

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

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Product Information

**PegIntron™/REBETOL® Combo Pack
containing
PegIntron™ REDIPEN® Single-dose Delivery System (peginterferon alfa-2b)
and
REBETOL® (ribavirin, USP) Capsules**

Significant teratogenic and/or embryocidal effects have been demonstrated in all animal species exposed to ribavirin. In addition, ribavirin has a multiple-dose half-life of 12 days, and so it may persist in nonplasma compartments for as long as 6 months. Therefore, REBETOL® therapy is contraindicated in women who are pregnant and in the male partners of women who are pregnant. Extreme care must be taken to avoid pregnancy during therapy and for 6 months after completion of treatment in both female patients and in female partners of male patients who are taking REBETOL® therapy. At least two reliable forms of effective contraception must be utilized during treatment and during the 6-month posttreatment follow-up period. (See CONTRAINDICATIONS, WARNINGS, PRECAUTIONS—Information for Patients and Pregnancy Category X.)

The primary toxicity of ribavirin is hemolytic anemia. The anemia associated with REBETOL® therapy may result in a worsening of cardiac disease that has led to fatal and nonfatal myocardial infarctions. Patients with a history of significant or unstable cardiac disease should not be treated with REBETOL®. (See WARNINGS, ADVERSE REACTIONS, and DOSAGE AND ADMINISTRATION.)

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 Patients with persistently severe or worsening signs or symptoms of these conditions should be withdrawn from therapy.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

DESCRIPTION

PegIntron™/REBETOL® Combo Pack contains PegIntron™ REDIPEN® Single-dose Delivery System (peginterferon alfa-2b) and REBETOL® (ribavirin) capsules.

PegIntron™

PegIntron™, peginterferon alfa-2b, Powder for Injection is a covalent conjugate of recombinant human 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.

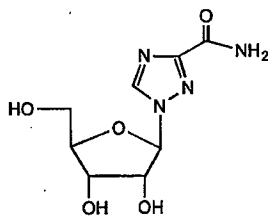
REDIPEN®

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 0.5 mL 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.

REBETOL®

REBETOL® is Schering Corporation's brand name for ribavirin, a nucleoside analog. The chemical name of ribavirin is 1-β-D-ribofuranosyl-1*H*-1,2,4-triazole-3-carboxamide and has the following structural formula:



Ribavirin is a white, crystalline powder. It is freely soluble in water and slightly soluble in anhydrous alcohol. The empirical formula is C₈H₁₂N₄O₅ and the molecular weight is 244.21.

REBETOL® Capsules consist of a white powder in a white, opaque, gelatin capsule. Each capsule contains 200 mg ribavirin and the inactive ingredients microcrystalline cellulose, lactose monohydrate, croscarmellose sodium, and magnesium stearate. The capsule shell consists of gelatin, sodium lauryl sulfate, silicon dioxide, and titanium dioxide. The capsule is printed with edible blue pharmaceutical ink which is made of shellac, anhydrous ethyl alcohol, isopropyl alcohol, n-butyl alcohol, propylene glycol, ammonium hydroxide, and FD&C Blue #2 aluminum lake.

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 primary effects such as the induction of certain enzymes and suppression of cell proliferation in the interferon receptor bearing cells, and secondary effects

including immunomodulating activities such as enhancement of the phagocytic activity of macrophages and augmentation of the specific cytotoxicity of lymphocytes for target cells. These primary and secondary effects inhibit virus replication in virus-infected cells. Interferon alfa upregulates the Th1 T-helper cell subset in cell culture studies. The clinical relevance of these findings is not known.

The mechanism of inhibition of hepatitis C virus (HCV) RNA by combination therapy with ribavirin and interferon products has not been established.

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

Peginterferon alfa-2b: Following a single subcutaneous (SC) dose of PegIntron™, 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 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 7-fold lower mean apparent clearance and a 5-fold greater mean half-life permitting a reduced dosing frequency.

At effective therapeutic doses, PegIntron™ has approximately ten-fold greater C_{max} and 50-fold greater AUC than interferon alfa-2b.

Ribavirin: Single- and multiple-dose pharmacokinetic properties in adults are summarized in **TABLE 1**. Ribavirin was rapidly and extensively absorbed following oral administration. However, due to first-pass metabolism, the absolute bioavailability averaged 64% (44%). There was a linear relationship between dose and AUC_{tf} (AUC from time zero to last measurable concentration) following single doses of 200-1200 mg ribavirin. The relationship between dose and C_{max} was curvilinear, tending to asymptote above single doses of 400-600 mg.

Upon multiple oral dosing, based on AUC_{12hr} , a 6-fold accumulation of ribavirin was observed in plasma. Following oral dosing with 600 mg BID, steady-state was reached by approximately 4 weeks, with mean steady state plasma concentrations of 2200 (37%) ng/mL. Upon discontinuation of dosing, the mean half-life was 298 (30%) hours, which probably reflects slow elimination from nonplasma compartments.

TABLE 1. Mean (% Coefficient of Variation) Pharmacokinetic Parameters for REBETOL® When Administered Individually to Adults

Parameter	REBETOL®	
	Single Dose 600 mg Capsules (N=12)	Multiple Dose 600 mg BID Capsules (N=12)
T_{max} (hr)	1.7 (46) ***	3 (60)
C_{max} *	782 (37)	3680 (85)
AUC_{tf} **	13400 (48)	228000 (25)
$T_{1/2}$ (hr)	43.6 (47)	298 (30)
Apparent Volume of Distribution (L)	2825 (9) †	
Apparent Clearance (L/hr)	38.2 (40)	
Absolute Bioavailability	64% (44) ††	

* ng/mL

** ng·hr/mL

*** N = 11

† data obtained from a single-dose pharmacokinetic study using ^{14}C labeled ribavirin; N = 5

†† N = 6

Effect of Food on Absorption of Ribavirin: Both $AUC_{0-\infty}$ 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. There are insufficient data to address the clinical relevance of these results. During clinical studies with PegIntron[™]/REBETOL[®], all subjects were instructed to take REBETOL[®] Capsules with food. (See **DOSAGE AND ADMINISTRATION.**)

Effect of Antacid on Absorption of Ribavirin: Coadministration of REBETOL[®] Capsules with an antacid containing magnesium, aluminum, and simethicone (Mylanta^{®1}) resulted in a 14% decrease in mean ribavirin $AUC_{0-\infty}$. The clinical relevance of results from this single-dose study is unknown.

Ribavirin transport into nonplasma compartments has been most extensively studied in red blood cells, and has been identified to be primarily via es-type equilibrative nucleoside transporter. This type of transporter is present on virtually all cell types and may account for the extensive volume of distribution. Ribavirin does not bind to plasma proteins.

Ribavirin has two pathways of metabolism: (i) a reversible phosphorylation pathway in nucleated cells; and (ii) a degradative pathway involving deribosylation and amide hydrolysis to yield a triazole carboxylic acid metabolite. Ribavirin and its triazole carboxamide and triazole carboxylic acid metabolites are excreted renally. After oral administration of 600 mg ¹⁴C-ribavirin, approximately 61% and 12% of the radioactivity was eliminated in the urine and feces, respectively, in 336 hours. Unchanged ribavirin accounted for 17% of the administered dose.

Results of *in vitro* studies using both human and rat liver microsome preparations indicated little or no cytochrome P450 enzyme-mediated metabolism of ribavirin, with minimal potential for P450 enzyme-based drug interactions.

1. Trademark of Johnson & Johnson-Merck Consumer Pharmaceuticals Co.

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 pharmacokinetics of ribavirin were assessed after administration of a single oral dose (400 mg) of ribavirin to non HCV infected subjects with varying degrees of renal dysfunction. The mean $AUC_{0-\infty}$ value was threefold greater in subjects with creatinine clearance values between 10 to 30 mL/min when compared to control subjects (creatinine clearance >90 mL/min). In subjects with creatinine clearance values between 30 to 60 mL/min, $AUC_{0-\infty}$ was twofold greater when compared to control subjects. The increased $AUC_{0-\infty}$ appears to be due to reduction of renal and non-renal clearance in these patients. Phase III efficacy trials included subjects with creatinine clearance values >50 mL/min. The multiple dose pharmacokinetics of ribavirin cannot be accurately predicted in patients with renal dysfunction. Ribavirin is not effectively removed by hemodialysis. Patients with creatinine clearance <50 mL/min should not be treated with PegIntron™/REBETOL® Combo Pack (see PRECAUTIONS).

Hepatic Dysfunction: The effect of hepatic dysfunction was assessed after a single oral dose of ribavirin (600 mg). The mean $AUC_{0-\infty}$ values were significantly different in subjects with mild, moderate, or severe hepatic dysfunction (Child-Pugh Classification A, B, or C) when compared to control subjects. However, the mean C_{max} values increased with severity of hepatic dysfunction and was twofold greater in subjects with severe hepatic dysfunction when compared to control subjects.

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. In ribavirin trials, there were no clinically significant pharmacokinetic differences noted in a single-dose study of eighteen male and eighteen female subjects.

