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Product Information

PegIntron™

(Peginterferon alfa-2b)

Powder For Injection

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 Patients with persistently severe or worsening signs or symptoms of these conditions should be withdrawn from therapy.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

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

DESCRIPTION

PegIntron™, 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 PegIntron 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.

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

Vials

Each vial contains either 74 mcg, 118.4 mcg, 177.6 mcg, or 222 mcg of PegIntron 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 PegIntron at strengths of either 50 mcg per 0.5 mL, 80 mcg per 0.5 mL, 120 mcg per 0.5 mL, or 150 mcg per 0.5 mL.

Redipen®

Redipen® is a dual-chamber glass cartridge containing lyophilized PegIntron 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 PegIntron Redipen® contains either 67.5 mcg, 108 mcg, 162 mcg, or 202.5 mcg of PegIntron, 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 PegIntron at strengths of either 50 mcg per 0.5 mL, 80 mcg per 0.5 mL, 120 mcg per 0.5 mL, or 150 mcg per 0.5mL for a single use. Because a small volume of reconstituted solution is lost during preparation of PegIntron, each Redipen® contains an excess amount of PegIntron powder and diluent to ensure delivery of the labeled dose.

CLINICAL PHARMACOLOGY

General: The biological activity of PegIntron 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: PegIntron 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 PegIntron, 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 PegIntron increase in a dose-related manner. After multiple dosing, there is an increase in bioavailability of PegIntron. 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 PegIntron elimination half-life is approximately 40 hours (range 22 to 60 hours) in patients with HCV infection. The apparent clearance of PegIntron 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 (PegIntron) whose clearance is lower than that of non-pegylated interferon alfa-2b. When compared to INTRON A, PegIntron (1 mcg/kg) has approximately a sevenfold lower mean apparent clearance and a fivefold greater mean half-life permitting a reduced dosing frequency. At effective therapeutic doses, PegIntron has approximately tenfold greater C_{max} and 50-fold greater AUC than interferon alfa-2b.

Special Populations

Renal Dysfunction

Following multiple dosing of PegIntron (1 mcg/kg SC given every week for four weeks) the clearance of PegIntron 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 PegIntron 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 PegIntron, 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 mcg/kg of PegIntron 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 PegIntron (1.5 mcg/kg) once weekly for 4 weeks. PegIntron treatment

resulted in a 28% (mean) increase in a measure of CYP2C8/9 activity. PegIntron 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 PegIntron on CYP2C19 activity were not assessed.

Methadone

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

Use with Ribavirin:

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

CLINICAL STUDIES

PegIntron Monotherapy-Study 1

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

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

Response to treatment was defined as undetectable HCV RNA and normalization of ALT at 24 weeks posttreatment. The response rates to the 1 and 1.5 mcg/kg PegIntron 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 PegIntron 0.5 mcg/kg (N=315)	B PegIntron 1 mcg/kg (N=298)	C INTRON A 3 MIU TIW (N=307)	B - C (95% CI) Difference between PegIntron 1 mcg/kg and INTRON A
Treatment Response (Combined Virologic Response and ALT Normalization)	17%	24%	12%	11 (5, 18)
Virologic Response[a]	18%	25%	12%	12 (6,19)
ALT Normalization	24%	29%	18%	11 (5,18)

[a] 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 PegIntron. Among patients with the two unfavorable prognostic variables, 8% (12/157) responded to PegIntron treatment and 2% (4/169) responded to INTRON A. Doses of PegIntron higher than the recommended dose did not result in higher response rates in these patients.

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

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

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

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.

PegIntron/REBETOL Combination Therapy-Study 2

A randomized study compared treatment with two PegIntron/REBETOL® (ribavirin, USP) regimens [PegIntron 1.5 mcg/kg SC once weekly (QW)/REBETOL 800 mg PO daily (in divided doses); PegIntron 1.5 mcg/kg SC QW for 4 weeks then 0.5 mcg/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 posttreatment. 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 posttreatment. The response rate to the PegIntron 1.5 mcg/kg plus ribavirin 800 mg dose was higher than the response rate to Intron A/REBETOL (see **Table 2**). The response rate to PegIntron 1.5→0.5 mcg/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

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

[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 (PegIntron/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 PegIntron (1.5 mcg/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 PegIntron/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

PegIntron is indicated for use alone or in combination with REBETOL 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

PegIntron is contraindicated in patients with:

- hypersensitivity to PegIntron 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.

