution should not be used if discolored or cloudy, or if
808 particulates are present.

809 The appropriate PegIntron™ dose should be withdrawn and injected
810 subcutaneously. PegIntron™ vials are for single use only and do not contain a
811 preservative. The reconstituted solution should be used immediately and cannot be
812 stored for more than 24 hours at 2°-8° C (see **Storage**). **DO NOT REUSE THE**
813 **VIAL**. The sterility of any remaining product can longer be guaranteed. **DISCARD**
814 **THE UNUSED PORTION**. Pooling of unused portions of some medications has
815 been linked to bacterial contamination and morbidity.

816 After preparation and administration of the PegIntron™ for injection, it is
817 essential to follow the state and/or local procedures for proper disposal of syringes,
818 needles, and the Redipen®. A puncture-resistant container should be used for
819 disposal. Patients should be instructed in how to properly dispose of used syringes,
820 needles, or the Redipen® and be cautioned against the reuse of these items.

821 **Storage**

822 **PegIntron™ Redipen®**

823 PegIntron™ Redipen® should be stored at 2°- 8°C (36°-46°F).

824 After reconstitution, the solution should be used immediately, but may be stored up
825 to 24 hours at 2° - 8°C (36° - 46°F). The reconstituted solution contains no
826 preservative, and is clear and colorless. **DO NOT FREEZE.**

827 **PegIntron™ Vials**

828 PegIntron™, should be stored at 25°C (77°F); excursions permitted to 15°-30°C
829 (59°-86°F) [see USP Controlled Room Temperature]. After reconstitution with
830 supplied Diluent the solution should be used immediately, but may be stored up to
831 24 hours at 2°-8°C (36°-46°F). The reconstituted solution contains no preservative,
832 is clear and colorless. **DO NOT FREEZE.**



833 **HOW SUPPLIED**834 **PegIntron™ Redipen®**

Each PegIntron™ Redipen® Package Contains:	
A box containing one 50 mcg per 0.5 mL PegIntron™ Redipen® and 1 B-D® needle and 2 alcohol swabs.	(NDC 0085-1323-01)
A box containing one 80 mcg per 0.5 mL PegIntron™ Redipen® and 1 B-D® needle and 2 alcohol swabs.	(NDC 0085-1316-01)
A box containing one 120 mcg per 0.5 mL PegIntron™ Redipen® and 1 B-D® needle and 2 alcohol swabs.	(NDC 0085-1297-01)
A box containing one 150 mcg per 0.5 mL PegIntron™ Redipen® and 1 B-D® needle and 2 alcohol swabs.	(NDC 0085-1370-01)

835

Each PegIntron™ Redipen® PAK 4 Contains:	
A box containing four 50 mcg per 0.5 mL PegIntron™ Redipen® units, each containing 1 B-D® needle and 2 alcohol swabs.	(NDC 0085-1323-02)
A box containing four 80 mcg per 0.5 mL PegIntron™ Redipen® units, each containing 1 B-D® needle and 2 alcohol swabs.	(NDC 0085-1316-02)
A box containing four 120 mcg per 0.5 mL PegIntron™ Redipen® units, each containing 1 B-D® needle and 2 alcohol swabs.	(NDC 0085-1297-02)
A box containing four 150 mcg per 0.5 mL PegIntron™ Redipen® units, each containing 1 B-D® needle and 2 alcohol swabs.	(NDC 0085-1370-02)

836

837

PegIntron™ Vials

Each PegIntron™ Package Contains:	
A box containing one 50 mcg per 0.5 mL vial of PegIntron™ Powder for Injection and one 1.25 mL vial of Diluent (Sterile Water for Injection, USP), 2 B-D® Safety Lok™ syringes with a safety sleeve and 2 alcohol swabs.	(NDC 0085-1368-01)
A box containing one 80 mcg per 0.5 mL vial of PegIntron™ Powder for Injection and one 1.25 mL vial of Diluent (Sterile Water for Injection, USP), 2 B-D® Safety Lok™ syringes with a safety sleeve and 2 alcohol swabs.	(NDC 0085-1291-01)
A box containing one 120 mcg per 0.5 mL vial of PegIntron™ Powder for Injection and one 1.25 mL vial of Diluent (Sterile Water for Injection, USP), 2 B-D® Safety Lok™ syringes with	(NDC 0085-1304-01)



a safety sleeve and 2 alcohol swabs.	
A box containing one 150 mcg per 0.5 mL vial of PegIntron™ Powder for Injection and one 1.25 mL vial of Diluent (Sterile Water for Injection, USP), 2 B-D® Safety Lok™ syringes with a safety sleeve and 2 alcohol swabs.	(NDC 0085-1279-01)

838 Schering Corporation

839 Kenilworth, NJ 07033 USA

840 **REV. 12/06**

841 U.S. Patent Nos. 5,908,621; 5,951,974; 6,042,822; 6,177,074; 6,180,096; 6,250,469;

842 6,482,613; 6,524,570; 6,610,830

843 Copyright© 2003, 2005, Schering Corporation, All rights reserved.

844 B-D is a registered trademark of Becton-Dickinson and Company.

845 Safety-Lok is a trademark of Becton Dickinson and Company



12-13-06-revsied MedGuide Powder-Final Draft**MEDICATION GUIDE****PegIntron™****Peginterferon alfa-2b****Including appendix with instructions for using PegIntron™ Powder for Injection**

Read this Medication Guide carefully before you start taking PegIntron™ (**Peg In-tron**) or PegIntron™/REBETOL (**REB-eh-tole**) combination therapy. Read the Medication Guide each time you refill your prescription because there may be new information. The information in this Medication Guide does not take the place of talking with your health care provider (doctor, nurse, nurse practitioner, or physician's assistant).

If you are taking PegIntron™/REBETOL combination therapy, also read the Medication Guide for REBETOL (ribavirin, USP) Capsules.

What is the most important information I should know about PegIntron™ and PegIntron™/REBETOL combination therapy?

PegIntron™ (peginterferon) is a treatment for some people who are infected with hepatitis C virus. However, PegIntron™ and PegIntron™/REBETOL combination therapy can have serious side effects that may cause death in rare cases. Before you decide to start treatment, you should talk to your health care provider about the possible benefits and side effects of PegIntron™ or PegIntron™/REBETOL combination therapy. If you begin treatment you will need to see your health care provider regularly for medical examinations and lab tests to make sure your treatment is working and to check for side effects.

REBETOL capsules may cause birth defects and/or death of an unborn child. If you are pregnant, you or your male partner must not take PegIntron™/REBETOL combination therapy. You must not become pregnant while either you or your partner are being treated with the combination PegIntron™/REBETOL therapy, or for 6 months after stopping therapy. Men and women should use birth control while taking the combination therapy and for 6 months afterwards. If you or your partner are being treated and you become pregnant, either during treatment or within 6 months of stopping treatment, call your health care provider right away.

