

1 10-15-04-revised PI submitted by Schering-Final Draft

2  
3 **PEG-Intron™**  
4 **(Peginterferon alfa-2b)**  
5 **Powder For Injection**

6 **Alpha interferons, including PEG-Intron, may cause or aggravate fatal or life-**  
7 **threatening neuropsychiatric, autoimmune, ischemic, and infectious disorders.**  
8 **Patients should be monitored closely with periodic clinical and laboratory**  
9 **evaluations. Patients with persistently severe or worsening signs or symptoms of**  
10 **these conditions should be withdrawn from therapy. In many but not all cases**  
11 **these disorders resolve after stopping PEG-Intron therapy. See WARNINGS,**  
12 **ADVERSE REACTIONS.**

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

17  
18 **DESCRIPTION**

19 PEG-Intron™, peginterferon alfa-2b, Powder for Injection is a covalent conjugate of  
20 recombinant alfa-2b interferon with monomethoxy polyethylene glycol (PEG). The  
21 average molecular weight of the PEG portion of the molecule is 12,000 daltons. The  
22 average molecular weight of the PEG-Intron molecule is approximately 31,000  
23 daltons. The specific activity of peginterferon alfa-2b is approximately  $0.7 \times 10^8$   
24 IU/mg protein.

25 Interferon alfa-2b, is a water-soluble protein with a molecular weight of 19,271  
26 daltons produced by recombinant DNA techniques. It is obtained from the bacterial  
27 fermentation of a strain of *Escherichia coli* bearing a genetically engineered plasmid  
28 containing an interferon gene from human leukocytes.

29  
30 **PEG-Intron is supplied in both vials and the Redipen™ for subcutaneous use.**  
31



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**Vials**

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

**Redipen™**

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

**CLINICAL PHARMACOLOGY-**

General: The biological activity of PEG-Intron is derived from its interferon alfa-2b moiety. Interferons exert their cellular activities by binding to specific membrane receptors on the cell surface and initiate a complex sequence of intracellular events. These include the induction of certain enzymes, suppression of cell proliferation, immunomodulating activities such as enhancement of the phagocytic activity of macrophages and augmentation of the specific cytotoxicity of lymphocytes for target cells, and inhibition of virus replication in virus-infected cells. Interferon alfa



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63 upregulates the Th1 T-helper cell subset in in vitro studies. The clinical relevance of  
64 these findings is not known.

65

66 **Pharmacodynamics:** PEG-Intron raises concentrations of effector proteins such as  
67 serum neopterin and 2'5' oligoadenylate synthetase, raises body temperature, and  
68 causes reversible decreases in leukocyte and platelet counts. The correlation  
69 between the *in vitro* and *in vivo* pharmacologic and pharmacodynamic and clinical  
70 effects is unknown.

71

72 **Pharmacokinetics:** Following a single subcutaneous (SC) dose of PEG-Intron, the  
73 mean absorption half-life ( $t_{1/2k_a}$ ) was 4.6 hours. Maximal serum concentrations  
74 ( $C_{max}$ ) occur between 15-44 hours post-dose, and are sustained for up to 48-72  
75 hours. The  $C_{max}$  and AUC measurements of PEG-Intron increase in a dose-related  
76 manner. After multiple dosing, there is an increase in bioavailability of PEG-Intron.  
77 Week 48 mean trough concentrations (320 pg/mL; range 0, 2960) are approximately  
78 3-fold higher than Week 4 mean trough concentrations (94 pg/mL; range 0, 416).  
79 The mean PEG-Intron elimination half-life is approximately 40 hours (range 22 to 60  
80 hours) in patients with HCV infection. The apparent clearance of PEG-Intron is  
81 estimated to be approximately 22.0 mL/hr·kg. Renal elimination accounts for 30% of  
82 the clearance. Pegylation of interferon alfa-2b produces a product (PEG-Intron)  
83 whose clearance is lower than that of non-pegylated interferon alfa-2b. When  
84 compared to INTRON A, PEG-Intron (1.0 µg/kg) has approximately a seven-fold  
85 lower mean apparent clearance and a five-fold greater mean half-life permitting a  
86 reduced dosing frequency. At effective therapeutic doses, PEG-Intron has  
87 approximately ten-fold greater  $C_{max}$  and 50-fold greater AUC than interferon alfa-2b.

## 88 **Special Populations**

89

### 90 **Renal Dysfunction**

91 Following multiple dosing of PEG-Intron (1 mcg/kg SC given every week for four  
92 weeks) the clearance of PEG-Intron is reduced by a mean of 17% in patients with  
93 moderate renal impairment (creatinine clearance 30-49 mL/min) and by a mean of



94 44% in patients with severe renal impairment (creatinine clearance 10-29 mL/min)  
95 compared to subjects with normal renal function. Clearance was similar in patients  
96 with severe renal impairment not on dialysis and patients who are receiving  
97 hemodialysis. The dose of PEG-Intron for monotherapy should be reduced in  
98 patients with moderate or severe renal impairment (See **DOSAGE AND**  
99 **ADMINISTRATION: DOSE REDUCTION**), REBETOL should not be used in patients  
100 with creatinine clearance < 50 mL/min (See **REBETOL Package Insert,**  
101 **WARNINGS**).

#### 102 **Gender**

103 During the 48 week treatment period with PEG-Intron, no differences in the  
104 pharmacokinetic profiles were observed between male and female patients with  
105 chronic hepatitis C infection .

#### 106 **Geriatric Patients**

107 The pharmacokinetics of geriatric subjects (> 65 years of age) treated with a single  
108 subcutaneous dose of 1.0 µg/kg of PEG-Intron were similar in C<sub>max</sub>, AUC, clearance,  
109 or elimination half-life as compared to younger subjects (28 to 44 years of age).

110 **Effect of Food on Absorption of Ribavirin** Both AUC<sub>0-∞</sub> and C<sub>max</sub> increased by  
111 70% when REBETOL Capsules were administered with a high-fat meal (841 kcal,  
112 53.8 g fat, 31.6 g protein, and 57.4 g carbohydrate) in a single-dose pharmacokinetic  
113 study. (See **DOSAGE AND ADMINISTRATION**).

114 **Drug Interactions:** It is not known if PEG-Intron therapy causes clinically significant  
115 drug-drug interactions with drugs metabolized by the liver in patients with hepatitis  
116 C. In 12 healthy subjects known to be CYP2D6 extensive metabolizers, a single  
117 subcutaneous dose of 1 µg/kg PEG-Intron did not inhibit CYP1A2, 2C8/9, 2D6,  
118 hepatic 3A4 or N-acetyltransferase; the effects of PEG-Intron on CYP2C19 were not  
119 assessed.