PegIntron/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 < 50 mL/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.

Neuropsychiatric events

Life-threatening or fatal neuropsychiatric events, including suicide, suicidal and homicidal ideation, depression, relapse of drug addiction/overdose, and aggressive behavior sometimes directed towards others have occurred in patients with and without a previous psychiatric disorder during PegIntron treatment and follow-up. Psychoses, hallucinations, bipolar disorders, and mania have been observed in patients treated with alpha interferons. PegIntron should be used with extreme caution in patients with a history of psychiatric disorders. Patients should be advised to report immediately any symptoms of depression and/or suicidal ideation to their prescribing physicians. Physicians should monitor all patients for evidence of depression and other psychiatric symptoms. If patients develop psychiatric problems, including clinical depression, it is recommended that the patients be carefully monitored during treatment and in the 6 month-follow-up period. If psychiatric symptoms persist or worsen, or suicidal ideation or aggressive behavior towards others is identified, it is recommended that treatment with PegIntron be discontinued, and the patient followed, with psychiatric intervention as appropriate. In severe cases, PegIntron should be stopped immediately and psychiatric intervention instituted. (See **DOSAGE AND ADMINISTRATION: Dose Reduction.**) Cases of

encephalopathy have been observed in some patients, usually elderly, treated with higher doses of PegIntron.

Bone marrow toxicity

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

Hepatic Failure

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

Endocrine disorders

PegIntron causes or aggravates hypothyroidism and hyperthyroidism. Hyperglycemia has been observed in patients treated with PegIntron. 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 PegIntron therapy. Patients who develop these conditions during treatment and cannot be controlled with medication should not continue PegIntron therapy.

Cardiovascular events

Cardiovascular events, which include hypotension, arrhythmia, tachycardia, cardiomyopathy, angina pectoris, and myocardial infarction, have been observed in

patients treated with PegIntron. PegIntron should be used cautiously in patients with cardiovascular disease. Patients with a history of myocardial infarction and arrhythmic disorder who require PegIntron therapy should be closely monitored (see **Laboratory Tests**). Patients with a history of significant or unstable cardiac disease should not be treated with PegIntron/REBETOL combination therapy. (See **REBETOL package insert**.)

Cerebrovascular disorders

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

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 PegIntron or alpha interferon therapy. Recurrence of respiratory failure has been observed with interferon rechallenge. PegIntron 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. PegIntron 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. PegIntron 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, and psoriasis) have been observed in patients receiving PegIntron. PegIntron 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 baseline. Patients with preexisting ophthalmologic disorders (e.g., diabetic or hypertensive retinopathy) should receive periodic ophthalmologic exams during interferon alpha treatment. Any patient who develops ocular symptoms should receive a prompt and complete eye examination. Peginterferon alfa-2b treatment should be discontinued in patients who develop new or worsening ophthalmologic disorders.

Hypersensitivity

Serious, acute hypersensitivity reactions (e.g., urticaria, angioedema, bronchoconstriction, anaphylaxis) and cutaneous eruptions (Stevens Johnson syndrome, toxic epidermal necrolysis) have been rarely observed during alpha interferon therapy. If such a reaction develops during treatment with PegIntron,

discontinue treatment and institute appropriate medical therapy immediately. Transient rashes do not necessitate interruption of treatment.

Use with Ribavirin—(see also REBETOL Package Insert)

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

Anemia

Ribavirin caused hemolytic anemia in 10% of PegIntron/REBETOL-treated patients within 1-4 weeks of initiation of therapy. Complete blood counts should be obtained pretreatment and at week 2 and week 4 of therapy or more frequently if clinically 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

- PegIntron alone or in combination with REBETOL has not been studied in patients who have failed other alpha interferon treatments.
- The safety and efficacy of PegIntron 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 PegIntron/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 PegIntron therapy. Hypertriglyceridemia may result in pancreatitis (see **WARNINGS: Pancreatitis**). Elevated triglyceride levels should be managed as clinically appropriate. Discontinuation of PegIntron therapy should be considered for patients with symptoms of potential pancreatitis, such as abdominal pain, nausea, or vomiting and persistently elevated triglycerides (e.g., 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 PegIntron. Patients with impaired renal function should be closely monitored for signs and symptoms of interferon toxicity, including increases in serum creatinine, and PegIntron dosing should be adjusted accordingly or discontinued (see **CLINICAL PHARMACOLOGY: Pharmacokinetics and DOSAGE AND ADMINISTRATION: Dose Reduction**). PegIntron 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 PegIntron 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 PegIntron and, if applicable, REBETOL..

