GLUE PANEL
MUST LEAVE BLANK

F-28362200 2192

PRODUCT INFORMATION

PEG-Intron®
(Peginterferon alfa-2b)
Powder for Injection

T 5

FPO
12 of 5

GLUE PANEL
MUST LEAVE BLANK

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 Patients with persistently severe or worsening signs or symptoms of these conditions should be withdrawn from therapy.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 x 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 0.5 mL 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 ($t_{1/2}$ 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/h•kg. Renal elimination accounts for 30% of the clearance. Single dose peginterferon alfa-2b pharmacokinetics following a subcutaneous 1.0 µg/kg dose suggest the clearance of peginterferon alfa-2b is reduced by approximately half in subjects with impaired renal function (creatinine clearance <50 mL/minute).

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.

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).

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.

Effect of Food on Absorption of Ribavirin: Both AUC_{tau} 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: It is not known if PEG-Intron therapy causes clinically significant drug-drug interactions with drugs metabolized by the liver in patients with hepatitis C. In 12 healthy subjects known to be CYP2D6 extensive metabolizers, a single subcutaneous dose of 1 µg/kg PEG-Intron did not inhibit CYP1A2, 2C8/9, 2D6, hepatic 3A4 or N-acetyltransferase; the effects of PEG-Intron on CYP2C19 were not assessed.

CLINICAL STUDIES

PEG-Intron Monotherapy-Study 1

A randomized study compared treatment with PEG-Intron (0.5, 1.0, or 1.5 µg/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 7 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 1.0 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%	12 (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 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 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.

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 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 PEG-Intron 1.5 µg/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 → 0.5 µg/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 1.5 µg/kg QW REBETOL 800 mg QD	INTRON A 3 MIU TIW REBETOL 1000/1200 mg QD
Overall [1,2] response	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
- decompensated liver disease

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 (eg, thalassemia major, sickle-cell anemia)

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 have occurred in patients with and without a previous psychiatric disorder during PEG-Intron treatment and follow-up. Psychoses, hallucinations, bipolar disorders, and mania have been observed in patients treated with alpha interferons. PEG-Intron 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. In severe cases, PEG-Intron should be stopped immediately and psychiatric intervention instituted. (See **DOSAGE AND ADMINISTRATION: Dose Reduction**.)

Bone marrow toxicity

PEG-Intron suppresses bone marrow function, sometimes resulting in severe cytopenias. PEG-Intron 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.

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 (eg, thyroiditis, thrombocytopenia, 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 baseline. Patients with preexisting ophthalmologic disorders (eg, diabetic or hypertensive retinopathy) should receive periodic ophthalmologic examinations 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 (eg, 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 PEG-Intron, 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 PEG-Intron/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

- 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 interferons including PEG-Intron therapy. Elevated triglyceride levels should be managed as clinically appropriate. Hypertriglyceridemia may result in pancreatitis. Discontinuation of PEG-Intron therapy should be considered for patients with persistently elevated triglycerides (eg, triglycerides >1000 mg/dL) associated with symptoms of potential pancreatitis, such as abdominal pain, nausea, or vomiting.

Patients with renal failure: Increases in serum creatinine levels have been observed in patients with renal insufficiency treated with interferons, including PEG-Intron. Patients with impairment of renal function should be closely monitored for signs and symptoms of interferon toxicity, including increases in serum creatinine, and doses of PEG-Intron should be adjusted accordingly. PEG-Intron should be used with caution in patients with creatinine clearance <50 mL/min; in considering these patients for PEG-Intron therapy, the potential risks must be evaluated against the potential benefits of treatment. REBETOL must not be used in patients with creatinine clearance <50 mL/min (see **DOSAGE AND ADMINISTRATION: Dose Reduction**).

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 **CONTRAINDICATIONS and REBETOL package insert**.)

Patients should be informed that there are no data regarding whether PEG-Intron therapy will prevent transmission of HCV infection to others. Also, it is not known if treatment with PEG-Intron 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 PEG-Intron may be minimized by bedtime administration of PEG-Intron 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™.

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

Patients on PEG-Intron or PEG-Intron/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. PEG-Intron or PEG-Intron/REBETOL combination therapy should be discontinued in patients with persistent high viral levels.

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

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/m^2 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/m^2 (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.

Nursing Mothers: It is not known whether the components of PEG-Intron are excreted in human 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 treatment, taking into account the importance of the product to the mother.

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.