#### 120 **Methadone**

121 The pharmacokinetics of concomitant administration of methadone and PEG-Intron  
122 were evaluated in a fixed-sequence study conducted in 18 PEG-Intron naïve chronic  
123 hepatitis C patients receiving 1.5 µg/kg/week PEG-Intron SC weekly. All  
124 patients were on stable methadone maintenance therapy receiving ≥40 mg/day prior



125 to initiating PEG-Intron. Mean methadone AUC was approximately 16% higher after  
126 4 weeks of PEG-Intron treatment as compared to baseline. In 2 patients,  
127 methadone AUC was approximately double after 4 weeks of PEG-Intron treatment  
128 as compared to baseline. (see **Precautions: Drug Interactions**).

129

130 **CLINICAL STUDIES**131 **PEG-Intron Monotherapy-Study 1**

132 A randomized study compared treatment with PEG-Intron (0.5, 1.0, or 1.5 µg/kg  
133 once weekly SC) to treatment with INTRON A, (3 million units three times weekly  
134 SC) in 1219 adults with chronic hepatitis from HCV infection. The patients were not  
135 previously treated with interferon alfa, had compensated liver disease, detectable  
136 HCV RNA, elevated ALT, and liver histopathology consistent with chronic hepatitis.  
137 Patients were treated for 48 weeks and were followed for 24 weeks post-treatment.  
138 Seventy percent of all patients were infected with HCV genotype 1, and 74 percent  
139 of all patients had high baseline levels of HCV RNA (more than 2 million copies per  
140 mL of serum), two factors known to predict poor response to treatment.

141

142 Response to treatment was defined as undetectable HCV RNA and normalization of  
143 ALT at 24 weeks post-treatment. The response rates to the 1.0 and 1.5 µg/kg PEG-  
144 Intron doses were similar (approximately 24%) to each other and were both higher  
145 than the response rate to INTRON A (12%). (See Table 1)

146

**Table 1. Rates of Response to Treatment-Study 1**

	A PEG-Intron 0.5 µg/kg (N=315)	B PEG-Intron 1.0 µg/kg (N=298)	C INTRON A 3 MIU TIW (N=307)	B - C (95% CI) Difference between PEG-Intron 1.0 µg/kg and INTRON A
Treatment Response (Combined Virologic Response and ALT Normalization)	17%	24%	12%	11 (5, 18)
Virologic Response <sup>a</sup>	18%	25%	12%	12 (6,19)
ALT Normalization	24%	29%	18%	11 (5,18)

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



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149  
150 Patients with both viral genotype 1 and high serum levels of HCV RNA at baseline  
151 were less likely to respond to treatment with PEG-Intron. Among patients with the  
152 two unfavorable prognostic variables, 8% (12/157) responded to PEG-Intron  
153 treatment and 2% (4/169) responded to INTRON A. Doses of PEG-Intron higher  
154 than the recommended dose did not result in higher response rates in these  
155 patients.

156  
157 Patients receiving PEG-Intron with viral genotype 1 had a response rate of 14%  
158 (28/199) while patients with other viral genotypes had a 45% (43/96) response rate.

159  
160 Ninety-six percent of the responders in the PEG-Intron groups and 100% of  
161 responders in the INTRON A group first cleared their viral RNA by week-24 of  
162 treatment. See **DOSAGE AND ADMINISTRATION**.

163  
164 The treatment response rates were similar in men and women. Response rates  
165 were lower in African American and Hispanic patients and higher in Asians  
166 compares to Caucasians. Although African Americans had a higher proportion of  
167 poor prognostic factors compared to Caucasians the number of Non-Caucasians  
168 studied (9 percent of the total) was insufficient to allow meaningful conclusions about  
169 differences in response rates after adjusting for prognostic factors.

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

174

#### 175 **PEG-Intron/REBETOL Combination Therapy-Study 2**

176 A randomized study compared treatment with two PEG-Intron/REBETOL regimens  
177 [PEG-Intron 1.5 µg/kg SC once weekly (QW)/REBETOL 800 mg PO daily (in divided  
178 doses) ; PEG-Intron 1.5 µg/kg SC QW for 4 weeks then 0.5 µg/kg SC QW for 44  
179 weeks/REBETOL 1000/1200 mg PO daily (in divided doses)] with INTRON A (3 MIU  
180 SC thrice weekly (TIW)/REBETOL 1000/1200 mg PO daily (in divided doses) in



181 1530 adults with chronic hepatitis C. Interferon naïve patients were treated for 48  
182 weeks and followed for 24 weeks post-treatment. Eligible patients had compensated  
183 liver disease, detectable HCV RNA, elevated ALT, and liver histopathology  
184 consistent with chronic hepatitis.

185

186 Response to treatment was defined as undetectable HCV RNA at 24 weeks post-  
187 treatment. The response rate to the PEG-Intron 1.5µg/kg plus ribavirin 800mg dose  
188 was higher than the response rate to Intron A/REBETOL (See **Table 2**). The  
189 response rate to PEG-Intron 1.5→0.5µg/kg/REBETOL was essentially the same as  
190 the response to INTRON A/REBETOL (data not shown).



191- **Table 2. Rates of Response to Treatment. Study 2**

192

	PEG-Intron 1.5µg/kg QW REBETOL 800 mg QD	INTRON A 3 MIU TIW REBETOL 1000/1200mg QD
Overall <sup>1,2</sup> response	52% (264/511)	46% (231/505)
Genotype 1	41% (141/348)	33% (112/343)
Genotype 2-6	75%(123/163)	73% (119/162)

193

194 <sup>1</sup>Serum HCV RNA is measured with a research-based quantitative polymerase chain reaction assay by a central  
195 laboratory.196 <sup>2</sup> Difference in overall treatment response (Peg-Intron/REBETOL vs. Intron A/REBETOL) is 6% with 95%  
197 confidence interval of ( 0.18, 11.63) adjusted for viral genotype and presence of cirrhosis at baseline.

198

199 Patients with viral genotype 1, regardless of viral load, had a lower response rate to  
200 PEG-Intron (1.5 µg/kg)/REBETOL compared to patients with other viral genotypes.  
201 Patients with both poor prognostic factors (genotype 1 and high viral load) had a  
202 response rate of 30% (78/256) compared to a response rate of 29% (71/247) with  
203 INTRON A/REBETOL.

