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Product Information

PEG-Intron®

(Peginterferon alfa-2b)

Powder For Injection

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 Patients with persistently severe or worsening signs or symptoms of these conditions should be withdrawn from therapy.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).

DESCRIPTION

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

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

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

PEG-Intron is supplied in both vials and the Redipen® for subcutaneous use.

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

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

Pharmacokinetics: Following a single subcutaneous (SC) dose of PEG-Intron, the mean absorption half-life ($t\ ½\ k_a$) was 4.6 hours. Maximal serum concentrations (C_{max}) occur between 15-44 hours post-dose, and are sustained for up to 48-72 hours. The C_{max} and AUC measurements of PEG-Intron increase in a dose-related manner. After multiple dosing, there is an increase in bioavailability of PEG-Intron. Week 48 mean trough concentrations (320 pg/mL; range 0, 2960) are approximately 3-fold higher than Week 4 mean trough concentrations (94 pg/mL; range 0, 416). The mean PEG-Intron elimination half-life is approximately 40 hours (range 22 to 60 hours) in patients with HCV infection. The apparent clearance of PEG-Intron is estimated to be approximately 22.0 mL/hr·kg. Renal elimination accounts for 30% of the clearance. Pegylation of interferon alfa-2b produces a product (PEG-Intron) whose clearance is lower than that of non-pegylated interferon alfa-2b. When

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

Special Populations

Renal Dysfunction

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

Gender

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

Geriatric Patients

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

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

Drug Interactions

Drugs Metabolized by Cytochrome P-450

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

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

Methadone

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

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 coinfected
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

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

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)

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

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

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

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

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

PEG-Intron/REBETOL Combination Therapy-Study 2

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

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

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)

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

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

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

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

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

INDICATIONS AND USAGE

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

CONTRAINDICATIONS

PEG-Intron is contraindicated in patients with:

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

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

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

WARNINGS

Patients should be monitored for the following serious conditions, some of which may become life threatening. Patients with persistently severe or worsening signs or 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 coinfected 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

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

Endocrine disorders

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

Cardiovascular events

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

Pulmonary disorders

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

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

Colitis

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

Pancreatitis

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

Autoimmune disorders

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

Ophthalmologic disorders

Decrease or loss of vision, retinopathy including macular edema, retinal artery or vein thrombosis, retinal hemorrhages and cotton wool spots, optic neuritis, and papilledema may be induced or aggravated by treatment with peginterferon alfa-2b 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

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

PRECAUTIONS

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

Triglycerides

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

Patients with Renal Insufficiency

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

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

Patients must be informed that REBETOL 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 during treatment with combination PEG-Intron/REBETOL therapy and for 6 months post-therapy. Combination PEG-Intron/REBETOL therapy should not be initiated until a report of a negative pregnancy test has been obtained immediately prior to initiation of therapy. It is recommended that patients undergo monthly pregnancy tests during therapy and for 6 months post-therapy (see **CONTRAINIDICATIONS and REBETOL package insert**).

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

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

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

Drug Interactions

Drugs Metabolized by Cytochrome P-450

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

Methadone

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

Use with Ribavirin:

Nucleoside Analogues

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

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

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

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

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

Carcinogenesis, Mutagenesis, and Impairment of Fertility

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

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

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

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

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

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

ADVERSE REACTIONS

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

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

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

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

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

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

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

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

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

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

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

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

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)
Application Site				
Injection Site Inflammation/Reaction	47	20	75	49
Autonomic Nervous Sys.				
Mouth Dry	6	7	12	8
Sweating Increased	6	7	11	7
Flushing	6	3	4	3
Body as a Whole				
Fatigue/Asthenia	52	54	66	63
Headache	56	52	62	58
Rigors	23	19	48	41
Fever	22	12	46	33
Weight Decrease	11	13	29	20
RUQ Pain	8	8	12	6
Chest Pain	6	4	8	7
Malaise	7	6	4	6
Central/Periph. Nerv. Sys.				
Dizziness	12	10	21	17
Endocrine				
Hypothyroidism	5	3	5	4

