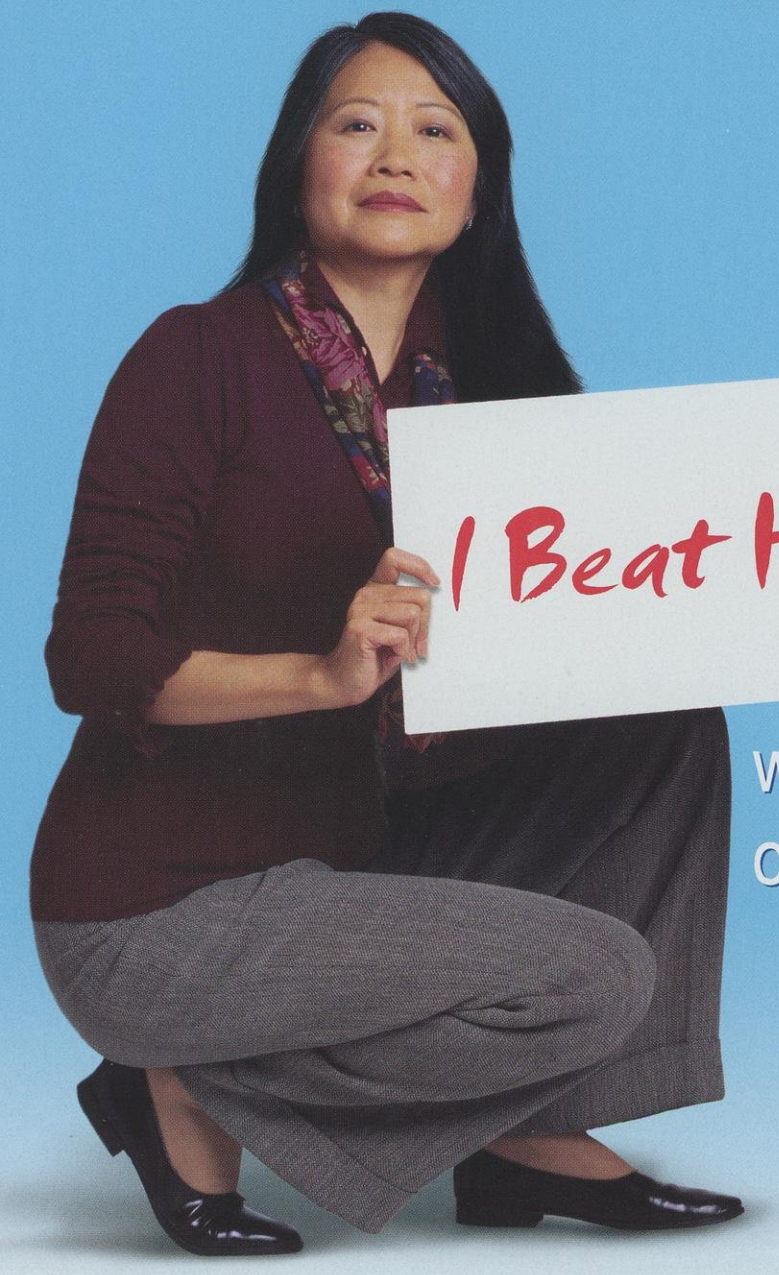
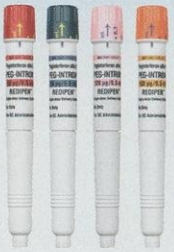
PEG-Intron advertisement.

[s.l.]: [s.n.], 2003



with the proven efficacy of PEG-INTRON®*



PEG-INTRON®
Peginterferon alfa-2b Powder for Injection
REDIPEN®
Single-dose Delivery System

Power to beat HCV

*In a clinical trial with PEG-INTRON®/REBETOL® (Ribavirin, USP) combination therapy, 52% of patients achieved SVR.

PEG-INTRON® is indicated for use alone or with ribavirin for the treatment of chronic hepatitis C in patients with compensated liver disease who have not been previously treated with interferon alpha and who are at least 18 years of age.