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

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 PEG-Intron 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 PEG-Intron, 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 PEG-Intron 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. 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 (eg, 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 (eg, 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 (eg, 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 *(cont)*

*Percentage of Patients Reporting Adverse Events**

	Study 1		Study 2	
	PEG-Intron 1.0 µg/kg (n=297)	INTRON A 3 MIU (n=303)	PEG-Intron 1.5 µg/kg/REBETOL (n=511)	INTRON A/REBETOL (n=505)
Adverse Events				
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 PEG-Intron 1.5/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, agravated psoriasis; urticaria, injection-site necrosis, vasculitis, phototoxicity.

Laboratory Values

Changes in selected laboratory values during treatment with PEG-Intron 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 <11 g/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 posttreatment. 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 (65%) and INTRON A/REBETOL (60%). Severe potentially life-threatening neutropenia (<0.5 x 10^9/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.

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 PEG-Intron (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 PEG-Intron/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 PEG-Intron therapy: seizures, hearing impairment, hearing loss, peripheral neuropathy, rhabdomyolysis, myositis, aphthous stomatitis, vertigo, renal insufficiency, renal failure, Stevens Johnson Syndrome, toxic epidermal necrolysis, and erythema multiforme. 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 PEG-Intron (32/1759) or INTRON A (11/728) with or without REBETOL developed low-titer (≤160) neutralizing antibodies to PEG-Intron or INTRON A. The clinical and pathological significance of the appearance of these 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 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 med

TABLE 5. Recommended PEG-Intron Combination Therapy 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
<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

* 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 PEG-Intron 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**. In the combination therapy trial dose reductions occurred among 42% of patients receiving PEG-Intron 1.5 µg/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 PEG-Intron or PEG-Intron/REBETOL and for Scheduling Visits for Patients with Depression

Depression Severity†	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		

† See DSM-IV for definitions

GLUE PANEL
MUST LEAVE BLANK

BLANK

BLANK

GLUE PANEL
MUST LEAVE BLANK

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	———	Decrease by 200 mg/day
	<8.5 g/dL	Permanently discontinue	Permanently discontinue
WBC	<1.5 x 10⁹/L	Reduce dose by 50%	———
	<1.0 x 10⁹/L	Permanently discontinue	Permanently discontinue
Neutrophil	<0.75 x 10⁹/L	Reduce dose by 50%	———
	<0.5 x 10⁹/L	Permanently discontinue	Permanently discontinue
Platelets	<80 x 10⁹/L	Reduce dose by 50%	———
	<50 x 10⁹/L	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 200 mg/day if a >2 g/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.

PEG-INTRON PI/MedGuide • RIC #28362200 • 2192 • Rev. 6/04
OUTSERT: 10.5" x 22" FLAT • 4.5" X 1.125" FOLDED
NOTE: A <1% DISCREPANCY SHOULD BE EXPECTED IN LASER PRINT DIMENSIONS.
4th submission 7/19/04

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°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°C (see **Storage**). **DO NOT REUSE THE VIAL.** 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.

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° 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™ and 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™ and 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™ and 1 B-D needle and 2 alcohol swabs.	(NDC 0085-1370-01)

PEG-Intron Vials

Each PEG-Intron Package Contains:	
A box containing one 50 µg 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 80 µg 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 120 µg 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 150 µg 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)

Schering Corporation
Kenilworth, NJ 07033 USA

Copyright © 2003, Schering Corporation. All rights reserved. Rev. 6/04
*Safety-Lok is a trademark of Becton, Dickinson and Company

27664423T

MEDICATION GUIDE

PEG-Intron®
(Peginterferon alfa-2b)

Including appendix with instructions for using PEG-Intron® Powder for Injection

Read this Medication Guide carefully before you start taking PEG-Intron **(Peg In-tron)** or PEG-Intron/REBETOL **(REB-eh-tole)** combination therapy. Read the Medication Guide each time you refill your prescription because there may be new information. The information in this Medication Guide does not take the place of talking with your doctor.

