

- 1 | 103105.revised PI-Final Draft
2 | **Product Information**
3 | **PEG-Intron®**
4 | **(Peginterferon alfa-2b)**
5 | **Powder For Injection**
6 |

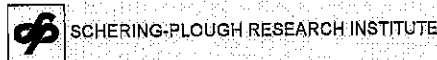
Alpha interferons, including PEG-Intron, may cause or aggravate fatal or life-threatening neuropsychiatric, autoimmune, ischemic, and infectious disorders. Patients should be monitored closely with periodic clinical and laboratory evaluations. Patients with persistently severe or worsening signs or symptoms of these conditions should be withdrawn from therapy. In many but not all cases these disorders resolve after stopping PEG-Intron 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 | PEG-Intron®, 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 PEG-Intron 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 **PEG-Intron is supplied in both vials and the Redipen® for subcutaneous use.**

19 **Vials**

20 Each vial contains either 74 µg, 118.4 µg, 177.6 µg or 222 µg of PEG-Intron as a
21 white to off-white tablet-like solid, that is whole/in pieces or as a loose powder, and
22 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 PEG-Intron at strengths of either 50 µg per 0.5 mL, 80 µg per 0.5 mL, 120
26 µg per 0.5 mL, or 150 µg per 0.5 mL.

27

28 **Redipen®**

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

41



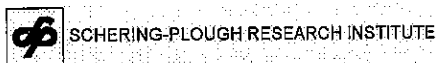
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42 CLINICAL PHARMACOLOGY

43 **General:** The biological activity of PEG-Intron is derived from its interferon alfa-2b
44 moiety. Interferons exert their cellular activities by binding to specific membrane
45 receptors on the cell surface and initiate a complex sequence of intracellular events.
46 These include the induction of certain enzymes, suppression of cell proliferation,
47 immunomodulating activities such as enhancement of the phagocytic activity of
48 macrophages and augmentation of the specific cytotoxicity of lymphocytes for target
49 cells, and inhibition of virus replication in virus-infected cells. Interferon alfa
50 upregulates the Th1 T-helper cell subset in *in vitro* studies. The clinical relevance of
51 these findings is not known.

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

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



71 compared to INTRON A, PEG-Intron (1.0 µg/kg) has approximately a seven-fold
72 lower mean apparent clearance and a five-fold greater mean half-life permitting a
73 reduced dosing frequency. At effective therapeutic doses, PEG-Intron has
74 approximately ten-fold greater C_{max} and 50-fold greater AUC than interferon alfa-2b.

75 **Special Populations**

76 77 **Renal Dysfunction**

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

89

90 **Gender**

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

94

95 **Geriatric Patients**

96 The pharmacokinetics of geriatric subjects (> 65 years of age) treated with a single
97 subcutaneous dose of 1.0 µg/kg of PEG-Intron were similar in C_{max} , AUC, clearance,
98 or elimination half-life as compared to younger subjects (28 to 44 years of age).



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100 **Effect of Food on Absorption of Ribavirin** Both AUC_{tr} and C_{max} increased by
101 70% when REBETOL Capsules were administered with a high-fat meal (841 kcal,
102 53.8 g fat, 31.6 g protein, and 57.4 g carbohydrate) in a single-dose pharmacokinetic
103 study (See **DOSAGE AND ADMINISTRATION**).

104

105 **Drug Interactions**

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

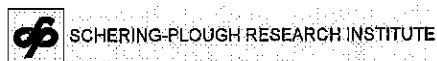
107 The pharmacokinetics of representative drugs metabolized by CYP1A2 (caffeine),
108 CYP2C8/9 (tolbutamide), CYP2D6 (dextromethorphan), CYP3A4 (midazolam) and
109 N-acetyltransferase (dapson) were studied in 22 patients with chronic hepatitis C
110 who received PEG-Intron (1.5mcg/kg) once weekly for 4 weeks. PEG-Intron
111 treatment resulted in a 28% (mean) increase in a measure of CYP2C8/9 activity.
112 PEG-Intron treatment also resulted in a 66% (mean) increase in a measure of
113 CYP2D6 activity; however, the effect was variable as 13 patients had an increase, 5
114 patients had a decrease, and 4 patients had no significant change (see
115 **PRECAUTIONS: Drug Interactions**).

116

117 No significant effect was observed on the pharmacokinetics of representative drugs
118 metabolized by CYP1A2, CYP3A4, or N-acetyltransferase. The effects of PEG-
119 Intron on CYP2C19 activity were not assessed.

120 **Methadone**

121 The pharmacokinetics of concomitant administration of methadone and PEG-Intron
122 were evaluated in 18 PEG-Intron naïve chronic hepatitis C patients receiving 1.5
123 ^{mcg}µg/kg/week PEG-Intron SC weekly. All patients were on stable methadone
124 maintenance therapy receiving ≥ 40 mg/day prior to initiating PEG-Intron. Mean
125 methadone AUC was approximately 16% higher after 4 weeks of PEG-Intron
126 treatment as compared to baseline. In 2 patients, methadone AUC was



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127 approximately double after 4 weeks of PEG-Intron treatment as compared to
128 baseline (see **PRECAUTIONS: Drug Interactions**).