204

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

209

210 Treatment response rates with PEG-Intron/REBETOL were 49% in men and 56% in  
211 women. Response rates were lower in African American and Hispanic patients and  
212 higher in Asians compared to Caucasians. Although African Americans had a higher  
213 proportion of poor prognostic factors compared to Caucasians, the number of non-  
214 Caucasians studied (11% of the total) was insufficient to allow meaningful  
215 conclusions about differences in response rates after adjusting for prognostic  
216 factors.



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217  
.18 Liver biopsies were obtained before and after treatment in 68% of patients.  
219 Compared to baseline approximately 2/3 of patients in all treatment groups were  
220 observed to have a modest reduction in inflammation.  
221

## 222 **INDICATIONS AND USAGE**

223 PEG-Intron, peginterferon alfa-2b, is indicated for use alone or in combination with  
224 REBETOL (ribavirin, USP) for the treatment of chronic hepatitis C in patients with  
225 compensated liver disease who have not been previously treated with interferon  
226 alpha and are at least 18 years of age.

## 227 228 **CONTRAINDICATIONS**

229  
230 **PEG-Intron is contraindicated in patients with:**

- 231 • hypersensitivity to PEG-Intron or any other component of the product
- 232 • autoimmune hepatitis
- 233 • decompensated liver disease

234  
235 **PEG-Intron/REBETOL combination therapy is additionally contraindicated in:**

- 236 • patients with hypersensitivity to ribavirin or any other component of the  
237 product
- 238 • women who are pregnant
- 239 • men whose female partners are pregnant
- 240 • patients with hemoglobinopathies (e.g., thalassemia major, sickle-cell  
241 anemia)
- 242 • patients with creatinine clearance < 50mL/min.



243 **WARNINGS**

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

247

248 **Neuropsychiatric events**

249 Life-threatening or fatal neuropsychiatric events, including suicide, suicidal and  
250 homicidal ideation, depression, relapse of drug addiction/overdose, and aggressive  
251 behavior have occurred in patients with and without a previous psychiatric disorder  
252 during PEG-Intron treatment and follow-up. Psychoses, hallucinations, bipolar  
253 disorders, and mania have been observed in patients treated with alpha interferons.  
254 PEG-Intron should be used with extreme caution in patients with a history of  
255 psychiatric disorders. Patients should be advised to report immediately any  
256 symptoms of depression and/or suicidal ideation to their prescribing physicians.  
257 Physicians should monitor all patients for evidence of depression and other  
258 psychiatric symptoms. In severe cases, PEG-Intron should be stopped immediately  
259 and psychiatric intervention instituted. (See **DOSAGE AND ADMINISTRATION:**

260 **Dose Reduction**)

261

262 **Bone marrow toxicity**

263 PEG-Intron suppresses bone marrow function, sometimes resulting in severe  
264 cytopenias. PEG-Intron should be discontinued in patients who develop severe  
265 decreases in neutrophil or platelet counts. (See **DOSAGE AND ADMINISTRATION:**  
266 **Dose Reduction**). Ribavirin may potentiate the neutropenia induced by interferon  
267 alpha. Very rarely alpha interferons may be associated with aplastic anemia.

268

269 **Endocrine disorders**

270 PEG-Intron causes or aggravates hypothyroidism and hyperthyroidism.  
271 Hyperglycemia has been observed in patients treated with PEG-Intron. Diabetes  
272 mellitus has been observed in patients treated with alpha interferons. Patients with



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273 these conditions who cannot be effectively treated by medication should not begin  
274 PEG-Intron therapy. Patients who develop these conditions during treatment and  
275 cannot be controlled with medication should not continue PEG-Intron therapy.

276

### 277 **Cardiovascular events**

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

286

### 287 **Pulmonary disorders**

288 Dyspnea, pulmonary infiltrates, pneumonia, bronchiolitis obliterans, interstitial  
289 pneumonitis and sarcoidosis, some resulting in respiratory failure and/or patient  
290 deaths, may be induced or aggravated by PEG-Intron or alpha interferon therapy.  
291 Recurrence of respiratory failure has been observed with interferon rechallenge.  
292 PEG-Intron combination treatment should be suspended in patients who develop  
293 pulmonary infiltrates or pulmonary function impairment. Patients who resume  
294 interferon treatment should be closely monitored.

295

### 296 **Colitis**

297 Fatal and nonfatal ulcerative or hemorrhagic/ischemic colitis have been observed  
298 within 12 weeks of the start of alpha interferon treatment. Abdominal pain, bloody  
299 diarrhea, and fever are the typical manifestations. PEG-Intron treatment should be  
300 discontinued immediately in patients who develop these symptoms and signs. The  
301 colitis usually resolves within 1-3 weeks of discontinuation of alpha interferons.

302



**303 Pancreatitis**

304 Fatal and nonfatal pancreatitis have been observed in patients treated with alpha  
305 interferon. PEG-Intron therapy should be suspended in patients with signs and  
306 symptoms suggestive of pancreatitis and discontinued in patients diagnosed with  
307 pancreatitis.

308

**309 Autoimmune disorders**

310 Development or exacerbation of autoimmune disorders (e.g. thyroiditis,  
311 thrombocytopenia, rheumatoid arthritis, interstitial nephritis, systemic lupus  
312 erythematosus, psoriasis) have been observed in patients receiving PEG-Intron.  
313 PEG-Intron should be used with caution in patients with autoimmune disorders.

**314 Ophthalmologic disorders**

315 Decrease or loss of vision, retinopathy including macular edema, retinal artery or  
316 vein thrombosis, retinal hemorrhages and cotton wool spots, optic neuritis, and  
317 papilledema may be induced or aggravated by treatment with peginterferon alfa-2b  
318 or other alpha interferons. All patients should receive an eye examination at  
319 baseline. Patients with preexisting ophthalmologic disorders (e.g. diabetic or  
320 hypertensive retinopathy) should receive periodic ophthalmologic exams during  
321 interferon alpha treatment. Any patient who develops ocular symptoms should  
322 receive a prompt and complete eye examination. Peginterferon alfa-2b treatment  
323 should be discontinued in patients who develop new or worsening ophthalmologic  
324 disorders.

325

**326 Hypersensitivity**

327 Serious, acute hypersensitivity reactions (e.g., urticaria, angioedema,  
328 bronchoconstriction, anaphylaxis) and cutaneous eruptions (Stevens Johnson  
329 syndrome, toxic epidermal necrolysis) have been rarely observed during alpha  
330 interferon therapy. If such a reaction develops during treatment with PEG-Intron,  
331 discontinue treatment and institute appropriate medical therapy immediately.  
332 Transient rashes do not necessitate interruption of treatment.



