HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use REBETOL safely and effectively. See full prescribing information for REBETOL.
REBETOL® (ribavirin USP) Capsules, Oral Solution
Initial U.S. Approval: 1998

WARNING: RISK OF SERIOUS DISORDERS AND RIBAVIRIN-ASSOCIATED EFFECTS

See full prescribing information for complete boxed warning.

- **REBETOL monotherapy is not effective for the treatment of chronic hepatitis C (5.10).**
- **The hemolytic anemia associated with REBETOL therapy may result in 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 (2.4, 5.2, 6.1).**
- **Significant teratogenic and embryocidal effects have been demonstrated in all animal species exposed to ribavirin. 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 (4, 5.1, 8.1, 13.1, 17.2).**

----------INDICATIONS AND USAGE----------
REBETOL is a nucleoside analogue indicated in combination with interferon alfa-2b (pegylated and nonpegylated) for the treatment of Chronic Hepatitis C (CHC) in patients 3 years of age or older with compensated liver disease. (1.1)

Patients with the following characteristics are less likely to benefit from re-treatment after failing a course of therapy: previous nonresponse, previous pegylated interferon treatment, significant bridging fibrosis or cirrhosis, and genotype 1 infection.

----------DOSAGE AND ADMINISTRATION----------
REBETOL is administered according to body weight. (2.1, 2.2)
Dose reduction or discontinuation is recommended in patients experiencing certain adverse reactions or renal dysfunction. (2.4, 2.5, 12.3)

----------DOSAGE FORMS AND STRENGTHS----------
REBETOL Capsules 200 mg (3)
REBETOL Oral Solution 40 mg per mL (3)

----------CONTRAINDICATIONS----------
- Pregnant women and men whose female partners are pregnant (4, 8.1)
- Known hypersensitivity reactions such as Stevens-Johnson syndrome, toxic, epidermal necrolysis, and erythema multiforme to ribavirin or any component of the product (4)
- Autoimmune hepatitis (4)
- Hemoglobinopathies (4)
- Creatinine clearance less than 50 mL/min (4)
- Coadministration with didanosine (4, 7.1)

----------WARNINGS AND PRECAUTIONS----------
- *Pregnancy Category X* (5.1, 8.1, 8.3)
  - Birth defects and fetal death with ribavirin: Patients must have a negative pregnancy test prior to therapy; use at least 2 forms of contraception and undergo monthly pregnancy tests.

Patients exhibiting the following conditions should be closely monitored and may require dose reduction or discontinuation of therapy:
- Monotherapy with ribavirin is not permitted. (5.10)
- Hemolytic anemia may occur with a significant initial drop in hemoglobin. (5.2)
- Pancreatitis. (5.3)
- Pulmonary infiltrates or pulmonary function impairment. (5.4)
- New or worsening ophthalmologic disorders. (5.5)
- Severe decreases in neutrophil and platelet counts, and hematologic, endocrine (e.g., TSH), and hepatic abnormalities. (5.6)
- Dental/periodontal disorders reported with combination therapy. (5.7)
- Concomitant administration of azathioprine. (5.8)
- Weight loss and growth inhibition reported with combination therapy in pediatric patients. (5.9)

----------ADVERSE REACTIONS----------
Hemolytic anemia. (6.1)
Most common adverse reactions (approximately 40%) in adult patients receiving REBETOL/PegIntron or INTRON A combination therapy are injection site reaction, fatigue/asthenia, headache, rigors, fevers, nausea, myalgia and anxiety/emotional lability/irritability. (6.1, 6.2)
Most common adverse reactions (greater than 25%) in pediatric patients receiving REBETOL/PegIntron therapy are: pyrexia, headache, neutropenia, fatigue, anorexia, injection site erythema, and vomiting. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Merck Sharp & Dohme Corp., a subsidiary of Merck & Co. Inc. at 1-877-888-4231 or FDA at 1-800-FDA-1088 or *www.fda.gov/medwatch.*

----------DRUG INTERACTIONS----------
Nucleoside analogues: Closely monitor for toxicities. Discontinue nucleoside reverse transcriptase inhibitors or reduce dose or discontinue interferon, ribavirin or both with worsening toxicities. (7.2)