129

130 **Use with Ribavirin:**

131 Ribavirin has been shown *in vitro* to inhibit phosphorylation of zidovudine,
132 lamivudine and stavudine. However, in a study with another pegylated interferon in
133 combination with ribavirin, no pharmacokinetic (e.g., plasma concentrations or
134 intracellular triphosphorylated active metabolite concentrations) or
135 pharmacodynamic (e.g., loss of HIV/HCV virologic suppression) interaction was
136 observed when ribavirin and lamivudine (n=18) stavudine (n=10) or zidovudine (n=6)
137 were co-administered as part of a multi-drug regimen to HIV/HCV coinfectd
138 patients. Exposure to didanosine or its active metabolite (dideoxyadenosine 5'-
139 triphosphate) is increased when didanosine is co-administered with ribavirin, which
140 could cause or worsen clinical toxicities (See **PRECAUTIONS :Drug Interactions**).

141

142 **CLINICAL STUDIES**

143 **PEG-Intron Monotherapy-Study 1**

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

153



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

158

159

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 ^a	18%	25%	12%	12 (6,19)
ALT Normalization	24%	29%	18%	11 (5,18)

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

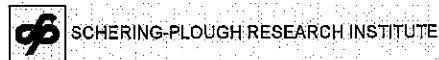
162

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

169

170 Patients receiving PEG-Intron with viral genotype 1 had a response rate of 14%
 171 (28/199) while patients with other viral genotypes had a 45% (43/96) response rate.
 172 Ninety-six percent of the responders in the PEG-Intron groups and 100% of
 173 responders in the INTRON A group first cleared their viral RNA by week-24 of
 174 treatment (See **DOSAGE AND ADMINISTRATION**).

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

182

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

186

187 **PEG-Intron/REBETOL Combination Therapy-Study 2**

188 A randomized study compared treatment with two PEG-Intron/REBETOL regimens
189 [PEG-Intron 1.5 $\mu\text{g}/\text{kg}$ SC once weekly (QW)/REBETOL 800 mg PO daily (in divided
190 doses) ; PEG-Intron 1.5 $\mu\text{g}/\text{kg}$ SC QW for 4 weeks then 0.5 $\mu\text{g}/\text{kg}$ SC QW for 44
191 weeks/REBETOL 1000/1200 mg PO daily (in divided doses)] with INTRON A (3 MIU
192 SC thrice weekly (TIW)/REBETOL 1000/1200 mg PO daily (in divided doses) in
193 1530 adults with chronic hepatitis C. Interferon naïve patients were treated for 48
194 weeks and followed for 24 weeks post-treatment. Eligible patients had compensated
195 liver disease, detectable HCV RNA, elevated ALT, and liver histopathology
196 consistent with chronic hepatitis.

197

198 Response to treatment was defined as undetectable HCV RNA at 24 weeks post-
199 treatment. The response rate to the PEG-Intron 1.5 $\mu\text{g}/\text{kg}$ plus ribavirin 800 mg dose
200 was higher than the response rate to Intron A/REBETOL (See Table 2). The
201 response rate to PEG-Intron 1.5 \rightarrow 0.5 $\mu\text{g}/\text{kg}$ /REBETOL was essentially the same as
202 the response to INTRON A/REBETOL (data not shown).



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Table 2. Rates of Response to Treatment - Study 2

	PEG-Intron 1.5µg/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)

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

206 ² Difference in overall treatment response (Peg-Intron/REBETOL vs. Intron A/REBETOL) is 6% with 95%
 207 confidence interval of (0.18, 11.63) adjusted for viral genotype and presence of cirrhosis at baseline.

208

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

214

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

219

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



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

230 INDICATIONS AND USAGE

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

235 236 CONTRAINDICATIONS

237
238 **PEG-Intron is contraindicated in patients with:**

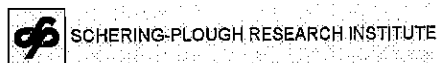
- 239 • hypersensitivity to PEG-Intron or any other component of the product
- 240 • autoimmune hepatitis
- 241 • hepatic decompensation (Child-Pugh score >6 [class B and C]) in cirrhotic CHC
242 patients before or during treatment.

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

- 244 • patients with hypersensitivity to ribavirin or any other component of the
245 product
- 246 • women who are pregnant
- 247 • men whose female partners are pregnant
- 248 • patients with hemoglobinopathies (e.g., thalassemia major, sickle-cell
249 anemia)
- 250 • patients with creatinine clearance < 50mL/min

251 WARNINGS

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



255 Neuropsychiatric events

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

268

269 Bone marrow toxicity

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

275

276 Hepatic Failure

277 Chronic hepatitis C (CHC) patients with cirrhosis may be at risk of hepatic
278 decompensation and death when treated with alpha interferons, including PEG-
279 Intron. Cirrhotic CHC patients coinfecting with HIV receiving highly active
280 antiretroviral therapy (HAART) and alpha interferons with or without ribavirin appear
281 to be at increased risk for the development of hepatic decompensation compared to
282 patients not receiving HAART. During treatment, patients' clinical status and hepatic



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283 function should be closely monitored, and PEG-Intron treatment should be
284 immediately discontinued if decompensation (Child-Pugh score >6) is observed (See
285 **CONTRAINDICATIONS**).