Please see following page for Important Safety Information.
Please see brief summary of full Prescribing Information following safety information page.

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Important Safety Information

WARNING

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 Patients with persistently severe or worsening signs or symptoms of these conditions should be withdrawn from therapy.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

Ribavirin causes hemolytic anemia. Anemia associated with REBETOL therapy may exacerbate 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®. It is advised that complete blood counts (CBC) be obtained at baseline and at weeks 2 and 4 of therapy or more frequently if clinically indicated.

REBETOL and combination REBETOL/PEG-INTRON therapy must not be used by women, or male partners of women, who are or may become pregnant during therapy and during the 6 months after stopping therapy. REBETOL and combination REBETOL/PEG-INTRON therapy should not be initiated until a report of a negative pregnancy test has been obtained immediately prior to initiation of therapy. Women of childbearing potential and men must use effective contraception (at least two reliable forms) during treatment and during the 6-month posttreatment follow-up period. Significant teratogenic and/or embryocidal effects have been demonstrated for ribavirin 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 REBETOL®. If pregnancy occurs in a patient or partner of a patient during treatment or during the 6 months after treatment stops, physicians are encouraged to report such cases by calling (800) 727-7064.

PEG-INTRON®

There are no new adverse events specific to PEG-INTRON® as compared to INTRON® A (Interferon alfa-2b, recombinant) for Injection, however, the incidence of some (eg, injection site reactions, fever, rigors, nausea) were higher. The most common adverse events associated with PEG-INTRON® were "flu-like" symptoms, occurring in approximately 50% of patients, which may decrease in severity as treatment continues. Application site disorders were common (47%), but all were mild (44%) or moderate (4%) and no patient discontinued, and included injection site inflammation and reaction (ie, bruise, itchiness, irritation). Injection site pain was reported in 2% of patients receiving PEG-INTRON®. Alopecia (thinning of the hair) is also often associated with alpha interferons including PEG-INTRON®.

Psychiatric adverse events, which include insomnia, were common (57%) with PEG-INTRON®, but similar to INTRON® A (58%). Depression was most common at 29%. Suicidal behavior including ideation, suicidal attempts, and completed suicides occurred in 1% of patients during or shortly after completing treatment with PEG-INTRON®.

PEG-INTRON®/REBETOL® is contraindicated in patients with autoimmune hepatitis, decompensated liver disease, and in patients with hemoglobinopathies (eg, thalassemia major, sickle-cell anemia).

The following serious or clinically significant adverse events have been reported at a frequency ≤1% with PEG-INTRON® or interferon alpha: Severe decreases in neutrophil or platelet counts, hypothyroidism, hyperglycemia, hypotension, arrhythmia, ulcerative and hemorrhagic colitis, development or exacerbation of autoimmune disorders including thyroiditis, RA, systemic lupus erythematosus, psoriasis, pulmonary disorders (dyspnea, pulmonary infiltrates, pneumonitis and pneumonia, some resulting in patient deaths), urticaria, angioedema, bronchoconstriction, anaphylaxis, retinal hemorrhages, and cotton wool spots.

In the PEG-INTRON/REBETOL combination trial the incidence of serious adverse events was 17% in the PEG-INTRON/REBETOL groups compared to 14% in the INTRON A/REBETOL group. The incidence of severe adverse events in the PEG-INTRON/REBETOL combination therapy trial was 23% in the INTRON A/REBETOL group and 31-34% in the PEG-INTRON/REBETOL groups. Dose reductions due to adverse reactions occurred in 42% of patients receiving PEG-INTRON® (1.5 µg/kg)/REBETOL® and in 34% of those receiving INTRON® A/REBETOL®.

REBETOL® should not be used in patients with creatinine clearance <50 mL/min.

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PRODUCT INFORMATION

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

BRIEF SUMMARY (For full Prescribing Information, see package insert.)