If you are taking PegIntron™ or PegIntron™/REBETOL therapy you should call your health care provider immediately if you develop any of these symptoms:

New or worsening mental health problems, such as thoughts about killing or hurting yourself or others, trouble breathing, chest pain, severe stomach or lower back pain, bloody diarrhea or bloody bowel movements, high fever, bruising, bleeding, or decreased vision.

The most serious possible side effects of PegIntron™ and PegIntron™/REBETOL therapy include:



47
48 **Problems with Pregnancy.** Combination PegIntron™/REBETOL therapy can cause
49 **death, serious birth defects, or other harm to your unborn child. If you are a woman**
50 **of childbearing age, you must not become pregnant during treatment and for 6 months**
51 **after you have stopped therapy. You must have a negative pregnancy test immediately**
52 **before beginning treatment, during treatment and for 6 months after you have stopped**
53 **therapy.** Both males and female patients must use effective forms of birth control
54 **during treatment and for the 6 months after treatment is completed. Male patients**
55 **should use a condom.** If you are a female, you must use birth control even if you believe
56 that you are not fertile or that your fertility is low. You should talk to your health care
57 provider about birth control for you and your partner.

58
59 **Mental health problems and suicide.** PegIntron™ and PegIntron™/REBETOL therapies
60 may cause patients to develop mood or behavioral problems. These can include irritability
61 (getting easily upset) and depression (feeling low, feeling bad about yourself, or feeling
62 hopeless). Some patients may have aggressive behavior. Former drug addicts may fall back
63 into drug addiction or overdose. Some patients think about hurting or killing themselves or
64 other people and some have killed (suicide) or hurt themselves or others. You must tell your
65 health care provider if you are being treated for a mental illness or had treatment in the past
66 for any mental illness, including depression and suicidal behavior. You should tell your
67 health care provider if you have ever been addicted to drugs or alcohol.

68
69 **Heart problems.** Some patients taking PegIntron™ or PegIntron™/REBETOL therapy
70 may develop problems with their heart, including low blood pressure, fast heart rate, and
71 very rarely, heart attacks. Tell your health care provider if you have had any heart problems
72 in the past.

73
74 **Blood problems.** PegIntron™ and PegIntron™/REBETOL therapies commonly lower two
75 types of blood cells (white blood cells and platelets). In some patients, these blood counts
76 may fall to dangerously low levels. If your blood counts become very low, this could lead to
77 infections or bleeding.

78
79 REBETOL therapy causes a decrease in the number of red blood cells you have (anemia).
80 This can be dangerous, especially for patients who already have heart or circulatory
81 (cardiovascular) problems. Talk with your health care provider before taking combination
82 PegIntron™/REBETOL therapy if you have, or have ever had any cardiovascular problems.

83
84 **Body organ problems.** Certain symptoms like severe stomach pain may mean that your
85 internal organs are being damaged.

86
87 *For other possible side effects, see “What are the possible side effects of PegIntron™ and*
88 *PegIntron™/REBETOL” in this Medication Guide.*

89
90 **What is PegIntron™ and PegIntron™/REBETOL combination therapy?**
91 The PegIntron™ product is a drug used to treat adults who have a lasting (chronic) infection
92 with hepatitis C virus and who show signs that the virus is damaging the liver.



93 PegIntron™/REBETOL combination therapy consists of two medications also used to treat
94 hepatitis C infection. Patients with hepatitis C have the virus in their blood and in their liver.
95 PegIntron™ reduces the amount of virus in the body and helps the body's immune system
96 fight the virus. REBETOL (ribavirin) is a drug that helps to fight the viral infection but does
97 not work when used by itself to treat chronic hepatitis C.

98
99 It is not known if PegIntron™ or PegIntron™/REBETOL therapies can cure hepatitis C
100 (permanently eliminate the virus), or if it can prevent liver failure or liver cancer that is
101 caused by hepatitis C infection.

102
103 It is also not known if PegIntron™ or PegIntron™/REBETOL combination therapy will
104 prevent one infected person from infecting another person with hepatitis C.

105
106 **Who should not take PegIntron™ or PegIntron™/REBETOL therapy?**

107 Do not take PegIntron™ or PegIntron™/REBETOL therapy if you:

- 108 • are pregnant, planning to get pregnant during treatment or during the 6 months after
109 treatment, or breast-feeding
- 110
111 • are a male patient with a female sexual partner who is pregnant or plans to become
112 pregnant at any time while you are being treated with REBETOL or during the 6
113 months after your treatment has ended.
- 114
115 • have hepatitis caused by your immune system attacking your liver (autoimmune
116 hepatitis) or unstable liver disease
- 117
118 • had an allergic reaction to another alpha interferon or are allergic to any of the
119 ingredients in PegIntron™ or REBETOL Capsules. If you have any doubts, ask your
120 health care provider.
- 121
122 • Do not take PegIntron™/REBETOL combination therapy if you have abnormal red
123 blood cells such as sickle-cell anemia or thalassemia major.

124
125 **If you have any of the following conditions or serious medical problems, discuss them**
126 **with your health care provider before taking PegIntron™ or PegIntron™/REBETOL**
127 **therapy:**

- 128 • depression or anxiety
- 129 • sleep problems
- 130 • high blood pressure
- 131 • previous heart attack, or other heart problems
- 132 • liver problems (other than hepatitis C infection)
- 133 • any kind of autoimmune disease (where the body's immune system attacks the body's
134 own cells), such as psoriasis, systemic lupus erythematosus, rheumatoid arthritis
- 135 • thyroid problems
- 136 • diabetes
- 137 • colitis (inflammation of the bowels)



- 138 • cancer
- 139 • hepatitis B infection
- 140 • HIV infection
- 141 • kidney problems
- 142 • bleeding problems
- 143 • alcoholism
- 144 • drug abuse or addiction
- 145 • body organ transplant and are taking medicine that keeps your body from rejecting your
- 146 transplant (suppresses your immune system).

147

148

149 **How should I take PegIntron™ or PegIntron™/REBETOL?**

150 Your health care provider will decide whether you will take PegIntron™ therapy alone or the
151 combination of PegIntron™/REBETOL, as well as the correct dose (based on your weight).
152 PegIntron™ and PegIntron™/REBETOL are given for one year. Take your prescribed dose
153 of PegIntron™ **ONCE A WEEK**, on the same day of each week and at approximately the
154 same time. Take the medicine for the full year and do not take more than the prescribed
155 dose. REBETOL Capsules should be taken with food. When you take REBETOL with
156 food, more of the medicine (70% more on average) is taken up by your body. You should
157 take REBETOL the same way every day (twice a day with food) to keep the medicine in
158 your body at a steady level. This will help your health care provider to decide how your
159 treatment is working and how to change the number of REBETOL capsules you take if you
160 have side effects from REBETOL. **Be sure to read the Medication Guide for REBETOL**
161 **(ribavirin, USP) for complete instructions on how to take the REBETOL capsules.**

162

163 You should be completely comfortable with how to prepare PegIntron™, how to set the dose
164 you take, and how to inject yourself before you use PegIntron™ for the first time.
165 PegIntron™ comes in two different forms, a powder in a single-use vial and a Redipen®
166 single-use delivery system. See the attached appendix for detailed instructions for preparing
167 and giving a dose of PegIntron™.