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333

334 **Use with Ribavirin—(See also REBETOL Package Insert)**

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

341

342 **Anemia**

343 Ribavirin caused hemolytic anemia in 10% of PEG-Intron/REBETOL treated patients  
344 within 1-4 weeks of initiation of therapy. Complete blood counts should be obtained  
345 pretreatment and at week 2 and week 4 of therapy or more frequently if clinically  
346 indicated. Anemia associated with REBETOL therapy may result in a worsening of  
347 cardiac disease. Decrease in dosage or discontinuation of REBETOL may be  
348 necessary. (See **DOSAGE AND ADMINISTRATION: Dose Reduction**)

349

350 **PRECAUTIONS**

351 • PEG-Intron alone or in combination with REBETOL has not been studied in  
352 patients who have failed other alpha interferon treatments.

353

354 • The safety and efficacy of PEG-Intron alone or in combination with REBETOL for  
355 the treatment of hepatitis C in liver or other organ transplant recipients have not  
356 been studied. In a small (n=16) single-center, uncontrolled case experience,  
357 renal failure in renal allograft recipients receiving interferon alpha and ribavirin  
358 combination therapy was more frequent than expected from the center's previous  
359 experience with renal allograft recipients not receiving combination therapy. The  
360 relationship of the renal failure to renal allograft rejection is not clear.

361

362 • The safety and efficacy of PEG-Intron/REBETOL for the treatment of patients  
363 with HCV co-infected with HIV or HBV have not been established.

364

365



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**366 Triglycerides**

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

374

**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 PEG-Intron. Patients with  
378 impaired renal function should be closely monitored for signs and symptoms of  
379 interferon toxicity, including increases in serum creatinine, and PEG-Intron dosing  
380 should be adjusted accordingly or discontinued (See **CLINICAL PHARMACOLOGY:**  
381 **Pharmacokinetics** and **DOSAGE AND ADMINISTRATION: Dose Reduction**).  
382 PEG-Intron 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

388 **Information for Patients:** Patients receiving PEG-Intron alone or in combination  
389 with REBETOL should be directed in its appropriate use, informed of the benefits  
390 and risks associated with treatment, and referred to the **MEDICATION GUIDES for**  
391 **PEG-Intron and, if applicable, REBETOL (ribavirin, USP)**.

392

393 Patients must be informed that REBETOL may cause birth defects and/or death of  
394 the unborn child. Extreme care must be taken to avoid pregnancy in female patients  
395 and in female partners of male patients during treatment with combination PEG-  
396 Intron/REBETOL therapy and for 6 months post-therapy. Combination PEG-  
397 Intron/REBETOL therapy should not be initiated until a report of a negative



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398 pregnancy test has been obtained immediately prior to initiation of therapy. It is  
399 recommended that patients undergo monthly pregnancy tests during therapy and for  
400 6 months post-therapy. (see **CONTRAINIDICATIONS** and **REBETOL package**  
401 **insert**).

402

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

407

408 Patients should be advised that laboratory evaluations are required before starting  
409 therapy and periodically thereafter (see **Laboratory Tests**). It is advised that  
410 patients be well hydrated, especially during the initial stages of treatment. "Flu-like"  
411 symptoms associated with administration of PEG-Intron may be minimized by  
412 bedtime administration of PEG-Intron or by use of antipyretics.

413

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

419

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

427



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

437

438 Patients who have pre-existing cardiac abnormalities should have  
439 electrocardiograms administered before treatment with PEG-Intron/REBETOL.

440

#### 441 **Drug Interactions**

442 In a pharmacokinetic study of 18 HCV chronic hepatitis C patients concomitantly  
443 receiving methadone, treatment with PEG-Intron once weekly for 4 weeks was  
444 associated with a mean increase of 16% in methadone AUC; in 2 out of 18 patients,  
445 methadone AUC doubled (see **Clinical Pharmacology: Drug Interactions**). The  
446 clinical significance of this finding is unknown; however, patients should be  
447 monitored for the signs and symptoms of increased narcotic effect.

448

#### 449 **Carcinogenesis, Mutagenesis, and Impairment of Fertility**

450

451 **Carcinogenesis and Mutagenesis:** PEG-Intron has not been tested for its  
452 carcinogenic potential. Neither PEG-Intron, nor its components interferon or  
453 methoxypolyethylene glycol caused damage to DNA when tested in the standard  
454 battery of mutagenesis assays, in the presence and absence of metabolic activation.

455

456 **Use with Ribavirin:** Ribavirin is genotoxic and mutagenic and should be  
457 considered a potential carcinogen. See REBETOL package insert for additional  
458 warnings relevant to PEG-Intron therapy in combination with ribavirin.



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459

460 **Impairment of Fertility:** PEG-Intron may impair human fertility. Irregular menstrual  
461 cycles were observed in female cynomolgus monkeys given subcutaneous injections  
462 of 4239  $\mu\text{g}/\text{m}^2$  PEG-Intron alone every other day for one month, (approximately 345  
463 times the recommended weekly human dose based upon body surface area). These  
464 effects included transiently decreased serum levels of estradiol and progesterone,  
465 suggestive of anovulation. Normal menstrual cycles and serum hormone levels  
466 resumed in these animals 2 to 3 months following cessation of PEG-Intron  
467 treatment. Every other day dosing with 262  $\mu\text{g}/\text{m}^2$  (approximately 21 times the  
468 weekly human dose) had no effects on cycle duration or reproductive hormone  
469 status. The effects of PEG-Intron on male fertility have not been studied.

470

471 **Pregnancy Category C: PEG-Intron monotherapy:** Non-pegylated Interferon alfa-  
472 2b, has been shown to have abortifacient effects in *Macaca mulatta* (rhesus  
473 monkeys) at 15 and 30 million IU/kg (estimated human equivalent of 5 and 10 million  
474 IU/kg, based on body surface area adjustment for a 60 kg adult). PEG-Intron should  
475 be assumed to also have abortifacient potential. There are no adequate and well-  
476 controlled studies in pregnant women. PEG-Intron therapy is to be used during  
477 pregnancy only if the potential benefit justifies the potential risk to the fetus.  
478 Therefore, PEG-Intron is recommended for use in fertile women only when they are  
479 using effective contraception during the treatment period.

480

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

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

486

487 If pregnancy occurs in a patient or partner of a patient during treatment with PEG-  
488 Intron and REBETOL or during the 6 months after treatment cessation, physicians  
489 should report such cases by calling (800) 727-7064.