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). Pharmacokinetic evaluations in elderly subjects with ribavirin have not been performed.

Pediatric Patients: Pharmacokinetic evaluations for combination PegIntron™ and REBETOL® therapy in pediatric subjects have not been performed.

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 (dapson) 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**).

Zidovudine, Lamivudine, and Stavudine: Ribavirin has been shown in cell culture to inhibit phosphorylation of lamivudine, and stavudine and zidovudine. 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. (see **PRECAUTIONS: Drug Interactions**).

Didanosine: 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

Clinical Study 1 evaluated PegIntron monotherapy. See PegIntron Powder for Injection Package Insert for information about this study.

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)

¹Serum 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. Response to treatment was defined as undetectable HCV RNA (100 copies/mL) at 24 weeks posttreatment.

Patients with viral genotype 1, regardless of viral load, had a lower response rate to PegIntron™ (1.5 mcg/kg)/REBETOL® (800 mg) 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 in this study.

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.

PegIntron™/REBETOL® Combination Therapy-Study 3

In a large United States community-based study (Study 3), 4913 patients with chronic hepatitis C were randomized to receive PegIntron™ 1.5 mcg/kg SC once weekly (QW) in combination with a REBETOL® dose of 800-1400 mg (weight-based dosing- [WBD]) or 800 mg (Flat) PO daily (in divided doses) for 24 or 48 weeks based on genotype. Response to treatment was defined as undetectable (based on an assay with a lower limit of detection of 125 IU/mL) HCV RNA at 24 weeks post-treatment.

Treatment with PegIntron™ 1.5 mcg/kg and REBETOL® 800-1400 mg resulted in a higher sustained virologic response compared to PegIntron™ in combination with a flat 800 mg daily dose of REBETOL® for all treated patients (p=0.01). Subjects weighing >105 kg obtained the greatest benefit with WBD, although a modest benefit was also observed in subjects weighing >85-105 kg (Table 3). The benefit of WBD in subjects weighing >85 kg was observed with HCV genotypes 1-3. Insufficient data were available to reach conclusions regarding other genotypes. Use of WBD resulted in an increased incidence of anemia (see ADVERSE REACTIONS and Laboratory Values).

Table 3. SVR Rate by Treatment and Baseline Weight- Study 3

Treatment Group	Subject Baseline Weight			
	<65 kg (<143 lb)	65-85 kg (143-188 lb)	>85-105 kg (>188-231 lb)	>105 kg (>231 lb)
WBD*	50% (173/348)	45% (449/994)	42% (351/835)	47% (138/292)

Flat	51% (173/342)	44% (443/1011)	39% (318/819)	33% (91/272)
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* p=0.01, primary efficacy comparison (based on data from subjects weighing 65 kg or higher at baseline and utilizing a logistic regression analysis that includes treatment [WBD or Flat], genotype and presence/absence of advanced fibrosis, in the model).

A total of 1552 subjects weighing >65 kg in Study 3 had genotype 2 or 3 and were randomized to 24 or 48 weeks of therapy. No additional benefit was observed with the longer treatment duration.

INDICATIONS AND USAGE

PegIntron™/REBETOL® Combo Pack therapy is indicated 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™/REBETOL® Combo Pack therapy is contraindicated in:

- Patients with hypersensitivity to PegIntron™ or ribavirin or any other component of the product
- Women who are pregnant
- Men whose female partners are pregnant
- Patients with autoimmune hepatitis
- Patients with hepatic decompensation (Child-Pugh score >6 [class B and C]) in cirrhotic CHC patients before or during treatment.
- Patients with hemoglobinopathies (e.g., thalassemia major, sickle-cell anemia)
- Patients with creatinine clearance <50 mL/min

WARNINGS

Pregnancy

REBETOL® Capsules may cause birth defects and/or death of the exposed fetus. Extreme care must be taken to avoid pregnancy in female patients and in female partners of male patients. REBETOL® has demonstrated significant teratogenic and/or embryocidal effects in all animal species in which adequate studies have been conducted. These effects occurred at doses as low as one

twentieth of the recommended human dose of ribavirin. 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 be instructed to use at least two forms of effective contraception during treatment and during the 6 month period after treatment has been stopped based on multiple-dose half-life of ribavirin of 12 days. Pregnancy testing should occur monthly during REBETOL[®] therapy and for 6 months after therapy has stopped (See BOXED WARNING, CONTRAINDICATIONS and PRECAUTIONS: Information for Patients and Pregnancy Category X).

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. Patients should then be followed as clinically appropriate.

Fatal and nonfatal myocardial infarctions have been reported in patients with anemia caused by REBETOL[®]. Patients should be assessed for underlying cardiac disease before initiation of therapy. Patients with pre-existing cardiac disease should have electrocardiograms administered before treatment, and should be appropriately monitored during therapy. If there is any deterioration of cardiovascular status, therapy should be suspended or discontinued. (See DOSAGE AND ADMINISTRATION: Guidelines for Dose Modification.) Because cardiac disease may be worsened by drug induced anemia, patients with a history of significant or unstable cardiac disease should not use PegIntron[™]/REBETOL[®] Combo Pack (See ADVERSE REACTIONS).

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™/REBETOL® Combo Pack 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™/REBETOL® Combo Pack be discontinued, and the patient followed, with psychiatric intervention as appropriate. In severe cases, PegIntron™/REBETOL® Combo Pack therapy 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™/REBETOL® Combo Pack therapy 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™/REBETOL® Combo Pack 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™/REBETOL® Combo Pack therapy. Patients who develop these conditions during treatment and cannot be controlled with medication should not continue PegIntron™/REBETOL® Combo Pack 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™/REBETOL® Combo Pack therapy should be used cautiously in patients with cardiovascular disease. Patients with a history of myocardial infarction and arrhythmic disorder who require PegIntron™/REBETOL® Combo Pack 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® Combo Pack.

Cerebrovascular disorders

Ischemic and hemorrhagic cerebrovascular events have been observed in patients with interferon alpha-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 alpha-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™/REBETOL® Combo Pack 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™/REBETOL® Combo Pack 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™/REBETOL® Combo Pack 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™/REBETOL® Combo Pack therapy 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. PegIntron™/REBETOL® Combo Pack treatment should be discontinued in patients who develop new or worsening ophthalmologic disorders.

Hypersensitivity

Serious, acute hypersensitivity reactions (e.g., urticaria, angioedema, bronchoconstriction, and 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™/REBETOL® Combo Pack, discontinue treatment and institute appropriate medical therapy immediately. Transient rashes do not necessitate interruption of treatment.

PRECAUTIONS

- PegIntron™ in combination with REBETOL® has not been studied in patients who have failed other alpha interferon treatments.
- The safety and efficacy of PegIntron™ 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 alpha including PegIntron™ therapy. Hypertriglyceridemia may result in pancreatitis (See **WARNINGS: Pancreatitis**). Elevated triglyceride levels should be managed as clinically appropriate. Discontinuation of PegIntron™/REBETOL® Combo Pack 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 alpha 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™/REBETOL® Combo Pack therapy must not be used in patients with creatinine clearance <50 mL/min (See **CLINICAL PHARMACOLOGY, Special populations**).

Information for Patients

Patients receiving PegIntron™/REBETOL® Combo Pack therapy should be directed in its appropriate use, informed of the benefits and risks associated with treatment, and referred to the MEDICATION GUIDE.

Patients must be informed that REBETOL® may cause birth defects and/or death of the unborn child. REBETOL® must not be used by women who are pregnant or by men whose female partners are pregnant. Extreme care must be taken to avoid pregnancy in female patients and in female partners of male patients during treatment with PegIntron™/REBETOL® Combo Pack therapy and for 6 months posttherapy. PegIntron™/REBETOL® Combo Pack therapy should not be initiated until a report of a negative pregnancy test has been obtained immediately prior to

initiation of therapy. Patients must perform a pregnancy test monthly during therapy and for 6 months posttherapy. Women of childbearing potential must be counseled about use of effective contraception (two reliable forms) prior to initiating therapy. Patients (male and female) must be advised of the teratogenic/embryocidal risks and must be instructed to practice effective contraception during treatment and for 6 months posttherapy. Patients (male and female) should be advised to notify the physician immediately in the event of a pregnancy (see **CONTRAINDICATIONS and WARNINGS**).

If pregnancy does occur during treatment or during 6 months posttherapy, the patient must be advised of the teratogenic risk of REBETOL[®] therapy to the fetus. Patients, or partners of patients, should immediately report any pregnancy that occurs during treatment or within 6 months after treatment cessation to their physician. Physicians should report such cases by calling 1-800- 593-2214.

The most common adverse experience occurring with REBETOL[®] Capsules is anemia, which may be severe. (See **ADVERSE REACTIONS**.) 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 disposal of the used 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 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

Pregnancy testing should occur monthly during therapy and for 6 months after therapy has stopped in women of childbearing potential.