168

169 If you miss a dose of the PegIntron™ product, take the missed dose as soon as possible
170 during the same day or the next day, then continue on your regular dosing schedule. If
171 several days go by after you miss a dose, check with your health care provider about what to
172 do. Do not double the next dose or take more than one dose a week without talking to your
173 health care provider. Call your health care provider right away if you take more than your
174 prescribed PegIntron™ dose. Your health care provider may wish to examine you more
175 closely, and take blood for testing.

176

177 If you miss a dose of REBETOL capsules, take the missed dose as soon as possible during
178 the same day. If an entire day has gone by, check with your health care provider about what
179 to do. Do not double the next dose.

180

181 You must get regular blood tests to help your health care provider check how the treatment is
182 working and to check for side effects.

183



184 Tell your health care provider if you are taking or planning to take other prescription or non-
185 prescription medicines, including vitamin and mineral supplements and herbal medicines.

186

187 **What should I avoid while taking PegIntron™ or PegIntron™/REBETOL therapies?**

188 • If you are pregnant do not start taking PegIntron™/REBETOL combination therapy.

189 • Avoid becoming pregnant while taking PegIntron™ or PegIntron™/REBETOL.

190 PegIntron™ and PegIntron™/REBETOL may harm your unborn child (death or serious birth
191 defects) or cause you to lose your baby (miscarry). **If you or your partner becomes**

192 **pregnant during treatment or during the 6 months after treatment with**

193 **PegIntron™/REBETOL combination therapy, immediately report the pregnancy to**

194 **your health care provider. You or your health care provider should call (800) 727-7064.**

195 By calling this number, information about you and/or your partner will be added to a

196 pregnancy registry that will be used to help you and your health care provider make decisions

197 about your treatment for hepatitis in the future. You, your partner and/or your health care

198 provider will be asked to provide follow-up information on the outcome of the pregnancy.

199

200 • Do not breast-feed your baby while taking PegIntron™.

201

202 **What are the possible side effects of PegIntron™ and PegIntron™/REBETOL**
203 **combination therapy?**

204

205 **Possible, serious side effects include:**

206 **Mental health problems including suicide, blood problems, heart problems, body organ**
207 **problems.** See “What is the most important information I should know about PegIntron™

208 and PegIntron™/REBETOL combination therapy?”

209

210 **Other body organ problems.** A few patients have lung problems (such as pneumonia or
211 inflammation of the lung tissue), inflammation of the kidney, and eye disorders.

212

213 **New or worsening autoimmune disease.** Some patients taking PegIntron™ or
214 PegIntron™/REBETOL develop autoimmune diseases (a condition where the body’s

215 immune cells attack other cells or organs in the body), including rheumatoid arthritis,

216 systemic lupus erythematosus, and psoriasis. In some patients who already have an

217 autoimmune disease, the disease worsens on PegIntron™ and PegIntron™/REBETOL

218 combination therapy.

219

220 **Common but less serious side effects include:**

221

222 **Flu-like symptoms.** Most patients who take PegIntron™ or PegIntron™/REBETOL therapy
223 have "flu-like" symptoms (headache, muscle aches, tiredness, and fever). Some of these

224 symptoms (fever, headache) usually lessen after the first few weeks of therapy. You can

225 reduce some of these symptoms by injecting your PegIntron™ dose at bedtime. Over-the-

226 counter pain and fever reducers, such as acetaminophen or ibuprofen, can be used to prevent

227 or reduce the fever and headache.

228



229 **Extreme fatigue (tiredness).** Many patients become extremely tired while on PegIntron™
230 or PegIntron™/REBETOL combination therapy.

231

232 **Appetite problems.** Nausea, loss of appetite, and weight loss, occur commonly.

233

234 **Thyroid problems.** Some patients develop changes in the function of their thyroid.
235 Symptoms of thyroid changes include the inability to concentrate, feeling cold or hot all the
236 time, a change in your weight, and changes to your skin.

237

238 **Blood sugar problems.** Some patients develop problems with the way their body controls
239 their blood sugar, and may develop high blood sugar or diabetes.

240

241 **Skin reactions.** Redness, swelling, and itching are common at the site of injection. If after
242 several days these symptoms do not disappear contact your health care provider. You may
243 get a rash during therapy. If this occurs, your health care provider may recommend
244 medicine to treat the rash.

245

246 **Hair thinning.** Hair thinning is common during PegIntron™ and PegIntron™/REBETOL
247 treatment. Hair loss stops and hair growth returns after therapy is stopped.

248

249 These are not all of the side effects of PegIntron™ or PegIntron™/REBETOL combination
250 therapy. Your health care provider or pharmacist can give you a more complete list.

251

252 **General advice about prescription medicines:**

253 Medicines are sometimes prescribed for purposes other than those listed in a Medication
254 Guide. If you have any concerns about PegIntron™, ask your health care provider. Your
255 health care provider or pharmacist can give you information about PegIntron™ that was
256 written for health care professionals. Do not use PegIntron™ for a condition for which it was
257 not prescribed. Do not share this medication with other people.

258

259 **If you are taking PegIntron™/REBETOL combination therapy, also read the**
260 **Medication Guide for REBETOL (ribavirin, USP) Capsules.**

261

262 *This Medication Guide has been approved by the U.S. Food and Drug Administration.*

263

264 Manufactured by: Schering Corporation, Kenilworth, NJ 07033 USA

265 **DATE**

266

267 **How do I prepare and inject the PegIntron™ Dose?**

268 Before you inject PegIntron™, the powder must be mixed with **0.7 mL** of the supplied
269 DILUENT for PegIntron™, Sterile Water for Injection (diluent). You should carefully
270 follow the directions given to you by your health care provider.

271

272 The vial of mixed PegIntron™ should be used immediately. **DO NOT** prepare more than one
273 vial at a time. If you don't use the vial of the prepared solution right away, it must be stored
274 in a refrigerator and used within 24 hours.



275

276 Storing PegIntron™

277 PegIntron™ Powder should be stored at room temperature (25 ° C, 77°F); avoid exposure to
278 heat. After mixing, the PegIntron™ solution should be used immediately but may be stored
279 in the refrigerator up to 24 hours. The solution contains no preservatives. DO NOT
280 FREEZE.