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490

491 **Nursing Mothers**

492 It is not known whether the components of PEG-Intron and/or REBETOL are  
493 excreted in human milk. Studies in mice have shown that mouse interferons are  
494 excreted in breast milk. Because of the potential for adverse reactions from the drug  
495 in nursing infants, a decision must be made whether to discontinue nursing or  
496 discontinue the PEG-Intron and REBETOL treatment, taking into account the  
497 importance of the therapy to the mother.

498

499

500 **Pediatric.** Safety and effectiveness in pediatric patients below the age of 18 years  
501 have not been established.

502

503 **Geriatric.** In general, younger patients tend to respond better than older patients to  
504 interferon-based therapies. Clinical studies of PEG-Intron alone or in combination  
505 with REBETOL did not include sufficient numbers of subjects aged 65 and over,  
506 however, to determine whether they respond differently than younger subjects.  
507 Treatment with alpha interferons, including PEG-Intron, is associated with  
508 neuropsychiatric, cardiac, pulmonary, GI and systemic (flu-like) adverse effects.  
509 Because these adverse reactions may be more severe in the elderly, caution should  
510 be exercised in the use of PEG-Intron in this population. This drug is known to be  
511 substantially excreted by the kidney. Because elderly patients are more likely to  
512 have decreased renal function, the risk of toxic reactions to this drug may be greater  
513 in patients with impaired renal function. (See **CLINICAL PHARMACOLOGY**  
514 **Special Populations: Renal Dysfunction**). REBETOL should not be used in  
515 patients with creatinine clearance <50 mL/min. When using PEG-Intron/REBETOL  
516 therapy, refer also to the REBETOL Package Insert.

517

518 **ADVERSE REACTIONS**

519 Nearly all study patients in clinical trials experienced one or more adverse events. In  
520 the PEG monotherapy trial the incidence of serious adverse events was similar



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521 (about 12%) in all treatment groups. In the PEG-Intron/REBETOL combination trial  
522 the incidence of serious adverse events was 17% in the PEG-Intron/REBETOL  
523 groups compared to 14% in the INTRON A/REBETOL group.

524  
525 In many but not all cases, adverse events resolved after dose reduction or  
526 discontinuation of therapy. Some patients experienced ongoing or new serious  
527 adverse events during the 6-month follow-up period. In the PEG-Intron/REBETOL  
528 trial 13 patients experienced life-threatening psychiatric events (suicidal ideation or  
529 attempt) and one patient accomplished suicide.

530  
531 There have been five patient deaths which occurred in clinical trials: one suicide in a  
532 patient receiving PEG-Intron monotherapy and one suicide in a patient receiving  
533 PEG-Intron/REBETOL combination therapy; two deaths among patients receiving  
534 INTRON A monotherapy (1 murder/suicide and 1 sudden death) and one patient  
535 death in the INTRON A/REBETOL group (motor vehicle accident).

536  
537 Overall, 10-14% of patients receiving PEG-Intron, alone or in combination with  
538 REBETOL, discontinued therapy compared with 6% treated with INTRON A alone  
539 and 13% treated with INTRON A in combination with REBETOL. The most common  
540 reasons for discontinuation of therapy were related to psychiatric, systemic (e.g.  
541 fatigue, headache), or gastrointestinal adverse events.

542  
543 In the combination therapy trial, dose reductions due to adverse reactions occurred  
544 in 42% of patients receiving PEG-Intron (1.5 µg/kg)/REBETOL and in 34% of those  
545 receiving INTRON A/REBETOL. The majority of patients (57%) weighing 60 kg or  
546 less receiving Peg-Intron (1.5 µg/kg)/REBETOL required dose reduction. Reduction  
547 of interferon was dose related (PEG-Intron 1.5 µg/kg > PEG-Intron 0.5 µg/kg or  
548 INTRON A), 40%, 27%, 28%, respectively. Dose reduction for REBETOL was  
549 similar across all three groups, 33-35%. The most common reasons for dose  
550 modifications were neutropenia (18%), or anemia (9%). (see **Laboratory Values**).



551 Other common reasons included depression, fatigue, nausea, and  
552 thrombocytopenia.

553  
554 In the PEG-Intron/REBETOL combination trial the most common adverse events  
555 were psychiatric which occurred among 77% of patients and included most  
556 commonly depression, irritability, and insomnia, each reported by approximately 30-  
557 40% of subjects in all treatment groups. Suicidal behavior (ideation, attempts, and  
558 suicides) occurred in 2% of all patients during treatment or during follow-up after  
559 treatment cessation (see **WARNINGS**).

560  
561 PEG-Intron induced fatigue or headache in approximately two-thirds of patients, and  
562 induced fever or rigors in approximately half of the patients. The severity of some of  
563 these systemic symptoms (e.g. fever and headache) tended to decrease as  
564 treatment continues. The incidence tends to be higher with PEG-Intron than with  
565 Intron A therapy alone or in combination with REBETOL.

566  
567 Application site inflammation and reaction (e.g. bruise, itchiness, irritation) occurred  
568 at approximately twice the incidence with PEG-Intron therapies (in up to 75% of  
569 patients) compared with INTRON A. However injection site pain was infrequent (2-  
570 3%) in all groups.

571  
572 Other common adverse events in the PEG-Intron/REBETOL group included myalgia  
573 (56%), arthralgia (34%), nausea (43%), anorexia (32%), weight loss (29%), alopecia  
574 (36%), and pruritus (29%).

575  
576 In the PEG-Intron monotherapy trial the incidence of severe adverse events was  
577 13% in the INTRON A group and 17% in the PEG-Intron groups. In the PEG-  
578 Intron/REBETOL combination therapy trial the incidence of severe adverse events  
579 was 23% in the INTRON A/REBETOL group and 31-34% in the PEG-  
580 Intron/REBETOL groups. The incidence of life-threatening adverse events was ≤  
581 1% across all groups in the monotherapy and combination therapy trials.



582

583 Adverse events that occurred in the clinical trial at >5% incidence are provided in  
584 **Table 3** by treatment group. Due to potential differences in ascertainment  
585 procedures, adverse event rate comparisons across studies should not be made.