PegIntron[™]/REBETOL[®] Combo Pack therapy 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 function. Triglyceride levels are frequently elevated in patients receiving alpha interferon therapy including PegIntron[™] and should be periodically monitored.

Patients on PegIntron[™]/REBETOL[®] Combo Pack 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[™]/REBETOL[®] Combo Pack 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[®] Combo Pack.

Drug Interactions

Caution should be used when administering PegIntron™/REBETOL® Combo Pack therapy 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.

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 alpha interferons 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 should also be considered if worsening clinical toxicities are observed, including hepatic decompensation (e.g., Child-Pugh > 6).

Lamivudine, Stavudine and Zidovudine: Cell culture studies have shown ribavirin can reduce the phosphorylation of pyrimidine nucleoside analogues such as lamivudine, stavudine and zidovudine. Therefore, concomitant use of PegIntron™/REBETOL® Combo Pack therapy with these drugs should be used with caution. However, 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 lamivudine zidovudine

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 alpha 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 and didanosine is not recommended. Reports of fatal hepatic failure, as well as peripheral neuropathy, pancreatitis, and symptomatic hyperlactatemia/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.

Ribavirin did not cause an increase in any tumor type when administered for 6 months in the transgenic p53 deficient mouse model at doses up to 300 mg/kg (estimated human equivalent of 25 mg/kg based on body surface area adjustment for a 60 kg adult; approximately 1.9 times the maximum recommended human daily dose). Ribavirin was non-carcinogenic when administered for 2 years to rats at doses up to 40 mg/kg (estimated human equivalent of 5.71 mg/kg based on body surface area adjustment for a 60 kg adult). However, this dose was less than the maximum tolerated dose, and therefore the study was not adequate to fully characterize the carcinogenic potential of ribavirin.

Ribavirin demonstrated increased incidences of mutation and cell transformation in multiple genotoxicity assays. Ribavirin was active in the Balb/3T3 *In Vitro* Cell Transformation Assay. Mutagenic activity was observed in the mouse lymphoma

assay, and at doses of 20-200 mg/kg (estimated human equivalent of 1.67 - 16.7 mg/kg, based on body surface area adjustment for a 60 kg adult; 0.1 - 1 X the maximum recommended human 24-hour dose of ribavirin) in a mouse micronucleus assay. A dominant lethal assay in rats was negative, indicating that if mutations occurred in rats they were not transmitted through male gametes.

Ribavirin is genotoxic and mutagenic and should be considered a potential carcinogen.

Impairment of Fertility: No reproductive toxicology studies have been performed using peginterferon alfa-2b, recombinant in combination with ribavirin. However, evidence for peginterferon alfa-2b and ribavirin when administered alone indicate that both agents have adverse effects on reproduction. It should be assumed that the effect produced by either agent alone will also be caused by the combination of the two agents.

PegIntron™ may impair human fertility. Irregular menstrual cycles were observed in female cynomolgus monkeys given subcutaneous injections of 4239 mcg/m² 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/m² (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.

Ribavirin demonstrated significant embryocidal and/or teratogenic effects at doses well below the recommended human dose in all animal species in which adequate studies have been conducted.

Fertile women and partners of fertile women should not receive PegIntron™/REBETOL® Combo Pack therapy unless the patient and his/her partner

are using effective contraception (two reliable forms). Based on a multiple dose half-life ($t_{1/2}$) of ribavirin of 12 days, effective contraception must be utilized for 6 months posttherapy (e.g., 15 half-lives of clearance for ribavirin).

REBETOL[®] should be used with caution in fertile men. In studies in mice to evaluate the time course and reversibility of ribavirin-induced testicular degeneration at doses of 15 to 150 mg/kg/day (estimated human equivalent of 1.25 - 12.5 mg/kg/day, based on body surface area adjustment for a 60 kg adult; 0.1 - 0.8 X the maximum human 24-hour dose of ribavirin) administered for 3 or 6 months, abnormalities in sperm occurred. Upon cessation of treatment, essentially total recovery from ribavirin-induced testicular toxicity was apparent within 1 or 2 spermatogenesis cycles.

Animal Toxicology: Long-term studies in the mouse and rat (18 - 24 months; doses of 20 - 75 and 10 - 40 mg/kg/day, respectively {estimated human equivalent doses of 1.67 - 6.25 and 1.43 - 5.71 mg/kg/day, respectively, based on body surface area adjustment for a 60 kg adult; approximately 0.1 - 0.4 X the maximum human 24-hour dose of ribavirin}) have demonstrated a relationship between chronic ribavirin exposure and increased incidences of vascular lesions (microscopic hemorrhages) in mice. In rats, retinal degeneration occurred in controls, but the incidence was increased in ribavirin-treated rats.

Pregnancy Category X (see CONTRAINDICATIONS)

Ribavirin produced significant embryocidal and/or teratogenic effects in all animal species in which adequate studies have been conducted. Malformations of the skull, palate, eye, jaw, limbs, skeleton, and gastrointestinal tract were noted. The incidence and severity of teratogenic effects increased with escalation of the drug dose. Survival of fetuses and offspring was reduced. In conventional embryotoxicity/teratogenicity studies in rats and rabbits, observed no effect dose levels were well below those for proposed clinical use (0.3 mg/kg/day for both the rat and rabbit; approximately 0.06 X the recommended human 24-hour dose of ribavirin). No maternal toxicity or effects on offspring were observed in a

peri/postnatal toxicity study in rats dosed orally at up to 1 mg/kg/day (estimated human equivalent dose of 0.17 mg/kg based on body surface area adjustment for a 60 kg adult; approximately 0.01 X the maximum recommended human 24-hour dose of ribavirin).

Treatment and Posttreatment: Potential Risk to the Fetus: Ribavirin is known to accumulate in intracellular components from where it is cleared very slowly. It is not known whether ribavirin contained in sperm will exert a potential teratogenic effect upon fertilization of the ova. In a study in rats, it was concluded that dominant lethality was not induced by ribavirin at doses up to 200 mg/kg for 5 days (estimated human equivalent doses of 7.14 - 28.6 mg/kg, based on body surface area adjustment for a 60 kg adult; up to 1.7 X the maximum recommended human dose of ribavirin). However, because of the potential human teratogenic effects of ribavirin, male patients should be advised to take every precaution to avoid risk of pregnancy for their female partners.

Women of childbearing potential should not receive PegIntron™/REBETOL® Combo Pack therapy unless they are using effective contraception (two reliable forms) during the therapy period. In addition, effective contraception should be utilized for 6 months posttherapy based on a multiple-dose half-life ($t_{1/2}$) of ribavirin of 12 days.

Male patients and their female partners must practice effective contraception (two reliable forms) during treatment with PegIntron™/REBETOL® Combo Pack and for the 6-month posttherapy period (e.g., 15 half-lives for ribavirin clearance from the body).

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 six 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 serious adverse reactions from the drug in nursing infants, a decision must be made whether to discontinue nursing or discontinue PegIntron™/REBETOL® Combo Pack 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™ 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**). PegIntron™/REBETOL® Combo Pack therapy should not be used in patients with creatinine clearance <50 mL/min.

ADVERSE REACTIONS

The primary toxicity of ribavirin is hemolytic anemia. Reductions in hemoglobin levels occurred within the first 1-4 weeks of therapy. Cardiac and pulmonary events associated with anemia occurred in approximately 10% of patients. (See **WARNINGS**.)

Clinical Trial Experience:

Clinical Study 1 evaluated PegIntron monotherapy. See PegIntron Powder for Injection Package Insert for information about this study.

Study 2 compared combination therapy of PegIntron™/REBETOL® with combination therapy with INTRON® A/REBETOL®. In this study, nearly all study patients in clinical trials experienced one or more adverse events. As shown in **Table 4** the most common adverse events (>5%) in this study were comparable for both the PegIntron™/REBETOL® and INTRON® A/REBETOL® combination therapies.