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

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

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

If you are taking PEG-Intron or PEG-Intron/REBETOL therapy you should call your doctor immediately if you develop any of these symptoms:
New or worsening mental health problems such as thoughts about killing or hurting yourself or others, trouble breathing, chest pain, severe stomach or lower back pain, bloody diarrhea or bloody bowel movements, high fever, bruising, bleeding, or decreased vision.
The most serious possible side effects of PEG-Intron and PEG-Intron/REBETOL therapy include:
Problems with Pregnancy. Combination PEG-Intron/REBETOL therapy can cause death, serious birth defects, or other harm to your unborn child. If you are a woman of childbearing age you must not become pregnant during treatment and for 6 months after you have stopped therapy. You must have a negative pregnancy test immediately before beginning treatment, during treatment, and for 6 months after you have stopped therapy. Both male and female patients must use effective forms of birth control during treatment and for the 6 months after treatment is completed. Male patients should use a condom. If you are a female, you must use birth control even if you believe that you are not fertile or that your fertility is low. You should talk to your doctor about birth control for you and your partner.
Mental health problems and suicide. PEG-Intron and PEG-Intron/REBETOL therapies may cause patients to develop mood or behavioral problems. These can include irritability (getting easily upset) and depression (feeling low, feeling bad about yourself, or feeling hopeless). Some patients may have aggressive behavior. Former drug addicts may fall back into drug addiction or overdose. Some patients think about hurting or killing themselves or other people and some have killed (suicide) or hurt themselves or others. You must tell your doctor if you are being treated for a mental illness or had treatment in the past for any mental illness, including depression and suicidal behavior. You should tell your doctor if you have ever been addicted to drugs or alcohol.
Heart problems. Some patients taking PEG-Intron or PEG-Intron/REBETOL therapy may develop problems with their heart, including low blood pressure, fast heart rate, and very rarely, heart attacks. Tell your doctor if you have had any heart problems in the past.
Blood problems. PEG-Intron and PEG-Intron/REBETOL therapies commonly lower two types of blood cells (white blood cells and platelets). In some patients, these blood counts may fall to dangerously low levels. If your blood counts become very low, this could lead to infections or bleeding.

REBETOL therapy causes a decrease in the number of red blood cells you have (anemia). This can be dangerous, especially for patients who already have heart or circulatory (cardiovascular) problems. Talk with your doctor before taking combination PEG-Intron/REBETOL therapy if you have or have ever had any cardiovascular problems.
Body organ problems. Certain symptoms like severe stomach pain may mean that your internal organs are being damaged.

For other possible side effects, see "What are the possible side effects of PEG-Intron and PEG-Intron/REBETOL" in this Medication Guide.

What is PEG-Intron and PEG-Intron/REBETOL combination therapy?
The PEG-Intron product is a drug used to treat adults who have a lasting (chronic) infection with hepatitis C virus and who show signs that the virus is damaging the liver. PEG-Intron/REBETOL combination therapy consists of two medications also used to treat hepatitis C infection. Patients with hepatitis C have the virus in their blood and in their liver. PEG-Intron reduces the amount of virus in the body and helps the body's immune system fight the virus. REBETOL (ribavirin) is a drug that helps to fight the viral infection but does not work when used by itself to treat chronic hepatitis C.

It is not known if PEG-Intron or PEG-Intron/REBETOL therapies can cure hepatitis C (permanently eliminate the virus) or if it can prevent liver failure or liver cancer that is caused by hepatitis C infection.

It is also not known if PEG-Intron or PEG-Intron/REBETOL combination therapy will prevent one infected person from infecting another person with hepatitis C.

Who should not take PEG-Intron or PEG-Intron/REBETOL therapy?
Do not take PEG-Intron or PEG-Intron/REBETOL therapy if you
- are pregnant, planning to get pregnant during treatment or during the 6 months after treatment, or breast-feeding
- are a male patient with a female sexual partner who is pregnant or plans to become pregnant at any time while you are being treated with REBETOL or during the 6 months after your treatment has ended
- have hepatitis caused by your immune system attacking your liver (autoimmune hepatitis) or unstable liver disease
- had an allergic reaction to another alpha interferon or are allergic to any of the ingredients in PEG-Intron or REBETOL Capsules. If you have any doubts, ask your doctor.
- Do not take PEG-Intron/REBETOL combination therapy if you have abnormal red blood cells such as sickle-cell anemia or thalassemia major.