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586 **Table 3. Adverse Events Occurring in > 5% of Patients**  
587

Adverse Events	Percentage of Patients Reporting Adverse Events*			
	Study 1		Study 2	
	PEG-Intron1.0 µg/kg (n=297)	INTRON A 3 MIU (n=303)	PEG-Intron 1.5µg/kg/ REBETOL (n=511)	INTRON A/ REBETOL (n=505)
<b>Application Site</b>				
Injection Site	47	20	75	49
<b>Inflammation/Reaction</b>				
<b>Autonomic Nervous Sys.</b>				
Mouth Dry	6	7	12	8
Sweating Increased	6	7	11	7
Flushing	6	3	4	3
<b>Body as a Whole</b>				
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
<b>Central/Periph. Nerv. Sys.</b>				
Dizziness	12	10	21	17
<b>Endocrine</b>				
Hypothyroidism	5	3	5	4
<b>Gastrointestinal</b>				
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
<b>Hematologic Disorders</b>				
Neutropenia	6	2	26	14
Anemia	0	0	12	17
Leukopenia	<1	0	6	5
Thrombocytopenia	7	<1	5	2
<b>Liver and Biliary System</b>				
Hepatomegaly	6	5	4	4
<b>Musculoskeletal</b>				
Myalgia	54	53	56	50
Arthralgia	23	27	34	28
Musculoskeletal Pain	28	22	21	19
<b>Psychiatric</b>				
Insomnia	23	23	40	41
Depression	29	25	31	34
Anxiety/Emotional	28	34	47	47
<b>Lability/Irritability</b>				
Concentration Impaired	10	8	17	21
Agitation	2	2	8	5

Adverse Events	Percentage of Patients Reporting Adverse Events*			
	Study 1		Study 2	
	PEG-Intron 1.0 µg/kg (n=297)	INTRON A 3 MIU (n=303)	PEG-Intron 1.5µg/kg/ REBETOL (n=511)	INTRON A/ REBETOL (n=505)
Nervousness	4	3	6	6
<b>Reproductive, Female</b>				
Menstrual Disorder	4	3	7	6
<b>Resistance Mechanism</b>				
Infection Viral	11	10	12	12
Infection Fungal	<1	3	6	1
<b>Respiratory System</b>				
Dyspnea	4	2	26	24
Coughing	8	5	23	16
Pharyngitis	10	7	12	13
Rhinitis	2	2	8	6
Sinusitis	7	7	6	5
<b>Skin and Appendages</b>				
Alopecia	22	22	36	32
Pruritus	12	8	29	28
Rash	6	7	24	23
Skin Dry	11	9	24	23
<b>Special Senses Other,</b>				
Taste Perversion	<1	2	9	4
<b>Vision Disorders</b>				
Vision blurred	2	3	5	6
Conjunctivitis	4	2	4	5

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

588  
589  
590

591 Many patients continued to experience adverse events several months after  
592 discontinuation of therapy. By the end of the 6-month follow-up period the incidence  
593 of ongoing adverse events by body class in the PEG-INTRON 1.5/REBETOL group  
594 was 33% (psychiatric), 20% (musculoskeletal), and 10% (for endocrine and for GI).  
595 In approximately 10-15% of patients weight loss, fatigue and headache had not  
596 resolved.

597

598 Individual serious adverse events occurred at a frequency  $\leq 1\%$  and included suicide  
599 attempt, suicidal ideation, severe depression; psychosis, aggressive reaction,  
600 relapse of drug addiction/overdose; nerve palsy (facial, oculomotor);  
601 cardiomyopathy, myocardial infarction, angina, pericardial effusion, retinal ischemia,  
602 retinal artery or vein thrombosis, blindness, decreased visual acuity, optic neuritis,  
603 transient ischemic attack, supraventricular arrhythmias, loss of consciousness;  
604 neutropenia, infection (sepsis, pneumonia, abscess, cellulitis); emphysema,



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605 bronchiolitis obliterans, pleural effusion, gastroenteritis, pancreatitis, gout,  
606 hyperglycemia, hyperthyroidism and hypothyroidism, autoimmune thrombocytopenia  
607 with or without purpura, rheumatoid arthritis, interstitial nephritis, lupus-like  
608 syndrome, sarcoidosis, aggravated psoriasis; urticaria, injection-site necrosis,  
609 vasculitis, phototoxicity.

610

### 611 **Laboratory Values**

612 Changes in selected laboratory values during treatment with PEG-Intron alone or in  
613 combination with REBETOL treatment are described below. **Decreases in**  
614 **hemoglobin, neutrophils, and platelets may require dose reduction or**  
615 **permanent discontinuation from therapy. (See DOSAGE AND**  
616 **ADMINISTRATION- Dose Reduction)**

617

618 **Hemoglobin.** REBETOL induced a decrease in hemoglobin levels in approximately  
619 two thirds of patients. Hemoglobin levels decreased to <11g/dl in about 30% of  
620 patients. Severe anemia (<8 g/dl) occurred in < 1% of patients. Dose modification  
621 was required in 9 and 13% of patients in the PEG-Intron/REBETOL and INTRON A  
622 /REBETOL groups. Hemoglobin levels become stable by treatment week 4-6 on  
623 average. Hemoglobin levels return to baseline between 4 and 12 weeks post-  
624 treatment. In the PEG-Intron monotherapy trial hemoglobin decreases were  
625 generally mild and dose modifications were rarely necessary. (See **DOSAGE AND**  
626 **ADMINISTRATION: Dose Reduction**).

627

628 **Neutrophils.** Decreases in neutrophil counts were observed in a majority of  
629 patients treated with PEG-Intron alone (70%) or as combination therapy with  
630 REBETOL (85%) and INTRON A/REBETOL (60%). Severe potentially life-  
631 threatening neutropenia ( $<0.5 \times 10^9/L$ ) occurred in 1% of patients treated with PEG-  
632 Intron monotherapy, 2% of patients treated with INTRON A/REBETOL and in 4% of  
633 patients treated with PEG-Intron/REBETOL. Two percent of patients receiving PEG-  
634 Intron monotherapy and 18% of patients receiving PEG-Intron /REBETOL required  
635 modification of interferon dosage. Few patients ( $\leq 1\%$ ) required permanent



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636 discontinuation of treatment. Neutrophil counts generally return to pre-treatment  
637 levels within 4 weeks of cessation of therapy. (See **DOSAGE AND**  
638 **ADMINISTRATION: Dose Reduction**).

639

640 **Platelets.** Platelet counts decrease in approximately 20% of patients treated with  
641 PEG-Intron alone or with REBETOL and in 6% of patients treated with INTRON  
642 A/REBETOL. Severe decreases in platelet counts ( $<50,000/\text{mm}^3$ ) occur in  $<1\%$  of  
643 patients. Patients may require discontinuation or dose modification as a result of  
644 platelet decreases. (See **DOSAGE AND ADMINISTRATION: Dose Reduction**). In  
645 the PEG-Intron/REBETOL combination therapy trial 1% or 3% of patients required  
646 dose modification of INTRON A or PEG-Intron respectively. Platelet counts  
647 generally returned to pretreatment levels within 4 weeks of the cessation of therapy.