Table 4. Adverse Events Occurring in >5% of Patients

Adverse Events	Percentage of Patients Reporting Adverse Events*	
	Study 2	
	PegIntron™ 1.5 mcg/kg/ REBETOL® (n=511)	INTRON® A/REBETOL® (n=505)
Application Site		
Injection Site Inflammation/Reaction	75	49
Autonomic Nervous Sys.		
Mouth Dry	12	8
Sweating Increased	11	7
Flushing	4	3
Body as a Whole		
Fatigue/Asthenia	66	63
Headache	62	58
Rigors	48	41
Fever	46	33
Weight Decrease	29	20
RUQ Pain	12	6
Chest Pain	8	7
Malaise	4	6
Central/Periph. Nerv. Sys.		
Dizziness	21	17
Endocrine		
Hypothyroidism	5	4
Gastrointestinal		
Nausea	43	33
Anorexia	32	27

<i>Percentage of Patients Reporting Adverse Events*</i>		
Study 2		
Adverse Events	PegIntron™ 1.5 mcg/kg/ REBETOL® (n=511)	INTRON® A/REBETOL® (n=505)
Diarrhea	22	17
Vomiting	14	12
Abdominal Pain	13	13
Dyspepsia	9	8
Constipation	5	5
Hematologic Disorders		
Neutropenia	26	14
Anemia	12	17
Leukopenia	6	5
Thrombocytopenia	5	2
Liver and Biliary System		
Hepatomegaly	4	4
Musculoskeletal		
Myalgia	56	50
Arthralgia	34	28
Musculoskeletal Pain	21	19
Psychiatric		
Insomnia	40	41
Depression	31	34
Anxiety/Emotional Lability/Irritability	47	47
Concentration Impaired	17	21
Agitation	8	5
Nervousness	6	6
Reproductive, Female		
Menstrual Disorder	7	6
Resistance Mechanism		
Infection Viral	12	12
Infection Fungal	6	1
Respiratory System		
Dyspnea	26	24

<i>Percentage of Patients Reporting Adverse Events*</i>		
Study 2		
Adverse Events	PegIntron™ 1.5 mcg/kg/ REBETOL® (n=511)	INTRON® A/REBETOL® (n=505)
Coughing	23	16
Pharyngitis	12	13
Rhinitis	8	6
Sinusitis	6	5
Skin and Appendages		
Alopecia	36	32
Pruritus	29	28
Rash	24	23
Skin Dry	24	23
Special Senses Other,		
Taste Perversion	9	4
Vision Disorders		
Vision Blurred	5	6
Conjunctivitis	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.

The adverse event profile in Study 3, which compared PegIntron/weight-based REBETOL combination to a PegIntron/flat dose REBETOL regimen, revealed an increased rate of anemia with weight-based dosing (29% vs. 19% for weight-based vs. flat dose regimens, respectively). However, the majority of cases of anemia were mild and responded to dose reductions. The incidence of serious adverse events was comparable in all studies. In Study 2, the incidence of serious adverse events was 17% in the PegIntron™/REBETOL® group. In Study 3, there was a similar incidence of serious adverse events reported for the weight-based REBETOL® group (12%) and with the flat dose REBETOL® regimen.

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. There have been 19 patient

deaths which occurred during treatment or during follow-up in these clinical trials. There was one suicide in a patient receiving PegIntron monotherapy and two deaths among patients receiving INTRON A monotherapy (1 murder/suicide and 1 sudden death). In Study 2, there was one suicide in a patient receiving PegIntron/REBETOL combination therapy; and 1 patient death in the INTRON A/REBETOL group (motor vehicle accident). In Study 3, there were 14 deaths, 2 of which were probable suicides and one was an unexplained death in a person with a relevant medical history of depression.

In Study 2, 14% of patients receiving PegIntron™ in combination with REBETOL®, discontinued therapy compared with 13% treated with INTRON® A in combination with REBETOL®. Similarly in Study 3, 15% of patients receiving PegIntron™ in combination with weight-based REBETOL® and 14% of patients receiving PegIntron™ and flat dose REBETOL® discontinued therapy. The most common reasons for discontinuation of therapy were related to known interferon effects of psychiatric, systemic (e.g., fatigue, headache), or gastrointestinal adverse events.

In Study 2, 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 Study 3, dose modifications due to adverse events occurred more frequently with WBD compared flat dosing (29% and 23%, respectively).

In the PegIntron™/REBETOL® combination trials, the most common adverse events were psychiatric which occurred among 77% of patients in Study 2 and 68-69% of patients in Study 3. These psychiatric adverse events 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™ induces fatigue or headache in approximately two-thirds of patients, with fever or rigors in approximately half of the patients. The severity of some of these systemic symptoms (e.g., fever and headache) tends to decrease as treatment continues.

In Study 2, 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. In Study 3 there was a 23-24% incidence overall for injection site reactions or inflammation.

In Study 2, 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 PegIntron™ 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 $\leq 1\%$ 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™ 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. Hemoglobin levels decreased to <11 g/dL in about 30% of patients in Study 2. In Study 3, 47% of patients receiving WBD REBETOL® and 33% on flat dose REBETOL® had decreases in hemoglobin levels <11 g/dL. Reduction in hemoglobin to <9 g/dL occurred more frequently in patients receiving WBD compared to flat dosing (4% and 2%, respectively). In Study 2, dose modification was required in 9% and 13% of patients in the PegIntron™/REBETOL® and INTRON® A/REBETOL® groups. The typical pattern observed was a decrease in hemoglobin levels by treatment week 4 followed by stabilization and a plateau, which was maintained to the end of treatment. Hemoglobin levels return to baseline between 4 and 12 weeks posttreatment (see **DOSAGE AND ADMINISTRATION: Dose Reduction**).

Neutrophils. Decreases in neutrophil counts were observed in a majority of patients treated with PegIntron™/REBETOL® combination therapy (85%) and INTRON® A/REBETOL® (60%) in Study 2. Severe potentially life-threatening neutropenia (<0.5 x 10⁹/L) occurred in 2% of patients treated with INTRON® A/REBETOL®, and in approximately 4% of patients treated with PegIntron™/REBETOL®. In Study 2, 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 4 weeks after cessation of therapy. (See **DOSAGE AND ADMINISTRATION: Dose Reduction**.)

Platelets. Platelet counts decreased to $<100,000/\text{mm}^3$ in approximately 20% of patients treated with PegIntron™/REBETOL® and in 6% of patients treated with INTRON® A/REBETOL®. Severe decreases in platelet counts ($<50,000/\text{mm}^3$) occur in $<4\%$ of patients. Patients may require discontinuation or dose modification as a result of platelet decreases. (See **DOSAGE AND ADMINISTRATION: Dose Reduction.**) In Study 2, 1% or 3% of patients required dose modification of INTRON® A or PegIntron™, respectively. Platelet counts generally returned to pretreatment levels 4 weeks after the cessation of therapy.

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

Thyroid Function. Development of TSH abnormalities, with and without clinical manifestations, are associated with interferon therapies. In Study 2, 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 Study 2, 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, and vertigo. In addition, the following adverse reactions have been identified during use with PegIntron™/REBETOL® combination therapy: hearing disorder, aplastic anemia 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. 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 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.

Treatment discontinuation is also recommended for patients who do not achieve an undetectable HCV RNA viral load at 24 weeks of therapy. The recommended dose of PegIntron™ is 1.5 mcg/kg/week in combination with 800-1400 mg REBETOL® based on patient body weight. The volume of PegIntron™ to be injected depends on the strength of PegIntron™ and patient's body weight. (See **Table 5.**)

The treatment duration for patients with genotype 1 is 48 weeks. Patients with genotype 2 and 3 should be treated for 24 weeks.

TABLE 5. Recommended PegIntron™/REBETOL® Combo Pack Therapy Dosing

Body weight kg (lbs)	PegIntron™ REDIPEN® Strength to Use	Amount of PegIntron™ (mcg) to Administer	Volume (mL)* of PegIntron™ to Administer	REBETOL® Daily Dose	REBETOL® Number of Capsules
<40 (<87)	50 mcg per 0.5 mL	50	0.5	800 mg/day	2 x 200 mgcapsules A.M. 2 x 200 mgcapsules P.M.
40-50 (87-111)	80 mcg per 0.5 mL	64	0.4	800 mg/day	2 x 200 mg capsules A.M. 2 x 200 mg capsules P.M.
51-60 (112-133)		80	0.5	800 mg/day	2 x 200 mg capsules A.M. 2 x 200 mg capsules P.M.
61-65 (134-144)	120 mcg per 0.5 mL	96	0.4	800 mg/day	2 x 200 mg capsules A.M. 2 x 200 mg capsules P.M.
66-75 (145-166)		96	0.4	1000 mg/day	2 x 200 mg capsules A.M. 3 x 200 mg capsules P.M.
76-85 (167-188)		120	0.5	1000 mg/day	2 x 200 mg capsules A.M. 3 x 200 mg capsules P.M.
86-105 (189-231)	150 mcg per 0.5 mL	150	0.5	1200 mg/day	3 x 200 mg capsules A.M. 3 x 200 mg capsules P.M.
>105 (>231)				1400 mg/day	3 x 200 mg capsules A.M. 4 x 200 mg capsules P.M.

* When reconstituted as directed.

REBETOL[®] should be taken with food. PegIntron[™]/REBETOL[®] Combo Pack therapy 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.

Renal Function

PegIntron[™]/REBETOL[®] Combo Pack therapy should not be used in patients with creatinine clearance <50 mL/min. (See **PRECAUTIONS** and **CLINICAL PHARMACOLOGY, Special populations.**) Subjects with impaired renal function and/or those over the age of 50 should be more carefully monitored with respect to development of anemia.