286

287 **Endocrine disorders**

288 PEG-Intron causes or aggravates hypothyroidism and hyperthyroidism.
289 Hyperglycemia has been observed in patients treated with PEG-Intron. Diabetes
290 mellitus has been observed in patients treated with alpha interferons. Patients with
291 these conditions who cannot be effectively treated by medication should not begin
292 PEG-Intron therapy. Patients who develop these conditions during treatment and
293 cannot be controlled with medication should not continue PEG-Intron therapy.

294

295 **Cardiovascular events**

296 Cardiovascular events, which include hypotension, arrhythmia, tachycardia,
297 cardiomyopathy, angina pectoris, and myocardial infarction, have been observed in
298 patients treated with PEG-Intron. PEG-Intron should be used cautiously in patients
299 with cardiovascular disease. Patients with a history of myocardial infarction and
300 arrhythmic disorder who require PEG-Intron therapy should be closely monitored
301 (see **Laboratory Tests**). Patients with a history of significant or unstable cardiac
302 disease should not be treated with PEG-Intron/REBETOL combination therapy. (See
303 **REBETOL package insert**.)

304 **Pulmonary disorders**

305 Dyspnea, pulmonary infiltrates, pneumonia, bronchiolitis obliterans, interstitial
306 pneumonitis and sarcoidosis, some resulting in respiratory failure and/or patient
307 deaths, may be induced or aggravated by PEG-Intron or alpha interferon therapy.
308 Recurrence of respiratory failure has been observed with interferon rechallenge.
309 PEG-Intron combination treatment should be suspended in patients who develop



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310 pulmonary infiltrates or pulmonary function impairment. Patients who resume
311 interferon treatment should be closely monitored.

312

313 **Colitis**

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

319

320 **Pancreatitis**

321 Fatal and nonfatal pancreatitis have been observed in patients treated with alpha
322 interferon. PEG-Intron therapy should be suspended in patients with signs and
323 symptoms suggestive of pancreatitis and discontinued in patients diagnosed with
324 pancreatitis.

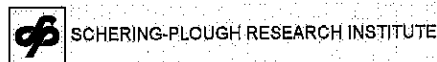
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326 **Autoimmune disorders**

327 Development or exacerbation of autoimmune disorders (e.g. thyroiditis, thrombotic
328 thrombocytopenic purpura, idiopathic thrombocytopenic purpura, rheumatoid
329 arthritis, interstitial nephritis, systemic lupus erythematosus, psoriasis) have been
330 observed in patients receiving PEG-Intron. PEG-Intron should be used with caution
331 in patients with autoimmune disorders.

332 **Ophthalmologic disorders**

333 Decrease or loss of vision, retinopathy including macular edema, retinal artery or
334 vein thrombosis, retinal hemorrhages and cotton wool spots, optic neuritis, and
335 papilledema may be induced or aggravated by treatment with peginterferon alfa-2b
336 or other alpha interferons. All patients should receive an eye examination at



337 baseline. Patients with preexisting ophthalmologic disorders (e.g. diabetic or
338 hypertensive retinopathy) should receive periodic ophthalmologic exams during
339 interferon alpha treatment. Any patient who develops ocular symptoms should
340 receive a prompt and complete eye examination. Peginterferon alfa-2b treatment
341 should be discontinued in patients who develop new or worsening ophthalmologic
342 disorders.

343

344 **Hypersensitivity**

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

351

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

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

359

360 **Anemia**

361 Ribavirin caused hemolytic anemia in 10% of PEG-Intron/REBETOL treated patients
362 within 1-4 weeks of initiation of therapy. Complete blood counts should be obtained
363 pretreatment and at week 2 and week 4 of therapy or more frequently if clinically
364 indicated. Anemia associated with REBETOL therapy may result in a worsening of



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365 cardiac disease. Decrease in dosage or discontinuation of REBETOL may be
366 necessary (See **DOSAGE AND ADMINISTRATION: Dose Reduction**).

367

368 **PRECAUTIONS**

- 369 • PEG-Intron alone or in combination with REBETOL has not been studied in
370 patients who have failed other alpha interferon treatments.
- 371 • The safety and efficacy of PEG-Intron alone or in combination with REBETOL for
372 the treatment of hepatitis C in liver or other organ transplant recipients have not
373 been studied. In a small (n=16) single-center, uncontrolled case experience,
374 renal failure in renal allograft recipients receiving interferon alpha and ribavirin
375 combination therapy was more frequent than expected from the center's previous
376 experience with renal allograft recipients not receiving combination therapy. The
377 relationship of the renal failure to renal allograft rejection is not clear.
- 378 • The safety and efficacy of PEG-Intron/REBETOL for the treatment of patients
379 with HCV co-infected with HIV or HBV have not been established.

380

381 **Triglycerides**

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

389



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390 **Patients with Renal Insufficiency**

391 Increases in serum creatinine levels have been observed in patients with renal
392 insufficiency receiving interferon alfa products, including PEG-Intron. Patients with
393 impaired renal function should be closely monitored for signs and symptoms of
394 interferon toxicity, including increases in serum creatinine, and PEG-Intron dosing
395 should be adjusted accordingly or discontinued (See **CLINICAL PHARMACOLOGY:**
396 **Pharmacokinetics and DOSAGE AND ADMINISTRATION: Dose Reduction**).
397 PEG-Intron monotherapy should be used with caution in patients with creatinine
398 clearance < 50 mL/min; the potential risks should be weighed against the potential
399 benefits in these patients. Combination therapy with REBETOL must not be used in
400 patients with creatinine clearance < 50 mL/min (See **REBETOL Package Insert**
401 **WARNINGS**).