648

649 **Triglycerides.** Elevated triglyceride levels have been observed in patients treated  
650 with interferon alphas including PEG-Intron.

651

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

659

660 **Bilirubin and uric acid.** In the PEG-Intron/REBETOL trial 10-14% of patients  
661 developed hyperbilirubinemia and 33-38% developed hyperuricemia in association  
662 with hemolysis. Six patients developed mild to moderate gout.

663

#### 664 **Postmarketing Experience**

665 The following adverse reactions have been identified and reported during post-  
666 approval use of PEG-Intron therapy: seizures, hearing impairment, hearing loss,



667 peripheral neuropathy, rhabdomyolysis, myositis, aphthous stomatitis, vertigo, renal  
668 insufficiency, renal failure, Stevens Johnson syndrome, toxic epidermal necrolysis  
669 and erythema multiforme. Because the reports of these reactions are voluntary and  
670 the population of uncertain size, it is not always possible to reliably estimate the  
671 frequency of the reaction or establish a causal relationship to drug exposure.

672

673 **Immunogenicity:** Approximately 2% of patients receiving PEG-Intron (32/1759) or  
674 INTRON A (11/728) with or without REBETOL developed low-titer ( $\leq 160$ )  
675 neutralizing antibodies to PEG-Intron or INTRON A. The clinical and pathological  
676 significance of the appearance of serum neutralizing antibodies is unknown. No  
677 apparent correlation of antibody development to clinical response or adverse events  
678 was observed. The incidence of post-treatment binding antibody ranged from 8 to  
679 15 percent. The data reflect the percentage of patients whose test results were  
680 considered positive for antibodies to PEG-Intron in a Biacore assay that is used to  
681 measure binding antibodies, and in an antiviral neutralization assay, which  
682 measures serum-neutralizing antibodies. The percentage of patients whose test  
683 results were considered positive for antibodies is highly dependent on the sensitivity  
684 and specificity of the assays. Additionally the observed incidence of antibody  
685 positivity in these assays may be influenced by several factors including sample  
686 timing and handling, concomitant medications, and underlying disease. For these  
687 reasons, comparison of the incidence of antibodies to PEG-Intron with the incidence  
688 of antibodies to other products may be misleading.

689

## 690 OVERDOSAGE

691 There is limited experience with overdosage. In the clinical studies, a few patients  
692 accidentally received a dose greater than that prescribed. There were no instances  
693 in which a participant in the monotherapy or combination therapy trials received  
694 more than 10.5 times the intended dose of PEG-Intron. The maximum dose  
695 received by any patient was 3.45  $\mu\text{g}/\text{kg}$  weekly over a period of approximately 12  
696 weeks. The maximum known overdosage of REBETOL was an intentional ingestion  
697 of 10 g (fifty 200 mg capsules). There were no serious reactions attributed to these



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698 overdosages. In cases of overdosing, symptomatic treatment and close observation  
699 of the patient are recommended.

700

## 701 **DOSAGE AND ADMINISTRATION**

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

706

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

710

### 711 **PEG-Intron Monotherapy**

712 The recommended dose of PEG-Intron regimen is 1.0 µg/kg/week subcutaneously  
713 for one year. The dose should be administered on the same day of the week.

714 The volume of PEG-Intron to be injected depends on patient weight (see **Table 4**  
715 **below**).

716

717 **Table 4 Recommended PEG-Intron Monotherapy Dosing**

Body weight kg	PEG-Intron Redipen™ or Vial Strength to use	Amount of PEG-Intron(µg) To Administer	Volume (mL) * of PEG-Intron to Administer
≤45	50µg per 0.5 ml	40	0.4
46 - 56		50	0.5
57 - 72	80 µg per 0.5 ml	64	0.4
73 - 88		80	0.5
89 - 106	120 µg per 0.5 ml	96	0.4
107 - 136		120	0.5



137 - 160	150 µg per 0.5 ml	150	0.5
-----------	-------------------	-----	-----

718 \* When reconstituted as directed

719 **PEG-Intron/REBETOL Combination Therapy**

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

723

724 **TABLE 5. Recommended PEG-Intron Combination Therapy Dosing**

725

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

726 \* When reconstituted as directed

727

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

731

732 **Dose Reduction**

733 If a serious adverse reaction develops during the course of treatment (See  
734 **WARNINGS**) discontinue or modify the dosage of PEG-Intron and/or REBETOL until  
735 the adverse event abates or decreases in severity. If persistent or recurrent serious  
736 adverse events develop despite adequate dosage adjustment, discontinue



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737 treatment. For guidelines for dose modifications and discontinuation based on  
738 laboratory parameters, see **Tables 6 and 7**. Dose reduction of PEG-Intron may be  
739 accomplished by utilizing a lower dose strength as shown in **Table 8 or 9**. For vials,  
740 50% dose reduction may also be accomplished by reducing the volume  
741 administered by one-half without changing the dose strength. In the combination  
742 therapy trial dose reductions occurred among 42% of patients receiving PEG-Intron  
743 1.5 µg/kg/REBETOL 800 mg daily including 57% of those patients weighing 60 kg or  
744 less (see **ADVERSE REACTIONS**).

745

746 **Table 6: Guidelines for Modification or Discontinuation of PEG-Intron or PEG-**  
747 **Intron/REBETOL and for Scheduling Visits for Patients with Depression**

Depression Severity <sup>1</sup>	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		

748 <sup>1</sup> See DSM-IV for definitions

749

750 **Table 7. Guidelines for Dose Modification and Discontinuation of PEG-Intron**  
751 **or PEG-Intron/REBETOL for Hematologic Toxicity**

Laboratory Values		PEG-Intron	REBETOL
Hgb*	<10.0 g/dl <8.5 g/dl	----- Permanently discontinue	Decrease by 200mg/day Permanently discontinue
WBC	<1.5 x10 <sup>9</sup> /L	Reduce dose by 50%	-----



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	<1.0 x10 <sup>9</sup> /L	Permanently discontinue	Permanently discontinue
Neutrophil	<0.75 x10 <sup>9</sup> /L	Reduce dose by 50%	-----
	<0.5 x10 <sup>9</sup> /L	Permanently discontinue	Permanently discontinue
Platelets	<80 x10 <sup>9</sup> /L	Reduce dose by 50%	-----
	<50 x10 <sup>9</sup> /L	Permanently discontinue	Permanently discontinue