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[™]/REBETOL[®] Combo Pack Therapy 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	Evaluate	Consider	If	(See severe)

	IFN dose 50%	once weekly (office visit at least every other week).	psychiatric consultation. Continue reduced dosing.	symptoms improve and are stable for 4 wks, may resume normal visit schedule. Continue reduced dosing or return to normal dose.	depression)
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™/REBETOL® Combo Pack Therapy for Hematologic Toxicity

Laboratory Values	PegIntron™	REBETOL®
Hgb* <10 g/dL <8.5 g/dL	----- Permanently discontinue	Decrease by 200 mg/day Permanently discontinue
WBC <1.5 x 10 ⁹ /L <1 x 10 ⁹ /L	Reduce dose by 50% Permanently discontinue	----- Permanently discontinue
Neutrophil <0.75 x 10 ⁹ /L <0.5 x 10 ⁹ /L	Reduce dose by 50% Permanently discontinue	----- Permanently discontinue
Platelets <80 x 10 ⁹ /L <50 x 10 ⁹ /L	Reduce dose by 50% 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 >2 g/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 (0.75 mcg/kg) for (1.5 mcg/kg) Combination Therapy

Body weight kg (lbs)	PegIntron™ REDIPEN® Strength to Use	Amount of PegIntron™ (mcg) to Administer	Volume (mL)** of PegIntron™ to Administer
<40 (<87)	50 mcg per 0.5 mL*	25	0.25
40-50 (<87-111)	50 mcg per 0.5 mL	30	0.3
51-60 (112-133)		40	0.4
61-75 (134-166)	50 mcg per 0.5 mL	50	0.5
76-85 (167-188)	80 mcg per 0.5 mL	64	0.4
>85 (>188)		80	0.5

* Must use vial. Minimum delivery for REDIPEN® 0.3 mL

** When reconstituted as directed

Preparation and Administration

PegIntron™ REDIPEN®

PegIntron™ 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 PegIntron™ 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 mcg per 0.5 mL, 80 mcg per 0.5 mL, 120 mcg per 0.5 mL, or 150 mcg 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 the solution if it is discolored or not clear, or if particulates are present.

Keeping the pen upright, attach the supplied needle and select the appropriate PegIntron™ 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 PegIntron™ solution is to be injected subcutaneously.

The PegIntron™ 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.

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

Storage

PegIntron™/REBETOL® Combo Pack package should be stored at 2°- 8°C (36°- 46°F).

When separated, the individual bottle of REBETOL® Capsules should be stored at 25°C (77°F); excursions permitted to 15°-30°C (59°-86°F) [See USP Controlled Room Temperature].

When separated, the 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**.

HOW SUPPLIED

PegIntron™ 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.

REBETOL® 200 mg Capsules are white, opaque capsules with REBETOL®, 200 mg, and the Schering Corporation logo imprinted on the capsule shell.

Each PegIntron™/REBETOL® Combo Pack Consists of:	
A box containing four 50 mcg per 0.5 mL PegIntron™ REDIPEN® Units, each containing 1 B-D® needle and 2 alcohol swabs, and two bottles of 56 REBETOL® Capsules.	(NDC 0085-1367-01)
A box containing four 80 mcg per 0.5 mL PegIntron™ REDIPEN® Units, each containing 1 B-D® needle and 2 alcohol swabs, and two bottles of 56 REBETOL® Capsules.	(NDC 0085-1375-01)
A box containing four 120 mcg per 0.5 mL PegIntron™ REDIPEN® Units, each containing 1 B-D® needle and 2 alcohol swabs, and two bottles of 70 REBETOL® Capsules.	(NDC 0085-1456-01)
A box containing four 150 mcg per 0.5 mL PegIntron™ REDIPEN® Units, each containing 1 B-D® needle and 2 alcohol swabs, and two bottles of 84 REBETOL® Capsules.	(NDC 0085-1555-01)
A box containing four 150 mcg per 0.5 mL PegIntron™ REDIPEN® Units, each containing 1 B-D® needle and 2 alcohol swabs, and two bottles of 98 REBETOL® Capsules.	(NDC 0085-1684-01)

Schering Corporation, Kenilworth, NJ 07033 USA.

5/08

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1 060308.final draft Med Guide

2
3 **MEDICATION GUIDE**

4 **PegIntron™/REBETOL® Combo Pack containing**

5 **PegIntron™ REDIPEN® Single-dose Delivery System (peginterferon alfa-2b) and**
6 **REBETOL® (ribavirin, USP) Capsules**

7
8 **Including appendix with instructions for using PegIntron™ REDIPEN® Single-dose**
9 **Delivery System**

10
11 Read this Medication Guide carefully before you start taking PegIntron™/REBETOL®
12 Combo Pack containing PegIntron™ (Peg In-tron) and REBETOL® (REB-eh-tole). Read
13 the Medication Guide each time you refill your prescription because there may be new
14 information. The information in this Medication Guide does not take the place of talking with
15 your health care provider (doctor, nurse, nurse practitioner, or physician's assistant).
16

17 **What is the most important information I should know about PegIntron™/REBETOL®**
18 **Combo Pack therapy?**

19
20 PegIntron™/REBETOL® Combo Pack is a treatment for some people who are infected with
21 hepatitis C virus. However, PegIntron™/REBETOL® Combo Pack therapy can have serious
22 side effects that may cause death in rare cases. Before you decide to start treatment, you
23 should talk to your health care provider about the possible benefits and side effects of
24 PegIntron™/REBETOL® Combo Pack therapy. If you begin treatment you will need to see
25 your health care provider regularly for medical examinations and lab tests to make sure your
26 treatment is working and to check for side effects.
27

28 **REBETOL® capsules may cause birth defects and/or death of an unborn child. If you**
29 **are pregnant, you or your male partner must not take PegIntron™/REBETOL® Combo**
30 **Pack therapy. You must not become pregnant while either you or your partner are**
31 **being treated with PegIntron™/REBETOL® Combo Pack therapy, or for 6 months**
32 **after stopping therapy. During this time you must use two forms of birth control and**
33 **you must have pregnancy test to show that you are not pregnant. Men and women**
34 **should use birth control while taking the combination therapy and for 6 months**
35 **afterwards. If you or your partner are being treated and you become pregnant, either**
36 **during treatment or within 6 months of stopping treatment, call your health care**
37 **provider right away. There is a Ribavirin Pregnancy Registry that collects information**
38 **about pregnancy outcomes in female patients and female partners of male patients**
39 **exposed to ribavirin. You or your health care provider are encouraged to contact the**
40 **Registry at 1-800-593-2214.**

41
42 Be assured that any information you tell the Registry will be kept confidential. (See
43 "What should I avoid while taking PegIntron™/REBETOL® Combo Pack therapy?")
44

45 **If you are taking PegIntron™/REBETOL® Combo Pack therapy you should call your**
46 **health care provider immediately if you develop any of these symptoms:**



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47
48 **New or worsening mental health problems, such as thoughts about killing or hurting**
49 **yourself or others, trouble breathing, chest pain, severe stomach or lower back pain,**
50 **bloody diarrhea or bloody bowel movements, high fever, bruising, bleeding, or**
51 **decreased vision.**

52
53 The most serious possible side effects of PegIntron™/REBETOL® Combo Pack therapy
54 include:

55
56 **Problems with Pregnancy.** PegIntron™/REBETOL® Combo Pack therapy can cause
57 **death, serious birth defects, or other harm to your unborn child. . If you are a woman**
58 **of childbearing age, you must not become pregnant during treatment and for 6 months**
59 **after you have stopped therapy. You must have a negative pregnancy test immediately**
60 **before beginning treatment, during treatment, and for 6 months after you have stopped**
61 **therapy. Both males and female patients must use effective forms of birth control**
62 **during treatment and for the 6 months after treatment is completed. Male patients**
63 **should use a condom. If you are a female, you must use birth control even if you believe**
64 **that you are not fertile or that your fertility is low. You should talk to your health care**
65 **provider about birth control for you and your partner.**

66
67 **Mental health problems and suicide.** PegIntron™/REBETOL® Combo Pack therapy may
68 cause patients to develop mood or behavioral problems. These can include irritability
69 (getting easily upset) and depression (feeling low, feeling bad about yourself, or feeling
70 hopeless). Some patients may have aggressive behavior. Former drug addicts may fall back
71 into drug addiction or overdose. Some patients think about hurting or killing themselves or
72 other people and some have killed (suicide) or hurt themselves or others. You must tell your
73 health care provider if you are being treated for a mental illness or had treatment in the past
74 for any mental illness, including depression and suicidal behavior. You should tell your
75 health care provider if you have ever been addicted to drugs or alcohol.

76
77 **Heart problems.** Some patients taking PegIntron™/REBETOL® Combo Pack therapy may
78 develop problems with their heart, including low blood pressure, fast heart rate, and very
79 rarely, heart attacks. Tell your health care provider if you have had any heart problems in the
80 past.

81
82 **Blood problems.** PegIntron™/REBETOL® Combo Pack therapy commonly lowers two
83 types of blood cells (white blood cells and platelets). In some patients, these blood counts
84 may fall to dangerously low levels. If your blood counts become very low, this could lead to
85 infections or bleeding.

86
87 REBETOL® can cause anemia, which is a decrease in the number of red blood cells. This
88 can be dangerous, especially for patients who already have heart or circulatory
89 (cardiovascular) or breathing problems. Talk with your health care provider before taking
90 PegIntron™/REBETOL® Combo Pack therapy if you have, or have ever had any
91 cardiovascular problems. Your health care provider should check your red blood cell count



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92 before you start therapy and often during the first 4 weeks of therapy. Your red blood cell
 93 count may be checked more often if you have any heart or breathing problems.