281 Preparing the PegIntron™ solution

282

283 1. Find a clean, well-lit, non-slip flat working surface and assemble all of the supplies you
284 will need for an injection. All of the supplies you will need for an injection are in the
285 PegIntron™ Powder for Injection package. The package contains:

286 ■ a vial of PegIntron™ powder

287

288 ■ a 1.25 mL vial of DILUENT

289

290 ■ 2 disposable syringes, and

291

292 ■ alcohol swabs

293

294 2. Check the date printed on the PegIntron™ carton to make sure that the expiration date
295 has not passed. Remove one vial and look at the contents. The PegIntron™ in the vial
296 should appear as a white to off-white tablet-like solid, that is whole/in pieces or as a
297 loose powder.

298

299 If you have already mixed the PegIntron™ solution and it has been stored properly in
300 the refrigerator, take it out of the refrigerator and allow the solution to come to room
301 temperature.

302

303 3. Wash your hands thoroughly with soap and water, rinse and towel dry. It is important to
304 keep your work area, your hands, and injection site clean to minimize the risk of
305 infection.

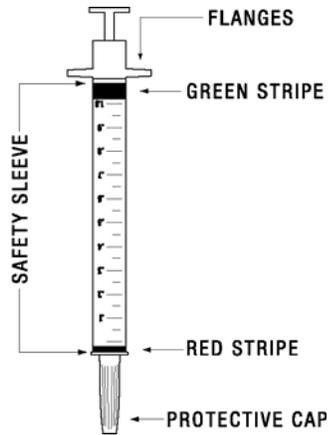
306

307 The disposable syringes have needles that are already attached and cannot be removed.
308 Each syringe has a clear plastic safety sleeve that is pulled over the needle for disposal
309 after use. The safety sleeve should remain tight against the flange while using the
310 syringe and moved over the needle only when ready for disposal (**Figure A**).

311

312 The syringes and needles are for single use only.





328 **Figure A**

330 4. Remove the protective wrapper from ONE of the syringes provided and use for the
331 following steps 5-7. Make sure that the syringe safety sleeve is sitting against the flange
332 (**Figure A**).

334 5. Remove the protective plastic cap from the tops of both the supplied DILUENT and the
335 PegIntron™ vials. Clean the rubber stopper on the top of both vials with an alcohol swab.
336

337 6. Carefully remove the protective cap straight off of the needle to avoid damaging the
338 needle point. Fill the syringe with air by pulling the plunger to 0.7 mL (**Figure B**). Hold the
339 DILUENT vial upright. Do not touch the cleaned top of the vial with your hands (**Figure C**).
340 Insert the needle through the center of the rubber stopper of the DILUENT vial, and inject
341 the air from the syringe into the vial (**Figure D**). Turn the vial upside down and make sure
342 the tip of the needle is in the liquid. Withdraw only 0.7 mL of DILUENT by pulling the
343 plunger back to 0.7 mL mark on the side of the syringe (**Figure E**). Remove the needle from
344 the vial (**Figure F**). **Discard the remaining DILUENT.**

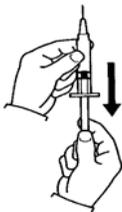


Figure B

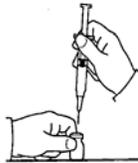


Figure C

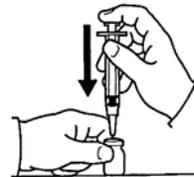


Figure D



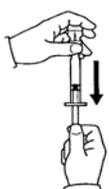


Figure E



Figure F

348

349

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351

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358

359

7. Insert the needle through the center of the rubber stopper of the PegIntron™ vial, and place the needle tip against the glass wall of the vial (**Figure G**). SLOWLY inject the 0.7 mL DILUENT so that the stream of DILUENT runs down the side of the vial. To prevent bubbles from forming, DO NOT AIM THE STREAM of diluent directly on the tablet-like SOLID or POWDER in the bottom of the vial. Remove the needle from the vial.

Firmly grasp the safety sleeve and pull it over the exposed needle until you hear a click. The green stripe on the safety sleeve will completely cover the red stripe on the needle. (See **Figure O** in the section: “Injecting the PegIntron™ dose.”) Discard the syringe and needle in the puncture proof container.

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8. GENTLY swirl the vial in a gentle circular motion (**Figure H**), until the PegIntron™ is completely dissolved. **DO NOT SHAKE** the vial. If any powder remains undissolved in the vial, gently turn the vial upside down until all of the powder is dissolved. It is not unusual for the solution to appear cloudy or bubbly for a few minutes. If air bubbles do form, wait until the solution has settled and all bubbles have risen to the top before withdrawing your dose from the vial.

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Figure G



Figure H

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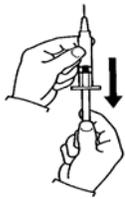
387

9. After the solution has settled and is completely dissolved it should be clear, colorless, and without particles, but there may be a ring of foam or bubbles on the surface, this is normal. Do not use it if you see particles or the color is not correct.

10. After the PegIntron™ powder is dissolved but before you withdraw your dose, clean the rubber stopper again with an alcohol swab.



388 11. Unwrap the second syringe provided. You will use it to give yourself the injection.
 389 Carefully remove the protective cap from the needle and fill the syringe with air by pulling
 390 the plunger to the number on the side of the syringe (mL) that corresponds to your prescribed
 391 dose (**Figure J**). Hold the PegIntron™ vial upright. DO NOT touch the cleaned top of the
 392 vial with your hands (**Figure K**). Insert the needle into the vial containing the PegIntron™
 393 solution and inject the air into the center of the vial (**Figure L**).
 394



395
 396
 397 **Figure J**

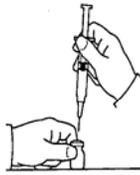


Figure K

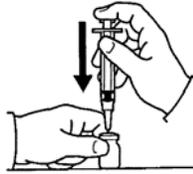
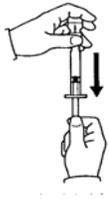


Figure L

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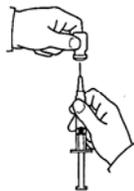
12. Turn the PegIntron™ vial upside down. Be sure the tip of needle is in the PegIntron™
 solution. While holding the vial and syringe with one hand slowly pull the plunger back to
 withdraw the exact amount of PegIntron™ into the syringe your health care provider told you
 to use (**Figure M**).



406
 407 **Figure M**

406
 407
 408
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 413

13. Remove the needle from the vial (**Figure N**) and check for air bubbles in the syringe. If
 you see any bubbles, hold the syringe with the needle pointing up and gently tap the syringe
 gently until the bubbles rise. Then push the plunger in slowly until the bubbles disappear.



414 **Figure N**

415

416

417 **Injecting the PegIntron™ Dose**

418 Selecting the Site for Injection.

419 The best sites for giving yourself an injection are those areas with a layer of fat between the
420 skin and muscle, like your thigh, the outer surface of your upper arm, and abdomen. Do not
421 inject yourself in the area near your navel or waistline. If you are very thin, you should only
422 use the thigh or outer surface of the arm for injection.