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 PegIntron/REBETOL therapy and for 6 months posttherapy. Combination PegIntron/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 posttherapy (see **CONTRAINIDICATIONS and REBETOL package insert**).

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

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

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

Dental and periodontal disorders: Dental and periodontal disorders have been reported in patients receiving PegIntron/REBETOL combination therapy. In addition, dry mouth could have a damaging effect on teeth and mucous membranes of the mouth during long-term treatment with the combination of REBETOL and PegIntron. Patients should brush their teeth thoroughly twice daily and have regular dental examinations. If vomiting occurs, patients should be advised to rinse out their mouth thoroughly afterwards.

Laboratory Tests: PegIntron alone or in combination with ribavirin may cause severe decreases in neutrophil and platelet counts, and hematologic, endocrine (e.g.,TSH) and hepatic abnormalities. Transient elevations in ALT (2- to 5-fold above baseline) were observed in 10% of patients treated with PegIntron, and was not associated with deterioration of other liver functions. Triglyceride levels are

frequently elevated in patients receiving alpha interferon therapy including PegIntron and should be periodically monitored.

Patients on PegIntron or PegIntron/REBETOL combination therapy should have hematology and blood chemistry testing before the start of treatment and then periodically thereafter. In the clinical trial CBC (including hemoglobin, neutrophil, and 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. PegIntron or PegIntron/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 PegIntron/REBETOL.

Drug Interactions

Caution should be used when administering PegIntron 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 PegIntron 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 Nucleoside 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., Child-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 co-infected 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: PegIntron has not been tested for its carcinogenic potential. Neither PegIntron, 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 PegIntron therapy in combination with ribavirin.

Impairment of Fertility: PegIntron may impair human fertility. Irregular menstrual cycles were observed in female cynomolgus monkeys given subcutaneous injections of 4239 mcg/m^2 PegIntron 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 PegIntron treatment. Every other day dosing with 262 mcg/m^2 (approximately 21 times the weekly human dose) had no effects on cycle duration or reproductive hormone status. The effects of PegIntron on male fertility have not been studied.

Pregnancy Category C: PegIntron 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). PegIntron should be assumed to also have abortifacient potential. There are no adequate and well-controlled studies in pregnant women. PegIntron therapy is to be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. Therefore, PegIntron is recommended for use in fertile women only when they are using effective contraception during the treatment period.

Pregnancy Category X : Use with Ribavirin

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

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

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

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

Geriatric: In general, younger patients tend to respond better than older patients to interferon-based therapies. Clinical studies of PegIntron alone or in combination with REBETOL did not include sufficient numbers of subjects aged 65 and over; however, to determine whether they respond differently than younger subjects. Treatment with alpha interferons, including PegIntron, is associated with neuropsychiatric, cardiac, pulmonary, GI, and systemic (flu-like) adverse effects. Because these adverse reactions may be more severe in the elderly, caution should be exercised in the use of PegIntron in this population. This drug is known to be substantially excreted by the kidney. Because elderly patients are more likely to 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 PegIntron/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 PegIntron/REBETOL combination trial, the incidence of serious adverse events was 17% in the PegIntron/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 PegIntron/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 PegIntron monotherapy and one suicide in a patient receiving PegIntron/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 PegIntron, 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 PegIntron (1.5 mcg/kg)/REBETOL and in 34% of those receiving INTRON A/REBETOL. The majority of patients (57%) weighing 60 kg or less receiving PegIntron (1.5 mcg/kg)/REBETOL required dose reduction. Reduction of interferon was dose related (PegIntron 1.5 mcg/kg > PegIntron 0.5 mcg/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 PegIntron/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**).

PegIntron 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 PegIntron than with INTRON A therapy alone or in combination with REBETOL.

Application site inflammation and reaction (e.g., bruise, itchiness, and irritation) occurred at approximately twice the incidence with PegIntron 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 PegIntron/REBETOL group included myalgia (56%), arthralgia (34%), nausea (43%), anorexia (32%), weight loss (29%), alopecia (36%), and pruritus (29%).