- 94
- 95 • **Do not take REBETOL Capsules or Oral Solution alone to treat hepatitis C**
 96 **infection.** REBETOL Capsules should be used in combination with interferon alfa-2b
 97 (INTRON A) or in combination with peginterferon alfa-2b (PegIntron) for treating
 98 chronic hepatitis C infection in adults. In children, safety and effectiveness of
 99 REBETOL Capsules or Oral Solution has only been shown when used in combination
 100 with interferon alfa-2b (INTRON A). Your health care provider or pharmacist should
 101 give you a copy of the INTRON A or PegIntron Medication Guide. They have
 102 additional important information about combination therapy not covered in this guide.
 103 PegIntron™/REBETOL® Combo Pack is not approved for the treatment of chronic
 104 hepatitis C in children.

105

106 **Body organ problems.** Certain symptoms like severe stomach pain may mean that your
 107 internal organs are being damaged. Cases of weakness, loss of coordination, and numbness
 108 due to stroke have been reported in patients taking combination PegIntron/REBETOL,
 109 including patients with few or no reported risk factors for stroke.

110

111 *For other possible side effects, see "What are the possible side effects of*
 112 *PegIntron™/REBETOL® Combo Pack therapy" in this Medication Guide.*

113

114 **What is PegIntron™/REBETOL® Combo Pack therapy?**

115 PegIntron™/REBETOL® Combo Pack consists of two medications used to treat hepatitis C
 116 infection. Patients with hepatitis C have the virus in their blood and in their liver.
 117 PegIntron™ reduces the amount of virus in the body and helps the body's immune system
 118 fight the virus. REBETOL® (ribavirin) is a drug that helps to fight the viral infection, but
 119 does not work when used by itself to treat chronic hepatitis C.

120

121 It is not known if PegIntron™/REBETOL® Combo Pack therapy can cure hepatitis C
 122 (permanently eliminate the virus), or if it can prevent liver failure or liver cancer that is
 123 caused by hepatitis C infection.

124

125 It is also not known if PegIntron™/REBETOL® Combo Pack therapy will prevent one
 126 infected person from infecting another person with hepatitis C.

127

128 **Who should not take PegIntron™/REBETOL® Combo Pack therapy?**

129 Do not take PegIntron™/REBETOL® Combo Pack therapy if you:

- 130 • are pregnant, planning to get pregnant during treatment or during the 6 months after
 131 treatment, or breast-feeding
- 132
- 133 • are a male patient with a female sexual partner who is pregnant, or plans to become
 134 pregnant at any time while you are being treated with REBETOL®, or during the 6
 135 months after your treatment has ended.

136



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- 137 • have hepatitis caused by your immune system attacking your liver (autoimmune
138 hepatitis) or unstable liver disease.
139
- 140 • had an allergic reaction to another alpha interferon or are allergic to any of the
141 ingredients in PegIntron™ or REBETOL® Capsules. If you have any doubts, ask
142 your health care provider.
143
- 144 • Do not take PegIntron™/REBETOL® Combo Pack therapy if you have abnormal red
145 blood cells such as sickle-cell anemia or thalassemia major.
146

147 **If you have any of the following conditions or serious medical problems, discuss them**
148 **with your health care provider before taking PegIntron™/REBETOL® Combo Pack**
149 **therapy:**

- 150 • depression or anxiety
151 • sleep problems
152 • high blood pressure
153 • previous heart attack, or other heart problems
154 • liver problems (other than hepatitis C infection)
155 • any kind of autoimmune disease (where the body's immune system attacks the body's
156 own cells), such as psoriasis, systemic lupus erythematosus, rheumatoid arthritis
157 • thyroid problems
158 • diabetes
159 • colitis (inflammation of the bowels)
160 • cancer
161 • hepatitis B infection
162 • HIV infection
163 • kidney problems
164 • bleeding problems
165 • alcoholism
166 • drug abuse or addiction
167 • body organ transplant and are taking medicine that keeps your body from rejecting your
168 transplant (suppresses your immune system).
169
170

171 **How should I take PegIntron™/REBETOL® Combo Pack therapy?**

172 Your health care provider will determine the correct dose (based on your weight).
173 PegIntron™/REBETOL® Combo Pack therapy is given for one year. Take your prescribed
174 dose of PegIntron™ ONCE A WEEK, on the same day of each week and at approximately
175 the same time. Take the medicine for the full year and do not take more than the prescribed
176 dose. REBETOL® Capsules should be taken with food. It is important to follow your
177 dosing schedule and your health care providers instructions on how to take your medicines.
178 Under no circumstances should REBETOL Capsules be opened, crushed or broken. When
179 you take REBETOL® with food, more of the medicine (70% more on average) is taken up by
180 your body. You should take REBETOL® the same way every day (twice a day with food) to



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181 keep the medicine in your body at a steady level. This will help your health care provider to
 182 decide how your treatment is working and how to change the number of REBETOL®
 183 capsules you take if you have side effects from REBETOL®. **Be sure to read the**
 184 **Medication Guide for PegIntron™/REBETOL® for complete instructions on how to**
 185 **take this medicine.**

186
 187 You should be completely comfortable with how to prepare PegIntron™, how to set the dose
 188 you take, and how to inject yourself before you use PegIntron™ for the first time.
 189 PegIntron™ comes as a REDIPEN® single-use delivery system. See the attached appendix
 190 for detailed instructions for preparing and giving a dose of PegIntron™.

191
 192 If you miss a dose of the PegIntron™ product, take the missed dose as soon as possible
 193 during the same day or the next day, then continue on your regular dosing schedule. If
 194 several days go by after you miss a dose, check with your health care provider about what to
 195 do. Do not double the next dose or take more than one dose a week without talking to your
 196 health care provider. Call your health care provider right away if you take more than your
 197 prescribed PegIntron™ dose. Your health care provider may wish to examine you more
 198 closely, and take blood for testing.

199
 200 If you miss a dose of REBETOL® capsules, take the missed dose as soon as possible during
 201 the same day. If an entire day has gone by, check with your health care provider about what
 202 to do. Do not double the next dose.

203
 204 You must get regular blood tests to help your health care provider check how the treatment is
 205 working and to check for side effects.

206
 207 Tell your health care provider if you are taking or planning to take other prescription or non-
 208 prescription medicines, including vitamin and mineral supplements and herbal medicines.

209
 210 **What should I avoid while taking PegIntron™/REBETOL® Combo Pack therapy?**

211 • If you are pregnant do not start taking PegIntron™/REBETOL® Combo Pack therapy.
 212 • Avoid becoming pregnant while taking PegIntron™/REBETOL® Combo Pack therapy.
 213 PegIntron™/REBETOL® Combo Pack therapy may harm your unborn child (death or serious
 214 birth defects) or cause you to lose your baby (miscarry). **If you or your partner becomes**
 215 **pregnant during treatment or during the 6 months after treatment with**
 216 **PegIntron™/REBETOL® Combo Pack therapy, immediately report the pregnancy to**
 217 **your health care provider. You or your health care provider should call 1-800-593-**
 218 **2214.** By calling this number, information about you and/or your partner will be added to a
 219 pregnancy registry that will be used to help you and your health care provider make decisions
 220 about your treatment for hepatitis in the future. You, your partner, and/or your health care
 221 provider will be asked to provide follow-up information on the outcome of the pregnancy. Be
 222 assured that any information you tell the Registry will be kept confidential.

223

224

225 • **Breastfeeding.** The medicine may pass through your milk and harm the baby.



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- 226 • **Drinking alcohol**, including beer, wine, and liquor. This may make your liver disease
227 worse.
- 228 • **Taking other medicines**. Take only medicines prescribed or approved by your health
229 care provider. These include prescription and nonprescription medicines and herbal
230 supplements.

231

232 **What are the most common side effects of REBETOL Capsules and Oral Solution?**

233 **The most serious possible side effects of REBETOL Capsules and Oral Solution are:**

234

- 235 • **Harm to unborn children**. REBETOL Capsules and Oral Solution may cause birth
236 defects or death of an unborn child. (For more details, see "What is the most
237 important information I should know about REBETOL Capsules or Oral
238 Solution?")
- 239
- 240 • **Anemia**. Anemia is a reduction in the number of red blood cells you have which can be
241 dangerous, especially if you have heart or breathing problems. Tell your health care
242 provider right away if you feel tired, have chest pain or shortness of breath. These
243 may be signs of low red blood cell counts.
- 244
- 245 • Do not breast-feed your baby while taking PegIntron™.

246

247 **What are the possible side effects of PegIntron™/REBETOL® Combo Pack therapy?**

248

249 **Possible, serious side effects include:**

250 **Mental health problems including suicide, blood problems, heart problems, body organ**
251 **problems**. See "What is the most important information I should know about
252 PegIntron™/REBETOL® Combo Pack therapy?"