423

424 You should use a different site each time you inject PegIntron™ to avoid soreness at any one
425 site. Do not inject PegIntron™ solution into an area where the skin is irritated, red, bruised,
426 infected or has scars, stretch marks, or lumps.

427

428 14. Clean the skin where the injection is to be given with an alcohol swab, and wait for the
429 area to dry. Remove the protective cap from the needle. Make sure the safety sleeve of the
430 syringe is pushed firmly against the syringe flange so that the needle is fully exposed (**Figure**
431 **A**).

432

433 15. With one hand, pinch a 2-inch fold of loose skin. With your other hand, pick up the
434 syringe and hold it like a pencil. Position the bevel of the needle facing up and insert the
435 needle approximately ¼ inch into the pinched skin at approximately a 45- to 90-degree angle
436 with a quick dart-like thrust. After the needle is in, remove the hand that you used to pinch
437 your skin and use it to hold the syringe barrel. Pull the plunger of the syringe back very
438 slightly. If blood comes into the syringe, the needle has entered a blood vessel. **Do not**
439 **inject**. Withdraw the needle and discard the syringe as outlined in step 17. Repeat the above
440 steps with a new vial to prepare a new syringe and inject the medicine at a new site. If no
441 blood is present in the syringe, inject the medicine by gently pressing the plunger all the way
442 down the syringe barrel.

443

444 16. Hold an alcohol swab near the needle and pull the needle straight out of the skin. Press
445 the alcohol swab over the injection site for several seconds. Do not massage the injection
446 site. If there is bleeding, cover it with a bandage.

447

448 17. After injecting your dose, firmly grasp the safety sleeve and pull it over the exposed
449 needle until you hear a click, and the green stripe on the safety sleeve covers the red stripe on
450 the needle (**Figure O**). Discard the syringe and needle in the Sharp's container supplied to
451 you.

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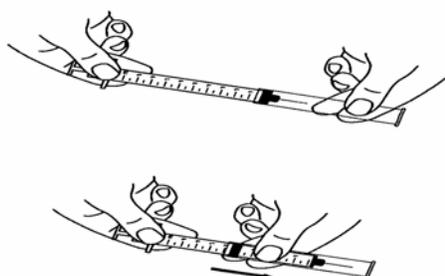
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460

461

**Figure O**

462 18. After 2 hours, check the injection site for redness, swelling, or tenderness. If you have a
463 skin reaction and it doesn't clear up in a few days, contact your health care provider or nurse.

464

465 **How do I dispose of the used syringes and needles?**

466 Discard used safety lock syringes and needles in a Sharp's container or other puncture-proof
467 container like a coffee can. DO NOT USE glass or clear plastic containers. Your health care
468 provider or nurse will tell you how to dispose of a full container. Always keep the container
469 out of reach of children.

470

471

472 Manufactured by: Schering Corporation, Kenilworth, NJ 07033 USA

473 **DATE 12/06**

474

475



1 **12-13-06-Med Guide Redipen-Final Draft**
2 **MEDICATION GUIDE**
3 **PegIntron™ Redipen® Single-dose Delivery System**
4 **Peginterferon alfa-2b**

5
6 **Including appendix with instructions for using PegIntron™ Redipen® Single-dose**
7 **Delivery System**
8

9 Read this Medication Guide carefully before you start taking PegIntron™ (**Peg In-tron**) or
10 PegIntron™/REBETOL (**REB-eh-tole**) combination therapy. Read the Medication Guide
11 each time you refill your prescription because there may be new information. The
12 information in this Medication Guide does not take the place of talking with your health care
13 provider (doctor, nurse, nurse practitioner, or physician's assistant).
14

15 **If you are taking PegIntron™/REBETOL combination therapy, also read the**
16 **Medication Guide for REBETOL (ribavirin, USP) Capsules.**
17

18 **What is the most important information I should know about PegIntron™ and**
19 **PegIntron™/REBETOL combination therapy?**
20

21 PegIntron™ (peginterferon) is a treatment for some people who are infected with hepatitis C
22 virus. However, PegIntron™ and PegIntron™/REBETOL combination therapy can have
23 serious side effects that may cause death in rare cases. Before you decide to start treatment,
24 you should talk to your health care provider about the possible benefits and side effects of
25 PegIntron™ or PegIntron™/REBETOL combination therapy. If you begin treatment you will
26 need to see your health care provider regularly for medical examinations and lab tests to
27 make sure your treatment is working and to check for side effects.
28

29 **REBETOL capsules may cause birth defects and/or death of an unborn child. If you**
30 **are pregnant, you or your male partner must not take PegIntron™/REBETOL**
31 **combination therapy. You must not become pregnant while either you or your partner**
32 **are being treated with the combination PegIntron™/REBETOL therapy, or for 6**
33 **months after stopping therapy. Men and women should use birth control while taking**
34 **the combination therapy and for 6 months afterwards. If you or your partner are being**
35 **treated and you become pregnant, either during treatment or within 6 months of**
36 **stopping treatment, call your health care provider right away. There is a Ribavirin**
37 **Pregnancy Registry that collects information about pregnancy outcomes in female**
38 **patients and female partners of male patients exposed to ribavirin. You or your health**
39 **care provider are encouraged to contact the Registry at 1-800-593-2214.**
40

41 **If you are taking PegIntron™ or PegIntron™/REBETOL therapy you should call your**
42 **health care provider immediately if you develop any of these symptoms:**
43

44 **New or worsening mental health problems, such as thoughts about killing or hurting**
45 **yourself or others, trouble breathing, chest pain, severe stomach or lower back pain,**



46 **bloody diarrhea or bloody bowel movements, high fever, bruising, bleeding, or**
47 **decreased vision.**

48

49 The most serious possible side effects of PegIntron™ and PegIntron™/REBETOL therapy
50 include:

51

52 **Problems with Pregnancy.** Combination PegIntron™/REBETOL therapy can cause
53 **death, serious birth defects, or other harm to your unborn child. If you are a woman of**
54 **childbearing age, you must not become pregnant during treatment and for 6 months**
55 **after you have stopped therapy. You must have a negative pregnancy test immediately**
56 **before beginning treatment, during treatment, and for 6 months after you have stopped**
57 **therapy.** Both males and female patients must use effective forms of birth control
58 **during treatment and for the 6 months after treatment is completed. Male patients**
59 **should use a condom.** If you are a female, you must use birth control even if you believe
60 that you are not fertile or that your fertility is low. You should talk to your health care
61 provider about birth control for you and your partner.