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

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

INDICATIONS AND USAGE

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

CONTRAINDICATIONS

PEG-Intron is contraindicated in patients with:

- hypersensitivity to PEG-Intron or any other component of the product
- autoimmune hepatitis
- decompensated liver disease

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

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

WARNINGS

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

Neuropsychiatric events

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

Bone marrow toxicity

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

Endocrine disorders

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

Cardiovascular events

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

Pulmonary disorders

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

Colitis

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

Pancreatitis

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

Autoimmune disorders

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

Ophthalmologic disorders

Decrease or loss of vision, retinopathy including macular edema, retinal artery or vein thrombosis, retinal hemorrhages and cotton wool spots, optic neuritis, and papilledema may be induced or aggravated by treatment with peginterferon alfa-2b or other alpha interferons. All patients should receive an eye examination at baseline. Patients with preexisting ophthalmologic disorders (eg, diabetic or hypertensive retinopathy) should receive periodic ophthalmologic exams during interferon alpha treatment. Any patient who develops ocular symptoms should receive a prompt and complete eye examination. Peginterferon alfa-2b treatment should be discontinued in patients who develop new or worsening ophthalmologic disorders.

Hypersensitivity

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

Use with Ribavirin–(**See also REBETOL Package Insert**.)

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

Anemia

Ribavirin caused hemolytic anemia in 10% of PEG-Intron/REBETOL treated patients within 1-4 weeks of initiation of therapy. Complete blood counts should be obtained pretreatment and at week 2 and week 4 of therapy or more frequently if clinically indicated. Anemia associated with REBETOL therapy may result in a worsening of cardiac disease. Decrease in dosage or discontinuation of REBETOL may be necessary. (See **DOSAGE AND ADMINISTRATION: Dose Reduction.**)

PRECAUTIONS

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

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

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

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

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

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

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

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

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

Patients on PEG-Intron or PEG-Intron/REBETOL combination therapy should have hematology and blood chemistry testing before the start of treatment and then periodically thereafter. In the clinical trial CBC (including hemoglobin, neutrophil and platelet counts) and chemistries (including AST, ALT, bilirubin, and uric acid) were measured during the treatment period at weeks 2, 4, 8, 12, and then at 6-week intervals or more frequently if abnormalities developed. TSH levels were measured every 12 weeks during the treatment period. HCV RNA should be measured at 6 months of treatment. PEG-Intron or PEG-Intron/REBETOL combination therapy should be discontinued in patients with persistent high viral levels.

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

Drug Interactions

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

Carcinogenesis, Mutagenesis, and Impairment of Fertility

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

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

Impairment of Fertility: PEG-Intron may impair human fertility. Irregular menstrual cycles were observed in female cynomolgus monkeys given subcutaneous injections of 4239 µg/m^2 PEG-Intron alone every other day for 1 month (approximately 345 times the recommended weekly human dose based upon body surface area). These effects included transiently decreased serum levels of estradiol and progesterone, suggestive of anovulation. Normal menstrual cycles and serum hormone levels resumed in these animals 2 to 3 months following cessation of PEG-Intron treatment. Every other day dosing with 262 µg/m^2 (approximately 21 times the weekly human dose) had no effects on cycle duration or reproductive hormone status. The effects of PEG-Intron on male fertility have not been studied.

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

Pregnancy Category X : Use with Ribavirin

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

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

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

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

Geriatric: In general, younger patients tend to respond better than older patients to interferon-based therapies. Clinical studies of PEG-Intron alone or in combination with REBETOL did not include sufficient numbers of subjects aged 65 and over, however, to determine whether they respond differently than younger subjects. Treatment with alpha interferons, including PEG-Intron, is associated with neuropsychiatric, cardiac, pulmonary, GI and systemic (flu-like) adverse effects. Because these adverse reactions may be more severe in the elderly, caution should be exercised in the use of PEG-Intron in this population. This drug is known to be substantially excreted by the kidney. Because elderly patients are more likely to have decreased renal function, the risk of toxic reactions to this drug may be greater in patients with impaired renal function (see **CLINICAL PHARMACOLOGY: Special Populations: Renal dysfunction**). REBETOL should not be used in patients with creatinine clearance <50 mL/min. When using PEG-Intron/REBETOL therapy, refer also to the REBETOL Package Insert.