----------USE IN SPECIFIC POPULATIONS----------
- **Ribavirin Pregnancy Registry: 1-800-593-2214.**
- Nursing mothers: Potential adverse reactions from the drug in nursing infants. (8.1, 8.3)
- Pediatrics: Safety and efficacy in patients less than 3 years old have not been established. (8.4)
- Organ transplant recipients: Safety and efficacy not studied. (8.6)
- Co-infected Patients: Safety and efficacy with HIV or HBV co-infection have not been established. (8.7)

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

Revised: 02/2013

FULL PRESCRIBING INFORMATION: CONTENTS*

* Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

WARNING: RISK OF SERIOUS DISORDERS AND RIBAVIRIN-ASSOCIATED EFFECTS

- **REBETOL monotherapy is not effective for the treatment of chronic hepatitis C virus infection and should not be used alone for this indication *[see Warnings and Precautions (5.10)].***
- **The primary toxicity of ribavirin is hemolytic anemia. The anemia associated with REBETOL therapy may result in 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 Dosage and Administration (2.4), Warnings and Precautions (5.2),* and *Adverse Reactions (6.1)].***
- **Significant teratogenic and 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 (4), Warnings and Precautions (5.1), Use in Specific Populations (8.1), Nonclinical Toxicology (13.1), and Patient Counseling Information (17.2)].***

1 INDICATIONS AND USAGE

1.1 Chronic Hepatitis C (CHC)

REBETOL® (ribavirin) in combination with interferon alfa-2b (pegylated and nonpegylated) is indicated for the treatment of Chronic Hepatitis C (CHC) in patients 3 years of age and older with compensated liver disease *[see Warnings and Precautions (5.9, 5.10), and Use in Specific Populations (8.4)].*

The following points should be considered when initiating REBETOL combination therapy with PegIntron or INTRON A:

- These indications are based on achieving undetectable HCV-RNA after treatment for 24 or 48 weeks and maintaining a Sustained Virologic Response (SVR) 24 weeks after the last dose.
- Combination therapy with REBETOL/PegIntron is preferred over REBETOL/INTRON A as this combination provides substantially better response rates *[see Clinical Studies (14)].*
- Patients with the following characteristics are less likely to benefit from re-treatment after failing a course of therapy: previous nonresponse, previous pegylated interferon treatment, significant bridging fibrosis or cirrhosis, and genotype 1 infection *[see Clinical Studies (14)].*
- No safety and efficacy data are available for treatment of longer than one year.

2 DOSAGE AND ADMINISTRATION

Under no circumstances should REBETOL Capsules be opened, crushed, or broken. REBETOL should be taken with food *[see Clinical Pharmacology (12.3)*]. REBETOL should not be used in patients with creatinine clearance less than 50 mL/min.

2.1 REBETOL/PegIntron Combination Therapy

Adult Patients

The recommended dose of PegIntron is 1.5 mcg/kg/week subcutaneously in combination with 800 to 1400 mg REBETOL Capsules orally based on patient body weight (see **Table 1**). The volume of PegIntron to be injected depends on the strength of PegIntron and patient's body weight (see **Table 1**).

Duration of Treatment – Interferon Alpha-naïve Patients

The treatment duration for patients with genotype 1 is 48 weeks. Discontinuation of therapy should be considered in patients who do not achieve at least a 2 $\log_{10}$ drop or loss of HCV-RNA at 12 weeks, or if HCV-RNA remains detectable after 24 weeks of therapy. Patients with genotype 2 and 3 should be treated for 24 weeks.

Duration of Treatment – Re-treatment with PegIntron/REBETOL of Prior Treatment Failures

The treatment duration for patients who previously failed therapy is 48 weeks, regardless of HCV genotype. Re-treated patients who fail to achieve undetectable HCV-RNA at week 12 of therapy, or whose HCV-RNA remains detectable after 24 weeks of therapy, are highly unlikely to achieve SVR and discontinuation of therapy should be considered *[see Clinical Studies (14.1)].*

Table 1: Recommended REBETOL/PegIntron Combination Therapy Dosing (Adults)

Body Weight kg (lbs)	PegIntron REDIPEN® or Vial 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-mg capsules A.M. 2 x 200-mg capsules 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.
76-80 (167-177)		120	0.5	1000 mg/day	2 x 200-mg capsules A.M. 3 x 200-mg capsules P.M.
81-85 (178-187)				1200 mg/day	3 x 200-mg capsules A.M. 3 x 200-mg capsules P.M.
86-105 (188-231)	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.
† For patients weighing greater than 105 kg (greater than 231 pounds), the PegIntron dose of 1.5 mcg/kg/week should be calculated based on the individual patient weight. Two vials of PegIntron may be necessary to provide the dose.