62

63 **Mental health problems and suicide.** PegIntron™ and PegIntron™/REBETOL therapies
64 may cause patients to develop mood or behavioral problems. These can include irritability
65 (getting easily upset) and depression (feeling low, feeling bad about yourself, or feeling
66 hopeless). Some patients may have aggressive behavior. Former drug addicts may fall back
67 into drug addiction or overdose. Some patients think about hurting or killing themselves or
68 other people and some have killed (suicide) or hurt themselves or others. You must tell your
69 health care provider if you are being treated for a mental illness or had treatment in the past
70 for any mental illness, including depression and suicidal behavior. You should tell your
71 health care provider if you have ever been addicted to drugs or alcohol.

72

73 **Heart problems.** Some patients taking PegIntron™ or PegIntron™/REBETOL therapy
74 may develop problems with their heart, including low blood pressure, fast heart rate, and
75 very rarely, heart attacks. Tell your health care provider if you have had any heart problems
76 in the past.

77

78 **Blood problems.** PegIntron™ and PegIntron™/REBETOL therapies commonly lower two
79 types of blood cells (white blood cells and platelets). In some patients, these blood counts
80 may fall to dangerously low levels. If your blood counts become very low, this could lead to
81 infections or bleeding.

82

83 REBETOL therapy causes a decrease in the number of red blood cells you have (anemia).
84 This can be dangerous, especially for patients who already have heart or circulatory
85 (cardiovascular) problems. Talk with your health care provider before taking combination
86 PegIntron™/REBETOL therapy if you have, or have ever had any cardiovascular problems.

87

88 **Body organ problems.** Certain symptoms like severe stomach pain may mean that your
89 internal organs are being damaged.

90



91 *For other possible side effects, see “What are the possible side effects of PegIntron™ and*
92 *PegIntron™/REBETOL” in this Medication Guide.*

93

94 **What is PegIntron™ and PegIntron™/REBETOL combination therapy?**

95 The PegIntron™ product is a drug used to treat adults who have a lasting (chronic) infection
96 with hepatitis C virus and who show signs that the virus is damaging the liver.

97

98 PegIntron™/REBETOL combination therapy consists of two medications also used to treat
99 hepatitis C infection. Patients with hepatitis C have the virus in their blood and in their liver.
100 PegIntron™ reduces the amount of virus in the body and helps the body's immune system
101 fight the virus. REBETOL (ribavirin) is a drug that helps to fight the viral infection, but does
102 not work when used by itself to treat chronic hepatitis C.

103

104 It is not known if PegIntron™ or PegIntron™/REBETOL therapies can cure hepatitis C
105 (permanently eliminate the virus), or if it can prevent liver failure or liver cancer that is
106 caused by hepatitis C infection.

107

108 It is also not known if PegIntron™ or PegIntron™/REBETOL combination therapy will
109 prevent one infected person from infecting another person with hepatitis C.

110

111 **Who should not take PegIntron™ or PegIntron™/REBETOL therapy?**

112 Do not take PegIntron™ or PegIntron™/REBETOL therapy if you:

113 • are pregnant, planning to get pregnant during treatment or during the 6 months after
114 treatment, or breast-feeding

115

116 • are a male patient with a female sexual partner who is pregnant, or plans to become
117 pregnant at any time while you are being treated with REBETOL, or during the 6
118 months after your treatment has ended.

119

120 • have hepatitis caused by your immune system attacking your liver (autoimmune
121 hepatitis) or unstable liver disease

122

123 • had an allergic reaction to another alpha interferon or are allergic to any of the
124 ingredients in PegIntron™ or REBETOL Capsules. If you have any doubts, ask your
125 health care provider.

126

127 • Do not take PegIntron™/REBETOL combination therapy if you have abnormal red
128 blood cells such as sickle-cell anemia or thalassemia major.

129

130 **If you have any of the following conditions or serious medical problems, discuss them**
131 **with your health care provider before taking PegIntron™ or PegIntron™/REBETOL**
132 **therapy:**

133 • depression or anxiety

134 • sleep problems

135 • high blood pressure

136 • previous heart attack, or other heart problems



- 137 • liver problems (other than hepatitis C infection)
- 138 • any kind of autoimmune disease (where the body's immune system attacks the body's
- 139 own cells), such as psoriasis, systemic lupus erythematosus, rheumatoid arthritis
- 140 • thyroid problems
- 141 • diabetes
- 142 • colitis (inflammation of the bowels)
- 143 • cancer
- 144 • hepatitis B infection
- 145 • HIV infection
- 146 • kidney problems
- 147 • bleeding problems
- 148 • alcoholism
- 149 • drug abuse or addiction
- 150 • body organ transplant and are taking medicine that keeps your body from rejecting your
- 151 transplant (suppresses your immune system).

152

153 **How should I take PegIntron™ or PegIntron™/REBETOL?**

154 Your health care provider will decide whether you will take PegIntron™ therapy alone or the
155 combination of PegIntron™/REBETOL, as well as the correct dose (based on your weight).
156 PegIntron™ and PegIntron™/REBETOL are given for one year. Take your prescribed dose
157 of PegIntron™ **ONCE A WEEK**, on the same day of each week and at approximately the
158 same time. Take the medicine for the full year and do not take more than the prescribed
159 dose. REBETOL Capsules should be taken with food. When you take REBETOL with
160 food, more of the medicine (70% more on average) is taken up by your body. You should
161 take REBETOL the same way every day (twice a day with food) to keep the medicine in
162 your body at a steady level. This will help your health care provider to decide how your
163 treatment is working and how to change the number of REBETOL capsules you take if you
164 have side effects from REBETOL. **Be sure to read the Medication Guide for REBETOL**
165 **(ribavirin, USP) for complete instructions on how to take the REBETOL capsules.**

166

167 You should be completely comfortable with how to prepare PegIntron™; how to set the dose
168 you take; and how to inject yourself before you use PegIntron™ for the first time.
169 PegIntron™ comes in two different forms, a powder in a single-use vial and a Redipen®
170 single-use delivery system. See the attached appendix for detailed instructions for preparing
171 and giving a dose of PegIntron™.

172

173 If you miss a dose of the PegIntron™ product, take the missed dose as soon as possible
174 during the same day or the next day, then continue on your regular dosing schedule. If
175 several days go by after you miss a dose, check with your health care provider about what to
176 do. Do not double the next dose or take more than one dose a week without talking to your
177 health care provider. Call your health care provider right away if you take more than your
178 prescribed PegIntron™ dose. Your health care provider may wish to examine you more
179 closely, and take blood for testing.

180



181 If you miss a dose of REBETOL capsules, take the missed dose as soon as possible during
182 the same day. If an entire day has gone by, check with your health care provider about what
183 to do. Do not double the next dose.

184

185 You must get regular blood tests to help your health care provider check how the treatment
186 is working and to check for side effects.

187

188 Tell your health care provider if you are taking or planning to take other prescription or non-
189 prescription medicines, including vitamin and mineral supplements and herbal medicines.