402

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

407

408 Patients must be informed that REBETOL may cause birth defects and/or death of
409 the unborn child. Extreme care must be taken to avoid pregnancy in female patients
410 and in female partners of male patients during treatment with combination PEG-
411 Intron/REBETOL therapy and for 6 months post-therapy. Combination PEG-
412 Intron/REBETOL therapy should not be initiated until a report of a negative
413 pregnancy test has been obtained immediately prior to initiation of therapy. It is
414 recommended that patients undergo monthly pregnancy tests during therapy and for
415 6 months post-therapy (see **CONTRAINdicATIONS and REBETOL package**
416 **insert**).

417



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

422

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

428

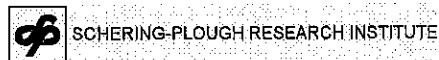
429 Patients should be advised to use a puncture-resistant container for the disposal of
430 used syringes, needles, and the Redipen®. The full container should be disposed of
431 in accordance with state and local laws. Patients should be thoroughly instructed in
432 the importance of proper disposal.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

434

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

442

443 Patients on PEG-Intron or PEG-Intron/REBETOL combination therapy should have
444 hematology and blood chemistry testing before the start of treatment and then
445 periodically thereafter. In the clinical trial CBC (including hemoglobin, neutrophil and
446 platelet counts) and chemistries (including AST, ALT, bilirubin, and uric acid) were



447 measured during the treatment period at weeks 2, 4, 8, 12, and then at 6-week
448 intervals or more frequently if abnormalities developed. TSH levels were measured
449 every 12 weeks during the treatment period. HCV RNA should be measured at 6
450 months of treatment. PEG-Intron or PEG-Intron/REBETOL combination therapy
451 should be discontinued in patients with persistent high viral levels.

452

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

455

456 Drug Interactions

457 Drugs Metabolized by Cytochrome P-450

458 Caution should be used when administering PEG-Intron with medications
459 metabolized by CYP2C8/9 (e.g., warfarin and phenytoin) or CYP2D6 (e.g.,
460 flecainide) (see **CLINICAL PHARMACOLOGY : Drug Interactions**).

461

462 Methadone

463 In a pharmacokinetic study of 18 chronic hepatitis C ~~XX~~ *inserted* patients concomitantly
464 receiving methadone, treatment with PEG-Intron once weekly for 4 weeks was
465 associated with a mean increase of 16% in methadone AUC; in 2 out of 18 patients,
466 methadone AUC doubled (see **CLINICAL PHARMACOLOGY: Drug Interactions**).
467 The clinical significance of this finding is unknown; however, patients should be
468 monitored for the signs and symptoms of increased narcotic effect.

469 Use with Ribavirin:

470 Nucleoside Analogues

471 Hepatic decompensation (some fatal) has occurred in cirrhotic HIV/HCV co-infected
472 patients receiving combination antiretroviral therapy for HIV and interferon alfa and
473 ribavirin. Adding treatment with alfa interferons alone or in combination with ribavirin
474 may increase the risk in this patient subset. Patients receiving interferon with



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475 ribavirin and Nucleotide Reverse Transcriptase Inhibitors (NRTIs) should be closely
476 monitored for treatment associated toxicities, especially hepatic decompensation
477 and anemia. Discontinuation of NRTIs should be considered as medically
478 appropriate (see **Individual NRTI Product Information**). Dose reduction or
479 discontinuation of interferon, ribavirin or both should also be considered if worsening
480 clinical toxicities are observed, including hepatic decompensation (e.g. Childs Pugh
481 > 6).

482
483 **Stavudine, Lamivudine and Zidovudine:** *In vitro* studies have shown ribavirin can
484 reduce the phosphorylation of pyrimidine nucleoside analogues such as stavudine,
485 lamivudine and zidovudine. In a study with another pegylated interferon alfa, no
486 evidence of a pharmacokinetic or pharmacodynamic (e.g., loss of HIV/HCV virologic
487 suppression) interaction was seen when ribavirin was co-administered with
488 zidovudine, lamivudine or stavudine in HIV/HCV coinfecting patients (See **CLINICAL**
489 **PHARMACOLOGY: Drug Interactions**).

490
491 Although there was no evidence of loss of HIV/HCV virologic suppression when
492 ribavirin was co-administered with zidovudine HIV/HCV co-infected patients who
493 were administered zidovudine in combination with pegylated interferon alfa and
494 ribavirin developed severe neutropenia (ANC <500) and severe anemia (hemoglobin
495 <8 g/dL) more frequently than similar patients not receiving zidovudine.

496 **Didanosine:** Co-administration of REBETOL Capsules or Oral Solution and
497 didanosine is not recommended. Reports of fatal hepatic failure, as well as
498 peripheral neuropathy, pancreatitis, and symptomatic hyperlactatemia/lactic
499 acidosis have been reported in clinical trials (See **CLINICAL PHARMACOLOGY:**
500 **Drug Interactions**).