If you have any of the following conditions or serious medical problems, discuss them with your doctor before taking PEG-Intron or PEG-Intron/REBETOL therapy:
- depression or anxiety
- sleep problems
- high blood pressure
- previous heart attack, or other heart problems
- liver problems (other than hepatitis C infection)
- any kind of autoimmune disease (where the body's immune system attacks the body's own cells), such as psoriasis, systemic lupus erythematosus, rheumatoid arthritis
- thyroid problems
- diabetes
- colitis (inflammation of the bowels)
- cancer
- hepatitis B infection
- HIV infection
- kidney problems
- bleeding problems
- alcoholism
- drug abuse or addiction
- body organ transplant and are taking medicine that keeps your body from rejecting your transplant (suppresses your immune system)

How should I take PEG-Intron or PEG-Intron/REBETOL?
Your doctor will decide whether you will take PEG-Intron therapy alone or the combination of PEG-Intron/REBETOL, as well as the correct dose (based on your weight). PEG-Intron and PEG-Intron/REBETOL are given for one year. Take your prescribed dose of PEG-Intron once a week, on the same day of each week and at approximately the same time. Take the medicine for the full year and do not take more than the prescribed dose. REBETOL Capsules should be taken with food. When you take REBETOL with food, more of the medicine (70% more on average) is taken up by your body. You should take REBETOL the same way every day (twice a day with food) to keep the medicine in your body at a steady level. This will help your doctor to decide how your treatment is working and how to change the number of REBETOL capsules you take if you have side effects from REBETOL. **Be sure to read the Medication Guide for REBETOL (ribavirin, USP) for complete instructions on how to take the REBETOL capsules.**

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

If you miss a dose of the PEG-Intron product, take the missed dose as soon as possible during the same day or the next day, then continue on your regular dosing schedule. If several days go by after you miss a dose, check with your doctor about what to do. Do not double the next dose or take more than one dose a week without talking to your doctor. Call your doctor right away if you take more than your prescribed PEG-Intron dose. Your doctor may wish to examine you more closely, and take blood for testing.

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

You must get regular blood tests to help your doctor check how the treatment is working and to check for side effects.

Tell your doctor if you are taking or planning to take other prescription or non-prescription medicines, including vitamin and mineral supplements and herbal medicines.

What should I avoid while taking PEG-Intron or PEG-Intron/ REBETOL therapies?
- If you are pregnant do not start taking PEG-Intron/REBETOL combination therapy.
- Avoid becoming pregnant while taking PEG-Intron or PEG-Intron/REBETOL. PEG-Intron and PEG-Intron/REBETOL may harm your unborn child (death or serious birth defects) or cause you to lose your baby (miscarry). **If you or your partner become pregnant during treatment or during the 6 months after treatment with PEG-Intron/REBETOL combination therapy, immediately report the pregnancy to your doctor. You or your doctor should call (800) 727-7064.** By calling this number, information about you and/or your partner will be added to a pregnancy registry that will be used to help you and your doctor make decisions about your treatment for hepatitis in the future. You, your partner and/or your physician will be asked to provide follow-up information on the outcome of the pregnancy.
- Do not breast-feed your baby while taking PEG-Intron.

What are the possible side effects of PEG-Intron and PEG-Intron/REBETOL combination therapy?
Possible, serious side effects include:
- **Mental health problems including suicide, blood problems, heart problems, body organ problems.** See "What is the most important information I should know about PEG-Intron and PEG-Intron/REBETOL combination therapy?"
- **Other body organ problems.** A few patients have lung problems (such as pneumonia or inflammation of the lung tissue), inflammation of the kidney, and eye disorders.
- **New or worsening autoimmune disease.** Some patients taking PEG-Intron or PEG-Intron/REBETOL develop autoimmune diseases (a condition where the body's immune cells attack other cells or organs in the body), including rheumatoid arthritis, systemic lupus erythematosus, and psoriasis. In some patients who already have an autoimmune disease, the disease worsens on PEG-Intron and PEG-Intron/REBETOL combination therapy.

Common but less serious side effects include:
- **Flu-like symptoms.** Most patients who take PEG-Intron or PEG-Intron/REBETOL therapy have "flu-like" symptoms (headache, muscle aches, tiredness and fever). Some of these symptoms (fever, headache) usually lessen after the first few weeks of therapy. You can reduce some of these symptoms by injecting your PEG-Intron dose at bedtime. Over-the-counter pain and fever reducers, such as acetaminophen or ibuprofen, can be used to prevent or reduce the fever and headache.
- **Extreme fatigue (tiredness).** Many patients become extremely tired while on PEG-Intron or PEG-Intron/REBETOL combination therapy.
- **Appetite problems.** Nausea, loss of appetite, and weight loss, occur commonly.
- **Thyroid problems.** Some patients develop changes in the function of their thyroid. Symptoms of thyroid changes include the inability to concentrate, feeling cold or hot all the time, a change in your weight and changes to your skin.
- **Blood sugar problems.** Some patients develop problems with the way their body controls their blood sugar and may develop high blood sugar or diabetes.
- **Skin reactions.** Redness, swelling, and itching are common at the site of injection. If after several days these symptoms do not disappear contact your doctor. You may get a rash during therapy. If this occurs, your doctor may recommend medicine to treat the rash.
- **Hair thinning.** Hair thinning is common during PEG-Intron and PEG-Intron/REBETOL treatment. Hair loss stops and hair growth returns after therapy is stopped.