ADVERSE REACTIONS

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

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

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

Overall, 10-14% of patients receiving PEG-Intron, alone or in combination with REBETOL, discontinued therapy compared with 6% treated with INTRON A alone and 13% treated with INTRON A in combination with REBETOL. The most common reasons for discontinuation of therapy were related to psychi-

atric, systemic (eg, fatigue, headache), or gastrointestinal adverse events.

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

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

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

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

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

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

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

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

	*Percentage of Patients Reporting Adverse Events**			
	Study 1		**Study 2**	
Adverse Events	**PEG-Intron 1.0 µg/kg (n=297)**	**INTRON A 3 MIU (n=303)**	**PEG-Intron 1.5 µg/kg/ REBETOL (n=511)**	**INTRON A/ REBETOL (n=505)**
Application Site				
Injection Site Inflammation/Reaction	47	20	75	49
Autonomic Nervous Sys.				
Mouth Dry	6	7	12	8
Sweating Increased	6	7	11	7
Flushing	6	3	4	3
Body as a Whole				
Fatigue/Asthenia	52	54	66	63
Headache	56	52	62	58
Rigors	23	19	48	41
Fever	22	12	46	33
Weight Decrease	11	13	29	20
RUQ Pain	8	8	12	6
Chest Pain	6	4	8	7
Malaise	7	6	4	6
Central/Periph. Nerv. Sys.				
Dizziness	12	10	21	17
Endocrine				
Hypothyroidism	5	3	5	4
Gastrointestinal				
Nausea	26	20	43	33
Anorexia	20	17	32	27
Diarrhea	18	16	22	17
Vomiting	7	6	14	12
Abdominal Pain	15	11	13	13
Dyspepsia	6	7	9	8
Constipation	1	3	5	5
Hematologic Disorders				
Neutropenia	6	2	26	14
Anemia	0	0	12	17
Leukopenia	<1	0	6	5
Thrombocytopenia	7	<1	5	2
Liver and Biliary System				
Hepatomegaly	6	5	4	4
Musculoskeletal				
Myalgia	54	53	56	50
Arthralgia	23	27	34	28
Musculoskeletal Pain	28	22	21	19
Psychiatric				
Insomnia	23	23	40	41
Depression	29	25	31	34
Anxiety/Emotional Lability/Irritability	28	34	47	47
Concentration Impaired	10	8	17	21
Agitation	2	2	8	5
Nervousness	4	3	6	6
Reproductive, Female				
Menstrual Disorder	4	3	7	6
Resistance Mechanism				
Infection Viral	11	10	12	12
Infection Fungal	<1	3	6	1
Respiratory System				
Dyspnea	4	2	26	24
Coughing	8	5	23	16
Pharyngitis	10	7	12	13
Rhinitis	2	2	8	6
Sinusitis	7	7	6	5
Skin and Appendages				
Alopecia	22	22	36	32
Pruritus	12	8	29	28
Rash	6	7	24	23
Skin Dry	11	9	24	23
Special Senses, Other				
Taste Perversion	<1	2	9	4
Vision Disorders				
Vision Blurred	2	3	5	6
Conjunctivitis	4	2	4	5

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

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

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

Laboratory Values

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

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

Neutrophils. Decreases in neutrophil counts were observed in a majority of patients treated with PEG-Intron alone (70%) or as combination therapy with REBETOL (85%) and INTRON A/REBETOL (60%). Severe potentially life-threatening neutropenia (<0.5 x 10^9/L) occurred in 1% of patients treated with PEG-Intron monotherapy, 2% of patients treated with INTRON A/REBETOL and in 4% of patients treated with PEG-Intron/REBETOL. Two percent of patients receiving PEG-Intron monotherapy and 18% of patients receiving PEG-Intron/REBETOL required modification of interferon dosage. Few patients (≤1%) required permanent discontinuation of treatment. Neutrophil counts generally return to pretreatment levels within 4 weeks of cessation of therapy. (See **DOSAGE AND ADMINISTRATION: Dose Reduction**.)