190

191 **What should I avoid while taking PegIntron™ or PegIntron™/REBETOL therapies?**

192 • If you are pregnant do not start taking PegIntron™/REBETOL combination therapy.

193 • Avoid becoming pregnant while taking PegIntron™ or PegIntron™/REBETOL.

194 PegIntron™ and PegIntron™/REBETOL may harm your unborn child (death or serious birth
195 defects) or cause you to lose your baby (miscarry). **If you or your partner becomes**
196 **pregnant during treatment or during the 6 months after treatment with**
197 **PegIntron™/REBETOL combination therapy, immediately report the pregnancy to**
198 **your health care provider. You or your health care provider should call 1-800-593-**
199 **2214.** By calling this number, information about you and/or your partner will be added to a
200 pregnancy registry that will be used to help you and your health care provider make decisions
201 about your treatment for hepatitis in the future. You, your partner, and/or your health care
202 provider will be asked to provide follow-up information on the outcome of the pregnancy.

203

204 • Do not breast-feed your baby while taking PegIntron™.

205

206 **What are the possible side effects of PegIntron™ and PegIntron™/REBETOL**
207 **combination therapy?**

208

209 **Possible, serious side effects include:**

210 **Mental health problems including suicide, blood problems, heart problems, body organ**
211 **problems.** See “What is the most important information I should know about PegIntron™
212 and PegIntron™/REBETOL combination therapy?”

213

214 **Other body organ problems.** A few patients have lung problems (such as pneumonia or
215 inflammation of the lung tissue), inflammation of the kidney, and eye disorders.

216

217 **New or worsening autoimmune disease.** Some patients taking PegIntron™ or
218 PegIntron™/REBETOL develop autoimmune diseases (a condition where the body’s
219 immune cells attack other cells or organs in the body), including rheumatoid arthritis,
220 systemic lupus erythematosus, and psoriasis. In some patients who already have an
221 autoimmune disease, the disease worsens on PegIntron™ and PegIntron™/REBETOL
222 combination therapy.

223

224 **Common but less serious side effects include:**

225



226 **Flu-like symptoms.** Most patients who take PegIntron™ or PegIntron™/REBETOL therapy
227 have "flu-like" symptoms (headache, muscle aches, tiredness, and fever). Some of these
228 symptoms (fever, headache) usually lessen after the first few weeks of therapy. You can
229 reduce some of these symptoms by injecting your PegIntron™ dose at bedtime. Over-the-
230 counter pain and fever reducers, such as acetaminophen or ibuprofen, can be used to prevent
231 or reduce the fever and headache.

232

233 **Extreme fatigue (tiredness).** Many patients become extremely tired while on PegIntron™
234 or PegIntron™/REBETOL combination therapy.

235

236 **Appetite problems.** Nausea, loss of appetite, and weight loss, occur commonly.

237

238 **Thyroid problems.** Some patients develop changes in the function of their thyroid.
239 Symptoms of thyroid changes include the inability to concentrate, feeling cold or hot all the
240 time, a change in your weight, and changes to your skin.

241 **Blood sugar problems.** Some patients develop problems with the way their body controls
242 their blood sugar and may develop high blood sugar or diabetes.

243

244 **Skin reactions.** Redness, swelling, and itching are common at the site of injection. If after
245 several days these symptoms do not disappear contact your health care provider. You may
246 get a rash during therapy. If this occurs, your health care provider may recommend medicine
247 to treat the rash.

248

249 **Hair thinning.** Hair thinning is common during PegIntron™ and PegIntron™/REBETOL
250 treatment. Hair loss stops and hair growth returns after therapy is stopped.

251

252 These are not all of the side effects of PegIntron™ or PegIntron™/REBETOL combination
253 therapy. Your health care provider or pharmacist can give you a more complete list.

254

255 **General advice about prescription medicines:**

256 Medicines are sometimes prescribed for purposes other than those listed in a Medication
257 Guide. If you have any concerns about PegIntron™, ask your health care provider. Your
258 health care provider or pharmacist can give you information about PegIntron™ that was
259 written for health care professionals. Do not use PegIntron™ for a condition for which it was
260 not prescribed. Do not share this medication with other people.

261

262 **If you are taking PegIntron™/REBETOL combination therapy, also read the**
263 **Medication Guide for REBETOL (ribavirin, USP) Capsules.**

264

265 *This Medication Guide has been approved by the U.S. Food and Drug Administration.*

266

267 **How do I prepare and inject the PegIntron™ Redipen® Dose?**

268

269 The PegIntron™ Redipen® system is for a single use, by one person only. The Redipen®
270 must not be shared. Use only the injection needle provided in the packaging for the

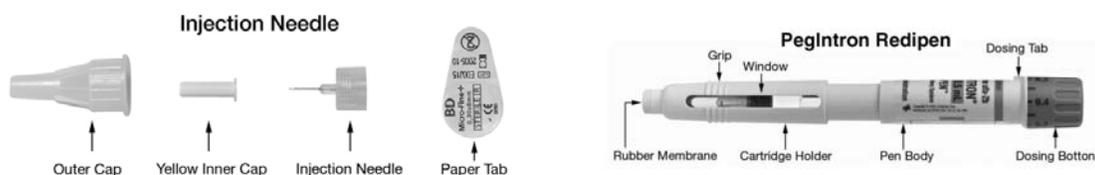


271 PegIntron™ Redipen® system. If you have problems with the Redipen® system or the
 272 PegIntron™ solution, you should contact your health care provider or pharmacist.

273

274 The following instructions explain how to prepare and inject yourself with the PegIntron™
 275 Redipen® system. Please read the instructions carefully and follow them step by step. Your
 276 health care provider will instruct you on how to self-inject with the PegIntron™ Redipen®.
 277 Do not attempt to inject yourself unless you are sure you understand the procedure and
 278 requirements for self-injection.

279



280

281

282 **How to use the PegIntron™ Redipen® single-dose delivery system.**

283

284 **Storing PegIntron™**

285 PegIntron™ Redipen® should be stored in the refrigerator at 2°C to 8°C (36°F to 46°F);
 286 avoid exposure to heat. After mixing, the PegIntron™ solution should be used immediately
 287 but may be stored in the refrigerator up to 24 hours at 2°C to 8°C (36°F to 46°F). The
 288 solution contains no preservatives. DO NOT FREEZE.

289

290 **Preparation**

291

292 1. Find a clean, well-lit, non-slip flat working surface and assemble all of the supplies you
 293 will need for an injection. All of the supplies you will need are in the PegIntron™
 294 Redipen® package. The package contains:

295

296

297

298

299

- a PegIntron™ Redipen® single-dose delivery system
- one disposable needle
- two alcohol swabs, and
- dosing tray; (The dosing tray is the bottom half of the Redipen® package.)