In the PegIntron monotherapy trial the incidence of severe adverse events was 13% in the INTRON A group and 17% in the PegIntron groups. In the PegIntron/REBETOL combination therapy trial, the incidence of severe adverse events was 23% in the INTRON A/REBETOL group and 31-34% in the PegIntron/REBETOL groups. The incidence of life-threatening adverse events was $\leq$ 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	
	PegIntron 1 mcg/kg (n=297)	INTRON A 3 MIU (n=303)	PegIntron 1.5 mcg/kg/ REBETOL (n=511)	INTRON A/ REBETOL (n=505)
Application Site				
Injection Site Inflammation/ Reaction	47	20	75	49
Autonomic Nervous Sys.				
Mouth Dry	6	7	12	8
Sweating Increased	6	7	11	7
Flushing	6	3	4	3
Body as a Whole				
Fatigue/Asthenia	52	54	66	63
Headache	56	52	62	58
Rigors	23	19	48	41
Fever	22	12	46	33
Weight Decrease	11	13	29	20
RUQ Pain	8	8	12	6
Chest Pain	6	4	8	7
Malaise	7	6	4	6
Central/Periph. Nerv. Sys.				
Dizziness	12	10	21	17
Endocrine				
Hypothyroidism	5	3	5	4
Gastrointestinal				
Nausea	26	20	43	33
Anorexia	20	17	32	27
Diarrhea	18	16	22	17
Vomiting	7	6	14	12
Abdominal Pain	15	11	13	13
Dyspepsia	6	7	9	8
Constipation	1	3	5	5
Hematologic Disorders				
Neutropenia	6	2	26	14
Anemia	0	0	12	17
Leukopenia	<1	0	6	5
Thrombocytopenia	7	<1	5	2

Adverse Events	*Percentage of Patients Reporting Adverse Events**			
	Study 1		Study 2	
	PegIntron 1 mcg/kg (n=297)	INTRON A 3 MIU (n=303)	PegIntron 1.5 mcg/kg/ REBETOL (n=511)	INTRON A/ REBETOL (n=505)
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/EmotionalL ability/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
ResistanceMechanism				
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.

Many patients continued to experience adverse events several months after discontinuation of therapy. By the end of the 6-month follow-up period, the incidence of ongoing adverse events by body class in the PegIntron1.5/REBETOL group was 33% (psychiatric), 20% (musculoskeletal), and 10% (for endocrine and for GI). In approximately 10-15% of patients weight loss, fatigue, and headache had not resolved.

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

Laboratory Values

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

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 PegIntron/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 PegIntron 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 PegIntron 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 PegIntron monotherapy, 2% of patients treated with INTRON A/REBETOL, and in 4% of patients treated with PegIntron/REBETOL. Two percent of patients receiving PegIntron monotherapy and 18% of patients receiving PegIntron /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 PegIntron alone or with REBETOL and in 6% of patients treated with INTRON A/REBETOL. Severe decreases in platelet counts (<50,000/mm^3) 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 PegIntron/REBETOL combination therapy trial, 1% or 3% of patients required dose modification of INTRON A or PegIntron, respectively. Platelet counts generally returned to pre-treatment levels within 4 weeks of the cessation of therapy.

Triglycerides. Elevated triglyceride levels have been observed in patients treated with interferon alfas including PegIntron.

Thyroid Function. Development of TSH abnormalities, with and without clinical manifestations, are associated with interferon therapies. Clinically apparent thyroid disorders occur among patients treated with either INTRON A or PegIntron (with or without REBETOL) at a similar incidence (5% for hypothyroidism and 3% for hyperthyroidism). Subjects developed new onset TSH abnormalities while on

treatment and during the follow-up period. At the end of the follow-up period, 7% of subjects still had abnormal TSH values.

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

Postmarketing Experience

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

Immunogenicity: Approximately 2% of patients receiving PegIntron (32/1759) or INTRON A (11/728) with or without REBETOL developed low-titer (≤160) neutralizing antibodies to PegIntron 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 posttreatment-binding antibody ranged from 8 to 15 percent. The data reflect the percentage of patients whose test results were considered positive for antibodies to PegIntron 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 PegIntron 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 PegIntron. The maximum dose received by any patient was 3.45 mcg/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 PegIntron 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 PegIntron, alone or in combination with ribavirin, be discontinued from therapy if HCV viral levels remain high after 6 months of therapy.

PegIntron Monotherapy

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

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

Table 4 Recommended PegIntron Monotherapy Dosing

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

* When reconstituted as directed.