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

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

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

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

Postmarketing Experience

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

Immunogenicity: Approximately 2% of patients receiving PEG-Intron (32/1759) or INTRON A (11/728) with or without REBETOL developed low-titer (≤160) neutralizing antibodies to PEG-Intron or INTRON A. The clinical and pathological significance of the appearance of serum neutralizing antibodies is unknown. No apparent correlation of antibody development to clinical response or adverse events was observed. The incidence of posttreatment binding antibody ranged from 8 to 15 percent. The data reflect the percentage of patients whose test results were considered positive for antibodies to PEG-Intron in a Biacore assay that is used to measure binding antibodies, and in an antiviral neutralization assay, which measures serum-neutralizing antibodies. The percentage of patients whose test results were considered positive for antibodies is highly dependent on the sensitivity and specificity of the assays. Additionally the observed incidence of antibody positivity in these assays may be influenced by several factors including sample timing and handling, concomitant medications, and underlying disease. For these reasons, comparison of the incidence of antibodies to PEG-Intron with the incidence of antibodies to other products may be misleading.

OVERDOSAGE

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

Schering®

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Kenilworth, NJ 07033 USA

Rev. 2/05

27664431T-JBS

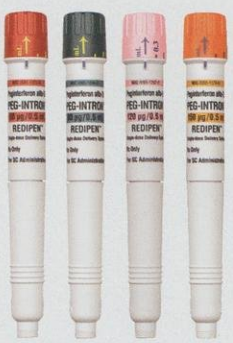

Power to face
HepC
head on

*In a clinical trial with PEG-INTRON®/REBETOL® (Ribavirin, USP) combination therapy, 52% of patients achieved SVR.

PEG-INTRON® is indicated for use alone or with ribavirin for the treatment of chronic hepatitis C in patients with compensated liver disease who have not been previously treated with interferon alpha and who are at least 18 years of age.

Please see following page for Important Safety Information.
Please see brief summary of full Prescribing Information following safety information page.

the proven efficacy of PEG-INTRON®*



PEG-INTRON®

Peginterferon alfa-2b Powder for Injection

REDIPEN™

Single-dose Delivery System

Power to beat HCV*

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Peginterferon alfa-2b Powder for Injection
REDIPEN™
Single-dose Delivery System

Power to beat HCV*

*In a clinical trial with PEG-INTRON®/REBETOL® (Ribavirin, USP) combination therapy, 52% of patients achieved SVR.

Important Safety Information

WARNING

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

Ribavirin causes hemolytic anemia. Anemia associated with REBETOL therapy may exacerbate 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®. It is advised that complete blood counts (CBC) be obtained at baseline and at weeks 2 and 4 of therapy or more frequently if clinically indicated.

REBETOL and combination REBETOL/PEG-INTRON therapy must not be used by women, or male partners of women, who are or may become pregnant during therapy and during the 6 months after stopping therapy. REBETOL and combination REBETOL/PEG-INTRON therapy should not be initiated until a report of a negative pregnancy test has been obtained immediately prior to initiation of therapy. Women of childbearing potential and men must use effective contraception (at least two reliable forms) during treatment and during the 6-month posttreatment follow-up period. Significant teratogenic and/or embryocidal effects have been demonstrated for ribavirin 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 REBETOL®. If pregnancy occurs in a patient or partner of a patient during treatment or during the 6 months after treatment stops, physicians are encouraged to report such cases by calling (800) 727-7064.

PEG-INTRON®

There are no new adverse events specific to PEG-INTRON® as compared to INTRON® A (Interferon alfa-2b, recombinant) for Injection, however, the incidence of some (eg, injection site reactions, fever, rigors, nausea) were higher. The most common adverse events associated with PEG-INTRON® were "flu-like" symptoms, occurring in approximately 50% of patients, which may decrease in severity as treatment continues. Application site disorders were common (47%), but all were mild (44%) or moderate (4%) and no patient discontinued, and included injection site inflammation and reaction (ie, bruise, itchiness, irritation). Injection site pain was reported in 2% of patients receiving PEG-INTRON®. Alopecia (thinning of the hair) is also often associated with alpha interferons including PEG-INTRON®.