752 \* For patients with a history of stable cardiac disease receiving PEG-Intron in combination with ribavirin, the  
 753 PEG-Intron dose should be reduced by half and the ribavirin dose by 200mg/day if a > 2g/dL decrease in  
 754 hemoglobin is observed during any 4 week period. Both PEG-Intron and ribavirin should be permanently  
 755 discontinued if patients have hemoglobin levels <12 g/dL after this ribavirin dose reduction.  
 756

757 **Table 8: Reduced PEG-Intron Dose (0.5µg /kg) for (1.0µg /kg) Monotherapy**  
 758

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

759 \* Must use vial. Minimum delivery for Redipen 0.3 mL

760 ^ When reconstituted as directed



761 **TABLE 9. Reduced PEG-Intron Dose (0.75µg /kg) for (1.5µg /kg) Combination**  
762 **Therapy**

763

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

764 \* Must use vial. Minimum delivery for Redipen 0.3 mL

765 ^ When reconstituted as directed

766

767 **Renal Function**

768 In patients with moderate renal dysfunction (creatinine clearance 30-50 mL/min), the  
769 PEG-Intron dose should be reduced by 25%. Patients with severe renal dysfunction  
770 (creatinine clearance 10-29 mL/min) including those on hemodialysis, should have  
771 PEG-Intron dose reduced by 50%. If renal function decreases during treatment,  
772 PEG-Intron therapy should be discontinued.

773

774 **Preparation and Administration**

775 **PEG-Intron Redipen™**

776 PEG-Intron Redipen™ consists of a dual-chamber glass cartridge with sterile,  
777 lyophilized peginterferon alfa-2b in the active chamber and Sterile Water for  
778 Injection, USP in the diluent chamber. The PEG-Intron in the glass cartridge should  
779 appear as a white to off-white tablet shaped solid that is whole or in pieces, or  
780 powder. To reconstitute the lyophilized peginterferon alfa-2b in the Redipen™, hold



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

789 Keeping the pen upright, attach the supplied needle and select the appropriate PEG-  
790 Intron dose by pulling back on the dosing button until the dark bands are visible and  
791 turning the button until the dark band is aligned with the correct dose. The prepared  
792 PEG-Intron solution is to be injected subcutaneously.  
793

794  
795 The PEG-Intron Redipen is a single use pen and does not contain a preservative.  
796 The reconstituted solution should be used immediately and cannot be stored for  
797 more than 24 hours at 2-8° C (See **Storage**). **DO NOT REUSE THE REDIPEN™**  
798 The sterility of any remaining product can no longer be guaranteed. **DISCARD THE**  
799 **UNUSED PORTION**. Pooling of unused portions of some medications has been  
800 linked to bacterial contamination and morbidity.

801

#### 802 **PEG-Intron Vials**

803 Two B-D Safety Lok™ syringes are provided in the package; one syringe is for the  
804 reconstitution steps and one for the patient injection. There is a plastic safety sleeve  
805 to be pulled over the needle after use. The syringe locks with an audible click when  
806 the green stripe on the safety sleeve covers the red stripe on the needle.  
807 Instructions for the preparation and administration of PEG-Intron Powder for  
808 Injection are provided below.

809

810 **Reconstitute the PEG-Intron lyophilized product with only 0.7 mL of 1 mL of**  
811 **supplied diluent** (Sterile Water for Injection, USP). **The diluent vial is for single**  
812 **use only. The remaining diluent should be discarded.** No other medications



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813 should be added to solutions containing PEG-Intron, and PEG-Intron should not be  
814 reconstituted with other diluents. Swirl gently to hasten complete dissolution of the  
815 powder. The reconstituted solution should be clear and colorless. Visually inspect  
816 the solution for particulate matter and discoloration prior to administration. The  
817 solution should not be used if discolored or cloudy or if particulates are present.

818

819 The appropriate PEG-Intron dose should be withdrawn and injected subcutaneously.  
820 PEG-Intron vials are for single use only and do not contain a preservative. The  
821 reconstituted solution should be used immediately and cannot be stored for more  
822 than 24 hours at 2-8° C (See **Storage**). **DO NOT REUSE THE VIAL**. The sterility of  
823 any remaining product can longer be guaranteed. **DISCARD THE UNUSED**  
824 **PORTION**. Pooling of unused portions of some medications has been linked to  
825 bacterial contamination and morbidity.

826

827 After preparation and administration of the PEG-Intron for injection, it is essential to  
828 follow the state and or local procedures for proper disposal of syringes, needles, and  
829 the Redipen™. A puncture-resistant container should be used for disposal. Patients  
830 should be instructed in how to properly dispose of used syringes needles or the  
831 Redipen™ and be cautioned against the reuse of these items.

832

### 833 **Storage**

#### 834 **PEG-Intron Redipen™**

835 PEG-Intron Redipen™ should be stored at 2°C to 8°C (36° to 46°F). After  
836 reconstitution, the solution should be used immediately, but may be stored up to 24  
837 hours at 2° to 8°C (36° to 46°F). The reconstituted solution contains no  
838 preservative, and is clear and colorless. **DO NOT FREEZE**.

839

#### 840 **PEG-Intron Vials**

841 PEG-Intron, should be stored at 25°C (77°F): excursions permitted to 15-30 °C (59-  
842 86 °F) [see USP Controlled Room Temperature]. After reconstitution with supplied  
843 Diluent the solution should be used immediately, but may be stored up to 24 hours



4 at 2° to 8°C (36° to 46°F). The reconstituted solution contains no preservative, is  
845 clear and colorless. **DO NOT FREEZE.**  
846



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847 **HOW SUPPLIED**

848

849 **PEG-Intron Redipen™**

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

850

851

852 **PEG-Intron Vials**

Each PEG-Intron Package Contains	
A box containing one 50µg per 0.5 mL vial of PEG-Intron Powder for Injection and one 1 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 80µg per 0.5 mL vial of PEG-Intron Powder for Injection and one 1 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 120µg per 0.5 mL vial of PEG-Intron Powder for Injection and one 1 mL vial of Diluent (Sterile Water for Injection, USP), 2 B-D Safety Lok™ syringes with a safety sleeve and 2 alcohol swabs.	(NDC 0085-1304-01)
A box containing one 150µg per 0.5 mL vial of PEG-Intron Powder for Injection and one 1 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)

853

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856

857 **REVISION: DATE**

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