These are not all of the side effects of PEG-Intron or PEG-Intron/REBETOL combination therapy. Your doctor or pharmacist can give you a more complete list.

General advice about prescription medicines:
Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. If you have any concerns about PEG-Intron, ask your doctor. Your doctor or pharmacist can give you information about PEG-Intron that was written for health care professionals. Do not use PEG-Intron for a condition for which it was not prescribed. Do not share this medication with other people.
If you are taking PEG-Intron/REBETOL combination therapy, also read the Medication Guide for REBETOL (ribavirin, USP) Capsules.

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

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

How do I prepare and inject the PEG-Intron Dose?
Before you inject PEG-Intron, the powder must be mixed with **0.7 mL** of the supplied DILUENT for PEG-Intron, Sterile Water for Injection (diluent). You should carefully follow the directions given to you by your doctor.

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

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

Preparing the PEG-Intron solution:
1. Find a clean, well-lit, non-slip flat working surface and assemble all of the supplies you will need for an injection. All of the supplies you will need for an injection are in the PEG-Intron Powder for Injection package. The package contains:
   - a vial of PEG-Intron powder
   - a 1.25-mL vial of DILUENT
   - 2 disposable syringes, and
   - alcohol swabs

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

If you have already mixed the PEG-Intron solution and it has been stored properly in the refrigerator, take it out of the refrigerator and allow the solution to come to room temperature.

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

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

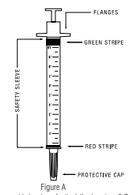
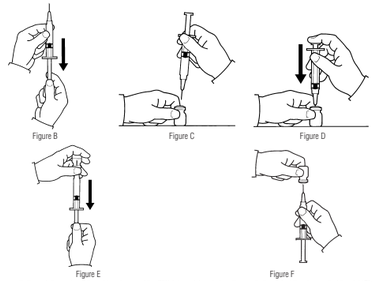


Figure A

4. Remove the protective wrapper from ONE of the syringes provided and use for the following steps 5-7. Make sure that the syringe safety sleeve is sitting against the flange (see **Figure A**).
5. Remove the protective plastic cap from the tops of both the supplied DILUENT and the PEG-Intron vials. Clean the rubber stopper on the top of both vials with an alcohol swab.
6. Carefully remove the protective cap straight off of the needle to avoid damaging the needle point. Fill the syringe with air by pulling the plunger to 0.7 mL (**Figure B**). Hold the DILUENT vial upright. Do not touch the cleaned top of the vial with your hands (**Figure C**). Insert the needle through the center of the rubber stopper of the DILUENT vial, and inject the air from the syringe into the vial (**Figure D**). Turn the vial upside down and make sure the tip of the needle is in the liquid. **Withdraw only 0.7 mL of DILUENT** by pulling the plunger back to the 0.7 mL mark on the side of the syringe (**Figure E**). Remove the needle from the vial (**Figure F**). **Discard the remaining DILUENT.**

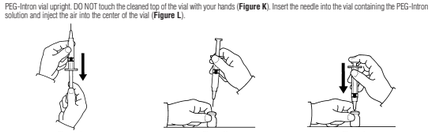

Figure B Figure C Figure D Figure E Figure F

7. Insert the needle through the center of the rubber stopper of the PEG-Intron vial, and place the needle tip against the glass wall of the vial (**Figure G**). SLOWLY inject the 0.7 mL DILUENT so that the stream of DILUENT runs down the side of the vial. To prevent bubbles from forming, DO NOT AIM THE STREAM of diluent directly on the tablet-like SOLID or POWDER in the bottom of the vial. Remove the needle from the vial.
Firmly grasp the safety sleeve and pull it over the exposed needle until you hear a click. The green stripe on the safety sleeve will completely cover the red stripe on the needle. (See **Figure O** in the section: "Injecting the PEG-Intron dose.") Discard the syringe and needle in the puncture proof container.
8. GENTLY swirl the vial in a gentle circular motion (**Figure H**), until the PEG-Intron is completely dissolved. **DO NOT SHAKE** the vial. If any powder remains undissolved in the vial, gently turn the vial upside down until all of the powder is dissolved. It is not unusual for the solution to appear cloudy or bubbly for a few minutes. If air bubbles do form, wait until the solution has settled and all bubbles have risen to the top before withdrawing your dose from the vial.