253

254 **Other body organ problems**. A few patients have lung problems (such as pneumonia or
255 inflammation of the lung tissue), inflammation of the kidney, and eye disorders.

256

257 **New or worsening autoimmune disease**. Some patients taking PegIntron™/REBETOL®
258 Combo Pack therapy develop autoimmune diseases (a condition where the body's immune
259 cells attack other cells or organs in the body), including rheumatoid arthritis, systemic lupus
260 erythematosus, and psoriasis. In some patients who already have an autoimmune disease, the
261 disease worsens on PegIntron™/REBETOL® Combo Pack therapy.

262

263 **Common but less serious side effects include:**

264

265 **Flu-like symptoms**. Most patients who take PegIntron™/REBETOL® Combo Pack therapy
266 have "flu-like" symptoms (headache, muscle aches, tiredness, and fever). Some of these
267 symptoms (fever, headache) usually lessen after the first few weeks of therapy. You can
268 reduce some of these symptoms by injecting your PegIntron™ dose at bedtime. Over-the-
269 counter pain and fever reducers, such as acetaminophen or ibuprofen, can be used to prevent
270 or reduce the fever and headache.

271



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272 **Extreme fatigue (tiredness).** Many patients become extremely tired while on
 273 PegIntron™/REBETOL® Combo Pack therapy.

274

275 **Appetite problems.** Nausea, loss of appetite, and weight loss, occur commonly.

276

277 **Thyroid problems.** Some patients develop changes in the function of their thyroid.
 278 Symptoms of thyroid changes include the inability to concentrate, feeling cold or hot all the
 279 time, a change in your weight, and changes to your skin.

280

281 **Blood sugar problems.** Some patients develop problems with the way their body controls
 282 their blood sugar, and may develop high blood sugar or diabetes.

283

284 **Skin reactions.** Redness, swelling, and itching are common at the site of injection. If after
 285 several days these symptoms do not disappear, contact your health care provider. You may
 286 get a rash during therapy. If this occurs, your health care provider may recommend
 287 medicine to treat the rash.

288

289 **Hair thinning.** Hair thinning is common during PegIntron™/REBETOL® Combo Pack
 290 treatment. Hair loss stops and hair growth returns after therapy is stopped.

291

292 These are not all of the side effects of PegIntron™/REBETOL® Combo Pack therapy. Your
 293 health care provider or pharmacist can give you a more complete list.

294

295 Call your doctor for medical advice about side effects. You may report side effects to FDA at
 296 1-800-FDA-1088.

297

298 **General advice about prescription medicines:**

299 Medicines are sometimes prescribed for purposes other than those listed in a Medication
 300 Guide. If you have any concerns about PegIntron™/REBETOL® Combo Pack therapy, ask
 301 your health care provider. Your health care provider or pharmacist can give you information
 302 about PegIntron™/REBETOL® Combo Pack therapy that was written for health care
 303 professionals. Do not use PegIntron™/REBETOL® Combo Pack therapy for a condition for
 304 which it was not prescribed. Do not share this medication with other people.

305

306

307 **How do I store my PegIntron™/REBETOL® Combo Pack package?**

308

309 The PegIntron™/REBETOL® Combo Pack package should be stored in the refrigerator at 2°-
 310 8°C (36°-46°F).

311

312 When separated, the individual bottle of REBETOL® Capsules should be stored at room
 313 temperature 25°C (77°F).

314

315 When separated, the PegIntron™ REDIPEN® should be stored in the refrigerator at 2°-8°C
 316 (36°-46°F); avoid exposure to heat. After mixing, the PegIntron™ solution should be used



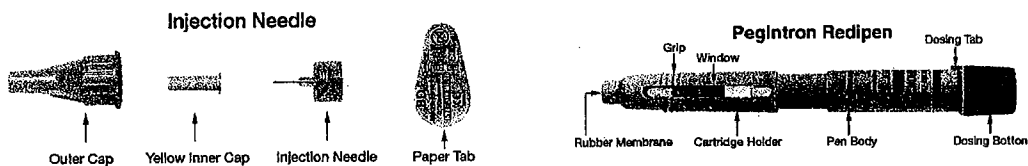
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317 immediately but may be stored in the refrigerator up to 24 hours at 2°-8°C (36°-46°F). The
 318 solution contains no preservatives. DO NOT FREEZE.

319
 320 **How do I prepare and inject the PegIntron™ REDIPEN® Dose?**

321
 322 The PegIntron™ REDIPEN® system is for a single use, by one person only, ONCE A
 323 WEEK. The REDIPEN® must not be shared. Use only the injection needle provided in the
 324 packaging for the PegIntron™ REDIPEN® system. If you have problems with the
 325 REDIPEN® system or the PegIntron™ solution, you should contact your health care
 326 provider, or pharmacist.

327
 328 The following instructions explain how to prepare and inject yourself with the PegIntron™
 329 REDIPEN® system. Please read the instructions carefully and follow them step by step. Your
 330 health care provider will instruct you on how to self-inject with the PegIntron™ REDIPEN®.
 331 Do not attempt to inject yourself unless you are sure you understand the procedure and
 332 requirements for self-injection.



333
 334

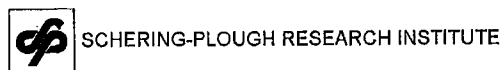
335 **How to use the PegIntron™ REDIPEN® Single-dose Delivery System.**

336

337 **Preparation**

338

- 339 1. Find a clean, well-lit, non-slip flat working surface and assemble all of the supplies you
 340 will need for an injection. All of the supplies you will need are in the PegIntron™
 341 REDIPEN® package. The package contains:
 342 ▪ a PegIntron™ REDIPEN® Single-dose Delivery System
 343 ▪ one disposable needle
 344 ▪ two alcohol swabs, and
 345 ▪ dosing tray (The dosing tray is the bottom half of the REDIPEN® package.)
 346
 347 2. Take the PegIntron™ REDIPEN® out of the refrigerator and allow the medicine to come
 348 to room temperature. Before removing the REDIPEN® from the carton, check the
 349 expiration date printed on the PegIntron™ REDIPEN® carton to make sure that the
 350 expiration date has not passed. Do not use if the expiration date has passed.
 351 3. After taking the PegIntron™ REDIPEN® out of the carton, look in the window of the
 352 REDIPEN® and make sure the PegIntron™ in the cartridge holder window is a white, to
 353 off- white tablet that is whole, in pieces, or powdered.
 354 4. Wash your hands thoroughly with soap and water, rinse, and towel dry. It is important
 355 to keep your work area, your hands, and the injection site clean to minimize the risk of
 356 infection.



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357

358 **1. Mix the Drug**

359

360 **Key points:**

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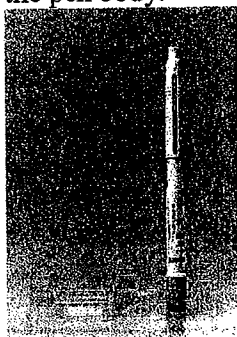
362 **Before you mix the PegIntron™, make sure it is at room temperature. It is important**
363 **that you keep the PegIntron™ REDIPEN® UPRIGHT (Dosing Button down) as shown in**
364 **Figure 1.**

365

366 a. Hold the PegIntron™ REDIPEN® **UPRIGHT (Figure 1a)** in the dosing tray on a hard,
367 flat, non-slip surface with the dosing button **down**. You may want to hold the REDIPEN®
368 using the grip.

369

370 b. To mix the powder and the liquid, keep the REDIPEN® upright in the dosing tray and
371 press the top half of the REDIPEN® downward toward the hard, flat, non-slip surface
372 **until you hear the click** (Figure 1b). Once you've heard the click, you will notice in the
373 window that both dark stoppers are now touching. The dosing button should be flush with
374 the pen body.

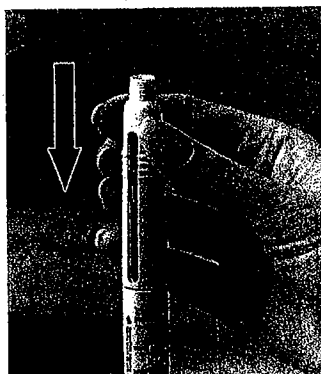


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377 **Figure 1a**

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380 **Figure 1b**

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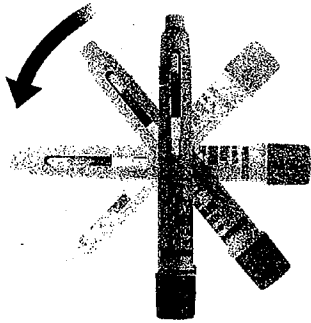
382 c. Wait several seconds for the powder to completely dissolve.

383



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384 d. Gently turn the PegIntron™ REDIPEN® upside down twice (Figure 2). To avoid
385 excessive foaming, DO NOT SHAKE.