PegIntron/REBETOL Combination Therapy

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

TABLE 5. Recommended PegIntron Combination Therapy Dosing

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

76-85		120	0.5
>85	150 mcg per 0.5 mL	150	0.5

* When reconstituted as directed.

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

Dose Reduction

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

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

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

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

				Continue reduced dosing or return to normal dose.	
Severe	Discontinue IFN/R permanently.	Obtain **immediate** psychiatric consultation.	Psychiatric therapy as necessary		

† See DSM-IV for definitions.

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

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

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

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

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

89-106	50 mcg per 0.5 mL	50	0.5
107-136	80 mcg per 0.5 mL	64	0.4
137-160		80	0.5

* Must use vial. Minimum delivery for Redipen® 0.3 mL.
** When reconstituted as directed.

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

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

* 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 PegIntron dose should be reduced by 25%. Patients with severe renal dysfunction (creatinine clearance 10-29 mL/min) including those on hemodialysis, should have the PegIntron dose reduced by 50%. If renal function decreases during treatment, PegIntron therapy should be discontinued. When PegIntron is administered in combination with REBETOL, subjects with impaired renal function and/or those over

762 the age of 50 should be more carefully monitored with respect to the development of
763 anemia.

764 **Preparation and Administration**

765 **PegIntron Redipen®**

766 PegIntron Redipen® consists of a dual-chamber glass cartridge with sterile,
767 lyophilized peginterferon alfa-2b in the active chamber and Sterile Water for
768 Injection, USP in the diluent chamber. The PegIntron in the glass cartridge should
769 appear as a white to off-white tablet shaped solid that is whole or in pieces, or
770 powder. To reconstitute the lyophilized peginterferon alfa-2b in the Redipen®, hold
771 the Redipen upright (dose button down) and press the two halves of the pen together
772 until there is an audible click. Gently invert the pen to mix the solution. **DO NOT**
773 **SHAKE**. The reconstituted solution has a concentration of either 50 mcg per 0.5 mL,
774 80 mcg per 0.5 mL, 120 mcg per 0.5 mL, or 150 mcg per 0.5 mL for a single
775 subcutaneous injection. Visually inspect the solution for particulate matter and
776 discoloration prior to administration. The reconstituted solution should be clear and
777 colorless. Do not use if the solution is discolored or cloudy, or if particulates are
778 present.

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

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

PegIntron 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 PegIntron Powder for Injection are provided below.

Reconstitute the PegIntron 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 PegIntron, and PegIntron 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 PegIntron dose should be withdrawn and injected subcutaneously. PegIntron 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° 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 PegIntron 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

PegIntron Redipen

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

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

PegIntron Vials

PegIntron 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°-8°C (36°-46°F). The reconstituted solution contains no preservative, is clear and colorless. **DO NOT FREEZE.**

HOW SUPPLIED

PegIntron Redipen

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

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

alcohol swabs.	

PegIntron Vials

Each PegIntron Package Contains:	
A box containing one 50 mcg per 0.5 mL vial of PegIntron Powder for Injection and one 1.25 mL vial of Diluent (Sterile Water for Injection, USP), 2 B-D® Safety Lok™ syringes with a safety sleeve and 2 alcohol swabs.	(NDC 0085-1368-01)
A box containing one 80 mcg per 0.5 mL vial of PegIntron Powder for Injection and one 1.25 mL vial of Diluent (Sterile Water for Injection, USP), 2 B-D® Safety Lok™ syringes with a safety sleeve and 2 alcohol swabs.	(NDC 0085-1291-01)
A box containing one 120 mcg per 0.5 mL vial of PegIntron Powder for Injection and one 1.25 mL vial of Diluent (Sterile Water for Injection, USP), 2 B-D® Safety Lok™ syringes with a safety sleeve and 2 alcohol swabs.	(NDC 0085-1304-01)
A box containing one 150 mcg per 0.5 mL vial of PegIntron Powder for Injection and one 1.25 mL vial of Diluent (Sterile Water for Injection, USP), 2 B-D® Safety Lok™ syringes with a safety sleeve and 2 alcohol swabs.	(NDC 0085-1279-01)

Schering Corporation

Kenilworth, NJ 07033 USA

REV. 5/07

XXXXXXXXU.S. Patent Nos. 5,908,621; 5,951,974; 6,042,822; 6,177,074; 6,180,096; 6,250,469; 6,482,613; 6,524,570; 6,610,830

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