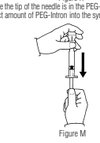


Figure G Figure H

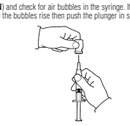
9. After the solution has settled and is completely dissolved it should be clear, colorless and without particles, but there may be a ring of foam or bubbles on the surface, this is normal. Do not use it if you see particles or the color is not correct.
10. After the PEG-Intron powder is dissolved but before you withdraw your dose, clean the rubber stopper again with an alcohol swab.
11. Unwrap the second syringe provided. You will use it to give yourself the injection. Carefully remove the protective cap from the needle and fill the syringe with air by pulling the plunger to the number on the side of the syringe (mL) that corresponds to your prescribed dose (**Figure J**). Hold the PEG-Intron vial upright. DO NOT touch the cleaned top of the vial with your hands (**Figure K**). Insert the needle into the vial containing the PEG-Intron solution and inject the air into the center of the vial (**Figure L**).


Figure J Figure K Figure L

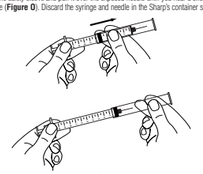
12. Turn the PEG-Intron vial upside down. Be sure the tip of the needle is in the PEG-Intron solution. While holding the vial and syringe with one hand slowly pull the plunger back to withdraw the exact amount of PEG-Intron into the syringe your doctor told you to use (**Figure M**).


Figure M

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


Figure N

Injecting the PEG-Intron Dose
Selecting the Site for Injection.
The best sites for giving yourself an injection are those areas with a layer of fat between the skin and muscle, like your thigh, the outer surface of your upper arm, and abdomen. Do not inject yourself in the area near your navel or waistline. If you are very thin, you should only use the thigh or outer surface of the arm for injection.
You should use a different site each time you inject PEG-Intron to avoid soreness at any one site. Do not inject PEG-Intron solution into an area where the skin is irritated, red, bruised, infected or has scars, stretch marks or lumps.
14. Clean the skin where the injection is to be given with an alcohol swab, and wait for the area to dry. Remove the protective cap from the needle. Make sure the safety sleeve of the syringe is pushed firmly against the syringe flange so that the needle is fully exposed (see **Figure A**).
15. With one hand, pinch a 2-inch fold of loose skin. With your other hand, pick up the syringe and hold it like a pencil. Position the bevel of the needle facing up and insert the needle approximately ½ inch into the pinched skin at approximately a 45 to 90 degree angle with a quick dart-like thrust. After the needle is in, remove the hand that you used to pinch your skin and use it to hold the syringe barrel. Pull the plunger of the syringe back very slightly. If blood comes into the syringe, the needle has entered a blood vessel. **Do not inject.** Withdraw the needle and discard the syringe as outlined in step 17. Repeat the above steps with a new vial to prepare a new syringe and inject the medicine at a new site. If no blood is present in the syringe, inject the medicine by gently pressing the plunger all the way down the syringe barrel.
16. Hold an alcohol swab near the needle and pull the needle straight out of the skin. Press the alcohol swab over the injection site for several seconds. Do not massage the injection site. If there is bleeding, cover it with a bandage.
17. After injecting your dose, firmly grasp the safety sleeve and pull it over the exposed needle until you hear a click, and the green stripe on the safety sleeve covers the red stripe on the needle (**Figure O**). Discard the syringe and needle in the Sharp's container supplied to you.


Figure O

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

How do I dispose of the used syringes and needles?
Discard used safety lock syringes and needles in a Sharp's container or other puncture proof container like a coffee can. DO NOT USE glass or clear plastic containers. Your doctor or nurse will tell you how to dispose of a full container. Always keep the container out of reach of children.

Schering®
Schering Corporation
Kenilworth, NJ 07033 USA

Copyright © 2001, 2002, Schering Corporation. All rights reserved.
Rev. 6/04

27853510T
B-28362200