300

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305

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311

1. Mix the Drug



SCHERING-PLOUGH RESEARCH INSTITUTE

312

313 **Key points:**

314

315 **Before you mix the PegIntron™, make sure it is at room temperature. It is important**
316 **that you keep the PegIntron™ Redipen® UPRIGHT (Dosing Button down) as shown in**
317 **Figure 1.**

318

319 a. Hold the PegIntron™ Redipen® **UPRIGHT (Figure 1a)** in the dosing tray on a hard,
320 flat, non-slip surface with the dosing button **down**. You may want to hold the Redipen®
321 using the grip.

322

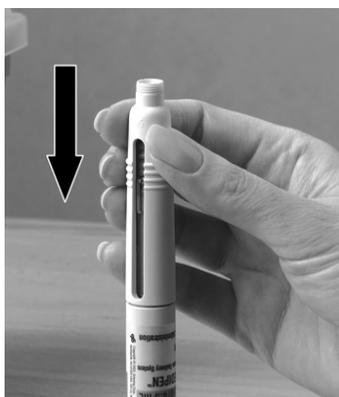
323 b. To mix the powder and the liquid, keep the Redipen® upright in the dosing tray and
324 press the top half of the Redipen® downward toward the hard, flat, non-slip surface **until**
325 **you hear the click** (Figure 1b). Once you've heard the click, you will notice in the
326 window that both dark stoppers are now touching. The dosing button should be flush with
327 the pen body.



328

329 **Figure 1a**

330



331

332 **Figure 1b**

333

334 c. Wait several seconds for the powder to completely dissolve.

335

336 **d. Gently turn the PegIntron™ Redipen® upside down twice (Figure 2). To avoid**
337 **excessive foaming, DO NOT SHAKE.**





338
339 **Figure 2**

340
341 e. Keeping the PegIntron™ Redipen® **UPRIGHT**, with the dosing button down, check
342 through the Redipen® window to see if the mixed PegIntron™ solution is completely
343 dissolved. The solution should be clear, colorless, and without particles **before use**. It is
344 normal to see some small bubbles near the top of the solution. Do not use if the solution
345 is not clear, or if you see particles.

346
347 **f. Place the PegIntron™ Redipen® back into the dosing tray provided in the**
348 **packaging (Figure 3). The dosing button will be on the bottom.**
349



350
351 **Figure 3**
352
353
354
355
356

357 **2. Attach the Needle**

- 358
359 a. Wipe the rubber membrane of the PegIntron™ Redipen® with one alcohol swab.
360 b. Remove the protective paper tab from the injection needle, but do NOT remove either the
361 outer cap or the yellow inner cap from the injection needle. Keeping the PegIntron™ Redipen®
362 **UPRIGHT** in the dosing tray, **FIRMLY** push the injection needle straight into the Redipen®
363 rubber membrane, and screw it firmly in place, in a clockwise direction (**Figure 4**). Remember



364 to leave the needle caps in place when you attach the needle to the Redipen[®]. Pushing the needle
365 through the rubber membrane, “primes” the needle and allows the extra liquid and air in the pen
366 to be removed.
367



Figure 4

368
369
370
371
372
373

NOTE: Some fluid will trickle out. This is **normal**. The dark stoppers move up and you will no longer see the fluid in the window once the needle is successfully primed.

374 c. **IMPORTANT:** Keep the Redipen[®] in the UPRIGHT position and keep the outer needle
375 cap on until you are ready to inject.
376

377 **3. Dialing the Dose**

378

379 a. **Remove the PegIntron[™] Redipen[®] from the dosing tray (Figure 5a).**

380 Holding the PegIntron[™] Redipen[®] firmly, pull the dosing button out as far as it will go.
381 You will see a dark band-

382

383 **Do not push the dosing button in until you are ready to self-inject the PegIntron[™]**
384 **dose.**





385
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392
393

Figure 5a

b. Turn the dosing button until your prescribed dose is lined up with the dosing tab (**Figure 5b**). The dosing button will turn freely. If you have trouble dialing your dose, check to make sure the dosing button has been pulled out **as far** as it will go (**Figure 5c**).



394
395

Figure 5b

Figure 5c

396
397
398

c. Carefully lay the PegIntron™ Redipen® down on a hard, flat, non-slip surface. Do NOT remove either of the needle caps and do NOT push the dosing button in until you are ready to self-inject the PegIntron™ dose.

402

4. Injecting the PegIntron™ Dose

404

Choosing an Injection Site

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The best sites for giving yourself an injection are those areas with a layer of fat between the skin and muscle, like your thigh, the outer surface of your upper arm, and abdomen. Do not inject yourself in the area near your navel or waistline. If you are very thin, you should only use the thigh or outer surface of the arm for injection.

410 You should use a different site each time you inject PegIntron™ to avoid soreness at any
411 one site. Do not inject PegIntron™ into an area where the skin is irritated, red, bruised,
412 infected, or has scars, stretch marks, or lumps.

413

414 a. Clean the skin where the injection is to be given with the second alcohol swab provided,
415 and wait for the area to dry.

416 b. Remove the **outer** cap from the needle (**Figure 6a**). There may be some liquid around the
417 yellow inner needle cap (**Figure 6b**). This is normal.

418

419

420



421

422 **Figure 6a**

Figure 6b

423

424 c. Once the injection site is dry, remove the **yellow** inner needle cap (**Figure 6c**). You are
425 now ready to inject.

426



427

428 **Figure 6c**

429

430 **d. Hold the PegIntron™ Redipen® with your fingers wrapped around the pen body**
431 **barrel and your thumb on the dosing button (Figure 7).**

432

433

434

- With your other hand, pinch the skin in the area you have cleaned for injection.
- Insert the needle into the pinched skin at an angle of 45° to 90°.
- Press the dosing button down slowly and firmly until you can't push it any further.



- 435
- 436
- 437
- Keep your thumb pressed down on the dosing button for an additional 5 seconds to ensure that you get the complete dose.
 - Remove the needle from your skin.



438

439 **Figure 7**

440

441 **e. Gently press the injection site with a small bandage or sterile gauze if necessary for a**
442 **few seconds but** do not massage the injection site. If there is bleeding, cover with an
443 adhesive bandage. **DO NOT RECAP THE NEEDLE and DO NOT REUSE the**
444 **Redipen®.**

445

446 **How do I Dispose of the Redipen®?**

447 Discard the Redipen® and needle and any solution remaining in the Redipen® in a sharps
448 container or other puncture-resistant container like a metal coffee can. DO NOT use glass or
449 clear plastic containers. Ask your health care provider how to dispose of a full container.
450 Always keep the container out of reach of children.

451

452 **After 2 hours, check the injection site for redness, swelling, or tenderness.**
453 **If you have a skin reaction and it doesn't clear up in a few days, contact**
454 **your health care provider.**

455

456

457 Manufactured by: Schering Corporation, Kenilworth, NJ 07033 USA

458 DATE 12/06

459