Psychiatric adverse events, which include insomnia, were common (57%) with PEG-INTRON®, but similar to INTRON® A (58%). Depression was most common at 29%. Suicidal behavior including ideation, suicidal attempts, and completed suicides occurred in 1% of patients during or shortly after completing treatment with PEG-INTRON®.

PEG-INTRON®/REBETOL® is contraindicated in patients with autoimmune hepatitis, decompensated liver disease, and in patients with hemoglobinopathies (eg, thalassemia major, sickle-cell anemia).

The following serious or clinically significant adverse events have been reported at a frequency ≤1% with PEG-INTRON® or interferon alpha: Severe decreases in neutrophil or platelet counts, hypothyroidism, hyperglycemia, hypotension, arrhythmia, ulcerative and hemorrhagic colitis, development or exacerbation of autoimmune disorders including thyroiditis, RA, systemic lupus erythematosus, psoriasis, pulmonary disorders (dyspnea, pulmonary infiltrates, pneumonitis and pneumonia, some resulting in patient deaths), urticaria, angioedema, bronchoconstriction, anaphylaxis, retinal hemorrhages, and cotton wool spots.

In the PEG-INTRON/REBETOL combination trial the incidence of serious adverse events was 17% in the PEG-INTRON/REBETOL groups compared to 14% in the INTRON A/REBETOL group. The incidence of severe adverse events in the PEG-INTRON/REBETOL combination therapy was 23% in the INTRON A/REBETOL group and 31-34% in the PEG-INTRON/REBETOL groups. Dose reductions due to adverse reactions occurred in 42% of patients receiving PEG-INTRON® (1.5 µg/kg)/REBETOL® and in 34% of those receiving INTRON® A/REBETOL®.

REBETOL® should not be used in patients with creatinine clearance <50 mL/min.

Printed in USA PG0478 5/04

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

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

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

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

CONTRAINDICATIONS
PEG-Intron is contraindicated in patients with:
- hypersensitivity to PEG-Intron or any other component of the product
- autoimmune hepatitis
- decompensated liver disease

PEG-Intron/REBETOL combination therapy is additionally contraindicated in:
- patients with hypersensitivity to ribavirin or any other component of the product
- women who are pregnant
- men whose female partners are pregnant
- patients with hemoglobinopathies (e.g., thalassemia major, sickle-cell anemia)

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

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

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

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

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

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

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

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

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

Ophthalmologic disorders
Decrease or loss of vision, retinopathy including macular edema, retinal artery or vein thrombosis, retinal hemorrhages and cotton wool spots, optic neuritis, and papilledema may be induced or aggravated by treatment with peginterferon alfa-2b or other alpha interferons. All patients should receive an eye examination at baseline. Patients with preexisting ophthalmologic disorders (e.g. diabetic or hypertensive retinopathy) should receive periodic ophthalmologic exams during interferon alpha treatment. Any patient who develops ocular symptoms should receive a prompt and complete eye examination. Peginterferon alfa-2b treatment should be discontinued in patients who develop new or worsening ophthalmologic disorders.

Hypersensitivity
Serious, acute hypersensitivity reactions (e.g., urticaria, angioedema, bronchoconstriction, anaphylaxis) have been rarely observed during alpha interferon therapy. If such a reaction develops during treatment with PEG-Intron, discontinue treatment and institute appropriate medical therapy immediately. Transient rashes do not necessitate interruption of treatment.

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

Anemia
Ribavirin caused hemolytic anemia in 10% of PEG-Intron/REBETOL treated patients within 1-4 weeks of [illegible] of therapy. Complete blood counts should be obtained pretreatment and at week 2 and week 4 [illegible] or more frequently if clinically indicated. Anemia associated with REBETOL therapy may result [illegible]ning of cardiac disease. Decrease in dosage or discontinuation of REBETOL may be necessary. [illegible]AGE AND ADMINISTRATION: Dose Reduction.)