501

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

503



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

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

511

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

522

523 **Pregnancy Category C: PEG-Intron monotherapy:** Non-pegylated Interferon alfa-
524 2b, has been shown to have abortifacient effects in *Macaca mulatta* (rhesus
525 monkeys) at 15 and 30 million IU/kg (estimated human equivalent of 5 and 10 million
526 IU/kg, based on body surface area adjustment for a 60 kg adult). PEG-Intron should
527 be assumed to also have abortifacient potential. There are no adequate and well-
528 controlled studies in pregnant women. PEG-Intron therapy is to be used during
529 pregnancy only if the potential benefit justifies the potential risk to the fetus.
530 Therefore, PEG-Intron is recommended for use in fertile women only when they are
531 using effective contraception during the treatment period.

532



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

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

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

541

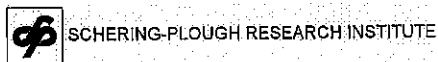
542 **Nursing Mothers:** It is not known whether the components of PEG-Intron and/or
543 REBETOL are excreted in human milk. Studies in mice have shown that mouse
544 interferons are excreted in breast milk. Because of the potential for adverse
545 reactions from the drug in nursing infants, a decision must be made whether to
546 discontinue nursing or discontinue the PEG-Intron and REBETOL treatment, taking
547 into account the importance of the therapy to the mother.

548

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

551
552 **Geriatric.** In general, younger patients tend to respond better than older patients to
553 interferon-based therapies. Clinical studies of PEG-Intron alone or in combination
554 with REBETOL did not include sufficient numbers of subjects aged 65 and over,
555 however, to determine whether they respond differently than younger subjects.

556 Treatment with alpha interferons, including PEG-Intron, is associated with
557 neuropsychiatric, cardiac, pulmonary, GI and systemic (flu-like) adverse effects.
558 Because these adverse reactions may be more severe in the elderly, caution should
559 be exercised in the use of PEG-Intron in this population. This drug is known to be
560 substantially excreted by the kidney. Because elderly patients are more likely to
561 have decreased renal function, the risk of toxic reactions to this drug may be greater



562 in patients with impaired renal function (See **CLINICAL PHARMACOLOGY: Special**
563 **Populations: Renal Dysfunction**). REBETOL should not be used in patients with
564 creatinine clearance <50 mL/min. When using PEG-Intron/REBETOL therapy, refer
565 also to the REBETOL Package Insert.
566

567 **ADVERSE REACTIONS**

568 Nearly all study patients in clinical trials experienced one or more adverse events. In
569 the PEG monotherapy trial the incidence of serious adverse events was similar
570 (about 12%) in all treatment groups. In the PEG-Intron/REBETOL combination trial
571 the incidence of serious adverse events was 17% in the PEG-Intron/REBETOL
572 groups compared to 14% in the INTRON A/REBETOL group.
573

574 In many but not all cases, adverse events resolved after dose reduction or
575 discontinuation of therapy. Some patients experienced ongoing or new serious
576 adverse events during the 6-month follow-up period. In the PEG-Intron/REBETOL
577 trial 13 patients experienced life-threatening psychiatric events (suicidal ideation or
578 attempt) and one patient accomplished suicide.
579

580 There have been five patient deaths which occurred in clinical trials: one suicide in a
581 patient receiving PEG-Intron monotherapy and one suicide in a patient receiving
582 PEG-Intron/REBETOL combination therapy; two deaths among patients receiving
583 INTRON A monotherapy (1 murder/suicide and 1 sudden death) and one patient
584 death in the INTRON A/REBETOL group (motor vehicle accident).

585 Overall, 10-14% of patients receiving PEG-Intron, alone or in combination with
586 REBETOL, discontinued therapy compared with 6% treated with INTRON A alone
587 and 13% treated with INTRON A in combination with REBETOL. The most common
588 reasons for discontinuation of therapy were related to psychiatric, systemic (e.g.
589 fatigue, headache), or gastrointestinal adverse events.
590



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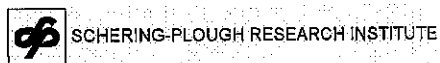
591 In the combination therapy trial, dose reductions due to adverse reactions occurred
592 in 42% of patients receiving PEG-Intron (1.5 µg/kg)/REBETOL and in 34% of those
593 receiving INTRON A/REBETOL. The majority of patients (57%) weighing 60 kg or
594 less receiving Peg-Intron (1.5 µg/kg)/REBETOL required dose reduction. Reduction
595 of interferon was dose related (PEG-Intron 1.5 µg/kg > PEG-Intron 0.5 µg/kg or
596 INTRON A), 40%, 27%, 28%, respectively. Dose reduction for REBETOL was
597 similar across all three groups, 33-35%. The most common reasons for dose
598 modifications were neutropenia (18%), or anemia (9%). (see **Laboratory Values**).
599 Other common reasons included depression, fatigue, nausea, and
600 thrombocytopenia.