386
387 **Figure 2**

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387

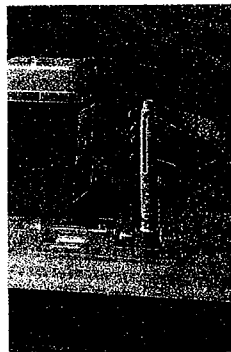
388

389 e. Keep the PegIntron™ REDIPEN® UPRIGHT, with the dosing button down. Then,
390 look through the REDIPEN® window to see that the mixed PegIntron™ solution is
391 completely dissolved. The solution should be clear and colorless **before use**. Before
392 attaching the needle, it is normal to see some small bubbles in the REDIPEN® window,
393 near the top of the solution. Do not use the solution if it is discolored, or not clear, or if
394 particulates are present.

395

396 f. Place the PegIntron™ REDIPEN® back into the dosing tray provided in the
397 packaging (Figure 3). The dosing button will be on the bottom.
398

398



399
400 **Figure 3**

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406 **2. Attach the Needle**

407

408 a. Wipe the rubber membrane of the PegIntron™ REDIPEN® with one alcohol swab.



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409 b. Remove the protective paper tab from the injection needle, but do NOT remove either the
 410 outer cap or the yellow inner cap from the injection needle. Keeping the PegIntron™ REDIPEN®
 411 UPRIGHT in the dosing tray, FIRMLY push the injection needle straight into the REDIPEN®
 412 rubber membrane, and screw it firmly in place, in a clockwise direction (**Figure 4**). Remember
 413 to leave the needle caps in place when you attach the needle to the REDIPEN®. Pushing the
 414 needle through the rubber membrane, “primes” the needle and allows the extra liquid and air in
 415 the pen to be removed.
 416

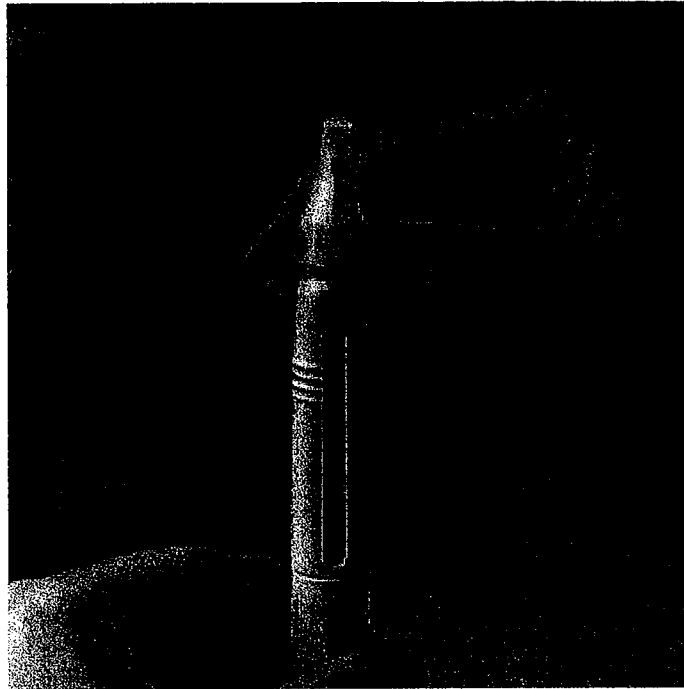


Figure 4

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NOTE: Some fluid will trickle out. This is **normal**. The dark stoppers move up and you will no longer see the fluid in the window once the needle is successfully primed.

3. Dialing the Dose

a. Remove the PegIntron™ REDIPEN® from the dosing tray (**Figure 5a**).
 Holding the PegIntron™ REDIPEN® firmly, pull the dosing button out as far as it will go. -You will see a dark band-

Do not push the dosing button in until you are ready to self-inject the PegIntron™ dose.



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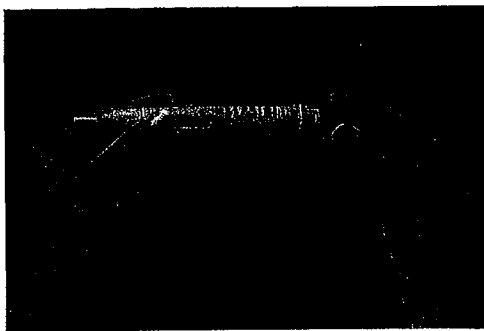


Figure 5a

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b. Turn the dosing button until your prescribed dose is lined up with the dosing tab (Figure 5b). The dosing button will turn freely. If you have trouble dialing your dose, check to make sure the dosing button has been pulled out as far as it will go (Figure 5c).

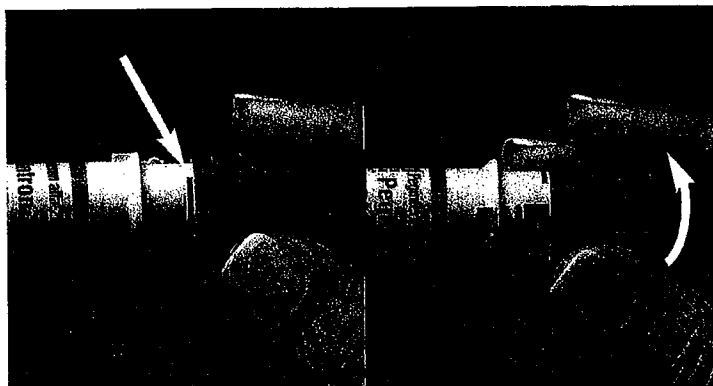


Figure 5b

Figure 5c

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c. Carefully lay the PegIntron™ REDIPEN® down on a hard, flat, non-slip surface. Do NOT remove either of the needle caps and do NOT push the dosing button in until you are ready to self-inject the PegIntron™ dose.

4. Injecting the PegIntron™ Dose
Choosing an Injection Site

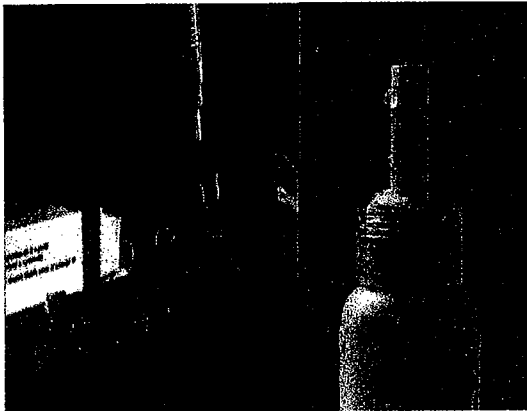
The best sites for giving yourself an injection are those areas with a layer of fat between the skin and muscle, like your thigh, the outer surface of your upper arm, and abdomen. Do not inject yourself in the area near your navel or waistline. If you are very thin, you should only use the thigh or outer surface of the arm for injection.



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460 You should use a different site each time you inject PegIntron™ to avoid soreness at any
461 one site. Do not inject PegIntron™ into an area where the skin is irritated, red, bruised,
462 infected, or has scars, stretch marks, or lumps.

- 463
- 464 a. Clean the skin where the injection is to be given with the second alcohol swab provided,
465 and wait for the area to dry.
- 466 b. Remove the outer cap from the needle (Figure 6a). There may be some liquid around the
467 yellow inner needle cap (Figure 6b). This is normal.
- 468
- 469
- 470



471
472 **Figure 6a**

Figure 6b

- 473
- 474
- 475 c. Once the injection site is dry, remove the yellow inner needle cap (Figure 6c). You are
476 now ready to inject.
- 477



478
479 **Figure 6c**

- 480
- 481 d. Hold the PegIntron™ REDIPEN® with your fingers wrapped around the pen body
482 barrel and your thumb on the dosing button (Figure 7).
- 483
- With your other hand, pinch the skin in the area you have cleaned for injection.



- 484 • Insert the needle into the pinched skin at an angle of 45° to 90°.
- 485 • Press the dosing button down slowly and firmly until you can't push it any further.
- 486 • Keep your thumb pressed down on the dosing button for an additional 5 seconds to
- 487 ensure that you get the complete dose.
- 488 • Remove the needle from your skin.



489
490 **Figure 7**

491 **e. Gently press the injection site with a small bandage or sterile gauze if necessary for a**
492 **few seconds but do not massage the injection site. If there is bleeding, cover with an**
493 **adhesive bandage. DO NOT RECAP THE NEEDLE and DO NOT REUSE the**
494 **REDIPEN®.**

495
496
497 **How do I Dispose of the REDIPEN®?**

498 Discard the REDIPEN® and needle and any solution remaining in the REDIPEN® in a sharps
499 container or other puncture-resistant container like a metal coffee can. DO NOT use glass or
500 clear plastic containers. Ask your health care provider how to dispose of a full container.
501 Always keep the container out of reach of children.

502
503 **After 2 hours, check the injection site for redness, swelling, or tenderness.**
504 **If you have a skin reaction and it doesn't clear up in a few days, contact**
505 **your health care provider.**

506
507 *This Medication Guide has been approved by the U.S. Food and Drug Administration.*

508
509 **Manufactured by: Schering Corporation, Kenilworth, NJ 07033 USA**
510 **DATE 06/08**



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