PRECAUTIONS
- PEG-Intron alone or in combination with REBETOL has not been studied in patients who have failed other alpha interferon treatments.
- The safety and efficacy of PEG-Intron alone or in combination with REBETOL for the treatment of hepatitis C in liver or other organ transplant recipients have not been studied. Preliminary data indicates that interferon alpha therapy may be associated with an increased rate of kidney graft rejection. Liver graft rejection has also been reported but a causal association to interferon alpha therapy has not been established.
- The safety and efficacy of PEG-Intron/REBETOL for the treatment of patients with HCV co-infected with HIV or HBV have not been established.

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

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

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

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

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

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

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

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

Patients on PEG-Intron or PEG-Intron/REBETOL combination therapy should have hematology and blood chemistry testing before the start of treatment and then periodically thereafter. In the clinical trial CBC (including hemoglobin, neutrophil and platelet counts) and chemistries (including AST, ALT, bilirubin, and uric acid) were measured during the treatment period at weeks 2, 4, 8, 12, and then at 6-week intervals or more frequently if abnormalities developed. TSH levels were measured every 12 weeks during the treatment period.

HCV RNA should be measured at 6 months of treatment. PEG-Intron or PEG-Intron/REBETOL combination therapy should be discontinued in patients with persistent high viral levels.

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

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

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

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

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

Nursing Mothers: It is not known whether the components of PEG-Intron are excreted in human milk. Because of the potential for adverse reactions from the drug in nursing infants, a decision must be made whether to discontinue nursing or discontinue the treatment, taking into account the importance of the product to the mother.

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

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

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

Geriatric. In general, younger patients tend to respond better than older patients to interferon-based therapies. Clinical studies of PEG-Intron alone or in combination with REBETOL did not include sufficient numbers of subjects aged 65 and over, however, to determine whether they respond differently than younger subjects. Treatment with alpha interferons, including PEG-Intron, is associated with neuropsychiatric, cardiac, pulmonary, GI and systemic (flu-like) adverse effects. Because these adverse reactions may be more severe in the elderly, caution should be exercised in use of PEG-Intron in this population. This drug is known to be substantially excreted by the kidney. Because elderly patients are more likely to have decreased renal function, the risk of toxic reactions to this drug may be greater in patients with impaired renal function. REBETOL should not be used in patients with creatinine clearance <50 mL/min. When using PEG-Intron/REBETOL therapy, refer also to the REBETOL Medication Guide.

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

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

ideation or attempt) and one patient accomplished suicide.