601
602 In the PEG-Intron/REBETOL combination trial the most common adverse events
603 were psychiatric which occurred among 77% of patients and included most
604 commonly depression, irritability, and insomnia, each reported by approximately 30-
605 40% of subjects in all treatment groups. Suicidal behavior (ideation, attempts, and
606 suicides) occurred in 2% of all patients during treatment or during follow-up after
607 treatment cessation (see **WARNINGS**).

608
609 PEG-Intron induced fatigue or headache in approximately two-thirds of patients, and
610 induced fever or rigors in approximately half of the patients. The severity of some of
611 these systemic symptoms (e.g. fever and headache) tended to decrease as
612 treatment continues. The incidence tends to be higher with PEG-Intron than with
613 Intron A therapy alone or in combination with REBETOL.

614
615 Application site inflammation and reaction (e.g. bruise, itchiness, irritation) occurred
616 at approximately twice the incidence with PEG-Intron therapies (in up to 75% of
617 patients) compared with INTRON A. However injection site pain was infrequent (2-
618 3%) in all groups.

619



620 Other common adverse events in the PEG-Intron/REBETOL group included myalgia
 621 (56%), arthralgia (34%), nausea (43%), anorexia (32%), weight loss (29%), alopecia
 622 (36%), and pruritus (29%).

623

624 In the PEG-Intron monotherapy trial the incidence of severe adverse events was
 625 13% in the INTRON A group and 17% in the PEG-Intron groups. In the PEG-
 626 Intron/REBETOL combination therapy trial the incidence of severe adverse events
 627 was 23% in the INTRON A/REBETOL group and 31-34% in the PEG-
 628 Intron/REBETOL groups. The incidence of life-threatening adverse events was \leq
 629 1% across all groups in the monotherapy and combination therapy trials.

630

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

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

635

Adverse Events	Percentage of Patients Reporting Adverse Events*			
	Study 1		Study 2	
	PEG- Intron 1.0 $\mu\text{g}/\text{kg}$ (n=297)	INTRON A 3 MIU (n=303)	PEG-Intron 1.5 $\mu\text{g}/\text{kg}/$ REBETOL (n=511)	INTRON A/ REBETOL (n=505)
Application Site				
Injection Site	47	20	75	49
Inflammation/Reaction				
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.				
Dizziness	12	10	21	17
Endocrine				
Hypothyroidism	5	3	5	4



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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)
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
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

636
637

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



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638
639 Many patients continued to experience adverse events several months after
640 discontinuation of therapy. By the end of the 6-month follow-up period the incidence
641 of ongoing adverse events by body class in the PEG-INTRON 1.5/REBETOL group
642 was 33% (psychiatric), 20% (musculoskeletal), and 10% (for endocrine and for GI).
643 In approximately 10-15% of patients weight loss, fatigue and headache had not
644 resolved.

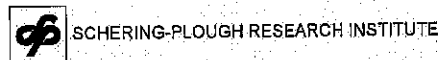
645
646 Individual serious adverse events occurred at a frequency $\leq 1\%$ and included suicide
647 attempt, suicidal ideation, severe depression; psychosis, aggressive reaction,
648 relapse of drug addiction/overdose; nerve palsy (facial, oculomotor);
649 cardiomyopathy, myocardial infarction, angina, pericardial effusion, retinal ischemia,
650 retinal artery or vein thrombosis, blindness, decreased visual acuity, optic neuritis,
651 transient ischemic attack, supraventricular arrhythmias, loss of consciousness;
652 neutropenia, infection (sepsis, pneumonia, abscess, cellulitis); emphysema,
653 bronchiolitis obliterans, pleural effusion, gastroenteritis, pancreatitis, gout,
654 hyperglycemia, hyperthyroidism and hypothyroidism, autoimmune thrombocytopenia
655 with or without purpura, rheumatoid arthritis, interstitial nephritis, lupus-like
656 syndrome, sarcoidosis, aggravated psoriasis; urticaria, injection-site necrosis,
657 vasculitis, phototoxicity.

658

659 **Laboratory Values**

660 Changes in selected laboratory values during treatment with PEG-Intron alone or in
661 combination with REBETOL treatment are described below. **Decreases in**
662 **hemoglobin, neutrophils, and platelets may require dose reduction or**
663 **permanent discontinuation from therapy. (See DOSAGE AND**
664 **ADMINISTRATION: Dose Reduction)**

665



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

675
676 **Neutrophils.** Decreases in neutrophil counts were observed in a majority of patients
677 treated with PEG-Intron alone (70%) or as combination therapy with REBETOL
678 (85%) and INTRON A/REBETOL (60%). Severe potentially life-threatening
679 neutropenia (<0.5 x 10⁹/L) occurred in 1% of patients treated with PEG-Intron
680 monotherapy, 2% of patients treated with INTRON A/REBETOL and in 4% of
681 patients treated with PEG-Intron/REBETOL. Two percent of patients receiving PEG-
682 Intron monotherapy and 18% of patients receiving PEG-Intron /REBETOL required
683 modification of interferon dosage. Few patients (< 1%) required permanent
684 discontinuation of treatment. Neutrophil counts generally return to pre-treatment
685 levels within 4 weeks of cessation of therapy (See **DOSAGE AND**
686 **ADMINISTRATION: Dose Reduction**).