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)
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

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

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 ≤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

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

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

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

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

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

OVERDOSAGE

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

DOSAGE AND ADMINISTRATION

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

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

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

PEG-Intron Monotherapy

The recommended dose of PEG-Intron regimen is 1.0 µg/kg/week subcutaneously for one year. The dose should be administered on the same day of the week. The volume of PEG-Intron to be injected depends on patient weight (see **Table 4 below).**

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

* When reconstituted as directed

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

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 [1] See DSM-IV for definitions
798

Table 7. Guidelines for Dose Modification and Discontinuation of PEG-Intron 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 x10^9/L <1.0 x10^9/L	Reduce dose by 50% Permanently discontinue	---------- Permanently discontinue
Neutrophil	<0.75 x10^9/L <0.5 x10^9/L	Reduce dose by 50% Permanently discontinue	---------- Permanently discontinue
Platelets	<80 x10^9/L <50 x10^9/L	Reduce dose by 50% Permanently discontinue	---------- Permanently discontinue

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

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

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

* Must use vial. Minimum delivery for Redipen 0.3 mL

^ When reconstituted as directed

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

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

* Must use vial. Minimum delivery for Redipen 0.3 mL

^ When reconstituted as directed

Renal Function

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

Preparation and Administration

PEG-Intron Redipen®

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

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

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

The PEG-Intron Redipen is a single use pen and does not contain a preservative. The reconstituted solution should be used immediately and cannot be stored for more than 24 hours at 2-8^0 C (See **Storage**). **DO NOT REUSE THE REDIPEN®.** The sterility of any remaining product can no longer be guaranteed. **DISCARD THE UNUSED PORTION.** Pooling of unused portions of some medications has been linked to bacterial contamination and morbidity.

PEG-Intron Vials

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

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

The appropriate PEG-Intron dose should be withdrawn and injected subcutaneously. PEG-Intron vials are for single use only and do not contain a preservative. The reconstituted solution should be used immediately and cannot be stored for more than 24 hours at 2-8^0 C (See **Storage**). **DO NOT REUSE THE VIAL.** The sterility of any remaining product can longer be guaranteed. **DISCARD THE UNUSED PORTION.** Pooling of unused portions of some medications has been linked to bacterial contamination and morbidity.

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

Storage

PEG-Intron Redipen®

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

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

PEG-Intron Vials

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

HOW SUPPLIED

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)

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)

896 **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 1.25 mL vial of Diluent (Sterile Water for Injection, USP), 2 B-D Safety Lok™ syringes with a safety sleeve and 2 alcohol swabs.	(NDC 0085-1368-01)
A box containing one 80μg per 0.5 mL vial of PEG-Intron Powder for Injection and one 1.25 mL vial of Diluent (Sterile Water for Injection, USP), 2 B-D Safety Lok™ syringes with a safety sleeve and 2 alcohol swabs.	(NDC 0085-1291-01)
A box containing one 120μg per 0.5 mL vial of PEG-Intron Powder for Injection and one 1.25 mL vial of Diluent (Sterile Water for Injection, USP), 2 B-D Safety Lok™ syringes with a safety sleeve and 2 alcohol swabs.	(NDC 0085-1304-01)
A box containing one 150μg per 0.5 mL vial of PEG-Intron Powder for Injection and one 1.25 mL vial of Diluent (Sterile Water for Injection, USP), 2 B-D Safety Lok™ syringes with a safety sleeve and 2 alcohol swabs.	(NDC 0085-1279-01)

897 Schering Corporation

898 Kenilworth, NJ 07033 USA

899 **REV. 10/05**

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902 6,482,613; 6,524,570; 6,610,830

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904 *Safety-Lok is a trademark of Becton Dickinson and Company

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