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

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

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

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

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

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

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

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

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

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

*Percentage of Patients Reporting Adverse Events**

	Study 1		Study 2	
Adverse Events	**PEG-Intron 1.0 μg/kg (n=297)**	**INTRON A 3 MIU (n=303)**	**PEG-Intron 1.5 μg/kg/ REBETOL (n=511)**	**INTRON A/ REBETOL (n=505)**
Application Site				
Injection Site Inflammation/Reaction	47	20	75	49
Autonomic Nervous Sys.				
Mouth Dry	6	7	12	8
Sweating Increased	6	7	11	7
Flushing	6	3	4	3
Body as a Whole				
Fatigue/Asthenia	52	54	66	63
Headache	56	52	62	58
Rigors	23	19	48	41
Fever	22	12	46	33
Weight Decrease	11	13	29	20
RUQ Pain	8	8	12	6
Chest Pain	6	4	8	7
Malaise	7	6	4	6
Central/Periph. Nerv. Sys.				
Dizziness	12	10	21	17
Endocrine				
Hypothyroidism	5	3	5	4
Gastrointestinal				
Nausea	26	20	43	33
Anorexia	20	17	32	27
Diarrhea	18	16	22	17
Vomiting	7	6	14	12
Abdominal Pain	15	11	13	13
Dyspepsia	6	7	9	8
Constipation	1	3	5	5
Hematologic Disorders				
Neutropenia	6	2	26	14
Anemia	0	0	12	17
Leukopenia	<1	0	6	5
Thrombocytopenia	7	<1	5	2
Liver and Biliary System				
Hepatomegaly	6	5	4	4
Musculoskeletal				
Myalgia	54	53	56	50
Arthralgia	23	27	34	28
Musculoskeletal Pain	28	22	21	19
Psychiatric				
Insomnia	23	23	40	41
Depression	29	25	31	34
Anxiety/Emotional Lability/Irritability	28	34	47	47
Concentration Impaired	10	8	17	21
Agitation	2	2	8	5
Nervousness	4	3	6	6
Reproductive, Female				
Menstrual Disorder	4	3	7	6
Resistance Mechanism				
Infection Viral	11	10	12	12
Infection Fungal	<1	3	6	1
Respiratory System				
Dyspnea	4	2	26	24
Coughing	8	5	23	16
Pharyngitis	10	7	12	13
Rhinitis	2	2	8	6
Sinusitis	7	7	6	5
Skin and Appendages				
Alopecia	22	22	36	32
Pruritus	12	8	29	28
Rash	6	7	24	23
Skin Dry	11	9	24	23
Special Senses Other,				
Taste Perversion	<1	2	9	4
Vision Disorders				
Vision blurred	2	3	5	6
Conjunctivitis	4	2	4	5

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

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

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

Laboratory Values

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

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

Neutrophils. Decreases in neutrophil counts were observed in a majority of patients treated with PEG-Intron alone (70%) or as combination therapy with REBETOL (85%) and INTRON A/REBETOL (60%). Severe potentially life-threatening neutropenia (<0.5 x 10^9/L) occurred in 1% of patients treated with PEG-Intron monotherapy, 2% of patients treated with INTRON A/REBETOL and in 4% of patients treated with PEG-Intron/REBETOL. Two percent of patients receiving PEG-Intron monotherapy and 18% of patients receiving PEG-Intron/REBETOL required modification of interferon dosage. Few patients (≤1%) required permanent discontinuation of treatment. Neutrophil counts generally return to pre-treatment levels within 4 weeks of cessation of therapy. (**See DOSAGE AND ADMINISTRATION: Dose Reduction**).

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

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

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

Postmarketing Experience

The following adverse reactions have been identified and reported during post-approval use of PEG-Intron therapy: seizures, hearing impairment, hearing loss, and peripheral neuropathy, cardiac ischemia, rhabdomyolysis, stomatitis, vertigo, renal insufficiency, renal failure, Stevens Johnson Syndrome, toxic epidermal necrolysis, and erythema multiforme. Because the reports of these reactions are voluntary and the population of uncertain size, it is not always possible to reliably estimate the frequency of the reaction or establish a causal relationship to drug exposure.

Immunogenicity: Approximately 2% of patients receiving PEG-Intron (32/1759) or INTRON A (11/728) with or without REBETOL developed low-titer (≤160) neutralizing antibodies to PEG-Intron or INTRON A. The clinical and pathological significance of the appearance of serum neutralizing antibodies is unknown. No apparent correlation of antibody development to clinical response or adverse events was observed. The incidence of posttreatment binding antibody ranged from 8 to 15 percent. The data reflect the percentage of patients whose test results were considered positive for antibodies to PEG-Intron in a Biacore assay that is used to measure binding antibodies, and in an antiviral neutralization assay, which measures serum-neutralizing antibodies. The percentage of patients whose test results were considered positive for antibodies is highly dependent on the sensitivity and specificity of the assays. Additionally the observed incidence of antibody positivity in these assays may be influenced by several factors including sample timing and handling, concomitant medications, and underlying disease. For these reasons, comparison of the incidence of antibodies to PEG-Intron with the incidence of antibodies to other products may be misleading.

OVERDOSAGE

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

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Schering Corporation
Kenilworth, NJ 07033 USA

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