687
688 **Platelets.** Platelet counts decrease in approximately 20% of patients treated with
689 PEG-Intron alone or with REBETOL and in 6% of patients treated with INTRON
690 A/REBETOL. Severe decreases in platelet counts (<50,000/mm³) occur in <1% of
691 patients. Patients may require discontinuation or dose modification as a result of
692 platelet decreases (See **DOSAGE AND ADMINISTRATION: Dose Reduction**). In
693 the PEG-Intron/REBETOL combination therapy trial 1% or 3% of patients required
694 dose modification of INTRON A or PEG-Intron respectively. Platelet counts
695 generally returned to pretreatment levels within 4 weeks of the cessation of therapy.



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696
697 **Triglycerides.** Elevated triglyceride levels have been observed in patients treated
698 with interferon alfas including PEG-Intron.

699
700 **Thyroid Function.** Development of TSH abnormalities, with and without clinical
701 manifestations, are associated with interferon therapies. Clinically apparent thyroid
702 disorders occur among patients treated with either Intron A or PEG-Intron (with or
703 without REBETOL) at a similar incidence (5% for hypothyroidism and 3% for
704 hyperthyroidism). Subjects developed new onset TSH abnormalities while on
705 treatment and during the follow-up period. At the end of the follow-up period 7% of
706 subjects still had abnormal TSH values.

707
708 **Bilirubin and uric acid.** In the PEG-Intron/REBETOL trial 10-14% of patients
709 developed hyperbilirubinemia and 33-38% developed hyperuricemia in association
710 with hemolysis. Six patients developed mild to moderate gout.

711

712 **Postmarketing Experience**

713 The following adverse reactions have been identified and reported during post-
714 approval use of PEG-Intron therapy: aphthous stomatitis, erythema multiforme,
715 hearing impairment, hearing loss, memory loss, migraine headache, myositis,
716 peripheral neuropathy, renal insufficiency, renal failure, rhabdomyolysis, seizures,
717 Stevens Johnson syndrome, thrombotic thrombocytopenic purpura, toxic epidermal
718 necrolysis, vertigo. Because the reports of these reactions are voluntary and the
719 population of uncertain size, it is not always possible to reliably estimate the
720 frequency of the reaction or establish a causal relationship to drug exposure.

721

722 **Immunogenicity:** Approximately 2% of patients receiving PEG-Intron (32/1759) or
723 INTRON A (11/728) with or without REBETOL developed low-titer (≤ 160)
724 neutralizing antibodies to PEG-Intron or INTRON A. The clinical and pathological



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725 significance of the appearance of serum neutralizing antibodies is unknown. No
726 apparent correlation of antibody development to clinical response or adverse events
727 was observed. The incidence of post-treatment binding antibody ranged from 8 to
728 15 percent. The data reflect the percentage of patients whose test results were
729 considered positive for antibodies to PEG-Intron in a Biacore assay that is used to
730 measure binding antibodies, and in an antiviral neutralization assay, which
731 measures serum-neutralizing antibodies. The percentage of patients whose test
732 results were considered positive for antibodies is highly dependent on the sensitivity
733 and specificity of the assays. Additionally the observed incidence of antibody
734 positivity in these assays may be influenced by several factors including sample
735 timing and handling, concomitant medications, and underlying disease. For these
736 reasons, comparison of the incidence of antibodies to PEG-Intron with the incidence
737 of antibodies to other products may be misleading.

738

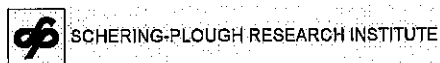
739 **OVERDOSAGE**

740 There is limited experience with overdosage. In the clinical studies, a few patients
741 accidentally received a dose greater than that prescribed. There were no instances
742 in which a participant in the monotherapy or combination therapy trials received
743 more than 10.5 times the intended dose of PEG-Intron. The maximum dose
744 received by any patient was 3.45 µg/kg weekly over a period of approximately 12
745 weeks. The maximum known overdosage of REBETOL was an intentional ingestion
746 of 10 g (fifty 200 mg capsules). There were no serious reactions attributed to these
747 overdosages. In cases of overdosing, symptomatic treatment and close observation
748 of the patient are recommended.

749

750 **DOSAGE AND ADMINISTRATION**

751 There are no safety and efficacy data on treatment for longer than one year. A
752 patient should self-inject PEG-Intron only if it has been determined that it is



753 appropriate and the patient agrees to medical follow-up as necessary and training in
754 proper injection technique has been given to him/her.

755

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

759

760 **PEG-Intron Monotherapy**

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

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

765 **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

766 * When reconstituted as directed

767



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

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

772

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

774

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

775 *When reconstituted as directed

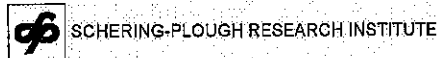
776

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

780

781 **Dose Reduction**

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



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786 treatment. For guidelines for dose modifications and discontinuation based on
 787 laboratory parameters, see **Tables 6 and 7**. Dose reduction of PEG-Intron may be
 788 accomplished by utilizing a lower dose strength as shown in **Table 8 or 9**. For vials,
 789 50% dose reduction may also be accomplished by reducing the volume
 790 administered by one-half without changing the dose strength.

791 In the combination therapy trial dose reductions occurred among 42% of patients
 792 receiving PEG-Intron 1.5 µg/kg/REBETOL 800 mg daily including 57% of those
 793 patients weighing 60 kg or less (see **ADVERSE REACTIONS**).

794

795 **Table 6: Guidelines for Modification or Discontinuation of PEG-Intron or PEG-**
 796 **Intron/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		

797 See DSM-IV for definitions
 798

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

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

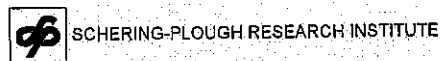
801 * For patients with a history of stable cardiac disease receiving PEG-Intron in combination with ribavirin, the
 802 PEG-Intron dose should be reduced by half and the ribavirin dose by 200mg/day if a > 2g/dL decrease in
 803 hemoglobin is observed during any 4 week period. Both PEG-Intron and ribavirin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

805 **Table 8: Reduced PEG-Intron Dose (0.5µg /kg) for (1.0µg /kg) Monotherapy**
 806
 807

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

808 * Must use vial. Minimum delivery for Redipen 0.3 mL

809 ^When reconstituted as directed



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

811

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

812 * Must use vial. Minimum delivery for Redipen 0.3 mL

813 ^ When reconstituted as directed.

814 **Renal Function**

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

820

821 **Preparation and Administration**822 **PEG-Intron Redipen®**

823 PEG-Intron Redipen® consists of a dual-chamber glass cartridge with sterile,
 824 lyophilized peginterferon alfa-2b in the active chamber and Sterile Water for
 825 Injection, USP in the diluent chamber. The PEG-Intron in the glass cartridge should
 826 appear as a white to off-white tablet shaped solid that is whole or in pieces, or



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827 powder. To reconstitute the lyophilized peginterferon alfa-2b in the Redipen®, hold
828 the Redipen® upright (dose button down) and press the two halves of the pen
829 together until there is an audible click. Gently invert the pen to mix the solution. **DO**
830 **NOT SHAKE.** The reconstituted solution has a concentration of either 50 µg per 0.5
831 mL, 80 µg per 0.5 mL, 120 µg per 0.5 mL or 150 µg per 0.5 mL for a single
832 subcutaneous injection. Visually inspect the solution for particulate matter and
833 discoloration prior to administration. The reconstituted solution should be clear and
834 colorless. Do not use if the solution is discolored or cloudy, or if particulates are
835 present.

836
837 Keeping the pen upright, attach the supplied needle and select the appropriate PEG-
838 Intron dose by pulling back on the dosing button until the dark bands are visible and
839 turning the button until the dark band is aligned with the correct dose. The prepared
840 PEG-Intron solution is to be injected subcutaneously.

841
842 The PEG-Intron Redipen is a single use pen and does not contain a preservative.
843 The reconstituted solution should be used immediately and cannot be stored for
844 more than 24 hours at 2-8° C (See **Storage**). **DO NOT REUSE THE REDIPEN®.**
845 The sterility of any remaining product can no longer be guaranteed. **DISCARD THE**
846 **UNUSED PORTION.** Pooling of unused portions of some medications has been
847 linked to bacterial contamination and morbidity.

848

849 **PEG-Intron Vials**

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



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856
857 **Reconstitute the PEG-Intron lyophilized product with only 0.7 mL of 1.25 mL**
858 **of supplied diluent (Sterile Water for Injection, USP). The diluent vial is for**
859 **single use only. The remaining diluent should be discarded.** No other
860 medications should be added to solutions containing PEG-Intron, and PEG-Intron
861 should not be reconstituted with other diluents. Swirl gently to hasten complete
862 dissolution of the powder. The reconstituted solution should be clear and colorless.
863 Visually inspect the solution for particulate matter and discoloration prior to
864 administration. The solution should not be used if discolored or cloudy or if
865 particulates are present.

866
867 The appropriate PEG-Intron dose should be withdrawn and injected subcutaneously.
868 PEG-Intron vials are for single use only and do not contain a preservative. The
869 reconstituted solution should be used immediately and cannot be stored for more
870 than 24 hours at 2-8^o C (See **Storage**). **DO NOT REUSE THE VIAL.** The sterility of
871 any remaining product can longer be guaranteed. **DISCARD THE UNUSED**
872 **PORTION.** Pooling of unused portions of some medications has been linked to
873 bacterial contamination and morbidity.

874
875 After preparation and administration of the PEG-Intron for injection, it is essential to
876 follow the state and or local procedures for proper disposal of syringes, needles, and
877 the Redipen®. A puncture-resistant container should be used for disposal. Patients
878 should be instructed in how to properly dispose of used syringes, needles or the
879 Redipen® and be cautioned against the reuse of these items.

880

881 **Storage**

882 **PEG-Intron Redipen®**

883 PEG-Intron Redipen® should be stored at 2°C to 8°C (36° to 46°F).



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

887 PEG-Intron Vials

888 PEG-Intron, should be stored at 25°C (77°F): excursions permitted to 15-30°C (59-
 889 86°F) [see USP Controlled Room Temperature]. After reconstitution with supplied
 890 Diluent the solution should be used immediately, but may be stored up to 24 hours
 891 at 2° to 8°C (36° to 46°F). The reconstituted solution contains no preservative, is
 892 clear and colorless. **DO NOT FREEZE.**

893 HOW SUPPLIED

894 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)

895

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



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