Pediatric Patients

Dosing for pediatric patients is determined by body surface area for PegIntron and by body weight for REBETOL. The recommended dose of PegIntron is 60 mcg/m^2/week subcutaneously in combination with 15 mg/kg/day of REBETOL orally in two divided doses (see **Table 2**) for pediatric patients ages 3-17 years. Patients who reach their 18th birthday while receiving PegIntron/REBETOL should remain on the pediatric dosing regimen. The treatment duration for patients with genotype 1 is 48 weeks. Patients with genotype 2 and 3 should be treated for 24 weeks.

Table 2: Recommended REBETOL* Dosing in Combination Therapy (Pediatrics)

Body Weight kg (lbs)	REBETOL Daily Dose	REBETOL Number of Capsules
<47 (<103)	15 mg/kg/day	Use REBETOL Oral Solution†
47-59 (103-131)	800 mg/day	2 x 200-mg capsules A.M. 2 x 200-mg capsules P.M.
60-73 (132-162)	1000 mg/day	2 x 200-mg capsules A.M. 3 x 200-mg capsules P.M.
>73 (>162)	1200 mg/day	3 x 200-mg capsules A.M. 3 x 200-mg capsules P.M.

* REBETOL to be used in combination with PegIntron 60 mcg/m^2 weekly.
† REBETOL Oral Solution may be used for any patient regardless of body weight.

2.2 REBETOL/INTRON A Combination Therapy

Adults

Duration of Treatment – Interferon Alpha-naïve Patients

The recommended dose of INTRON A is 3 million IU three times weekly subcutaneously. The recommended dose of REBETOL Capsules depends on the patient's body weight (refer to **Table 3**). The recommended duration of treatment for patients previously untreated with interferon is 24 to 48 weeks. The duration of treatment should be individualized to the patient depending on baseline disease characteristics, response to therapy, and tolerability of the regimen *[see Indications and Usage (1.1), Adverse Reactions (6.1), and Clinical Studies (14)].* After 24 weeks of treatment, virologic response should be assessed. Treatment discontinuation should be considered in any patient who has not achieved an HCV-RNA below the limit of detection of the assay by 24 weeks. There are no safety and efficacy data on treatment for longer than 48 weeks in the previously untreated patient population.

Duration of Treatment – Re-treatment with INTRON A/REBETOL in Relapse Patients
In patients who relapse following nonpegylated interferon monotherapy, the recommended duration of treatment is 24 weeks.

Table 3: Recommended Dosing

Body Weight	REBETOL Capsules
≤75 kg	2 x 200-mg capsules AM 3 x 200-mg capsules PM daily orally
>75 kg	3 x 200-mg capsules AM 3 x 200-mg capsules PM daily orally

Pediatrics The recommended dose of REBETOL is 15 mg/kg per day orally (divided dose AM and PM). Refer to **Table 2** for Pediatric Dosing of REBETOL in combination with INTRON A. INTRON A for Injection by body weight of 25 kg to 61 kg is 3 million IU/m^2 three times weekly subcutaneously. Refer to adult dosing table for greater than 61 kg body weight.

The recommended duration of treatment is 48 weeks for pediatric patients with genotype 1. After 24 weeks of treatment, virologic response should be assessed. Treatment discontinuation should be considered in any patient who has not achieved an HCV-RNA below the limit of detection of the assay by this time. The recommended duration of treatment for pediatric patients with genotype 2/3 is 24 weeks.

2.3 Laboratory Tests

The following laboratory tests are recommended for all patients treated with REBETOL, prior to beginning treatment and then periodically thereafter.

- Standard hematologic tests - including hemoglobin (pretreatment, Week 2 and Week 4 of therapy, and as clinically appropriate *[see Warnings and Precautions (5.2, 5.7)],* complete and differential white blood cell counts, and platelet count.
- Blood chemistries - liver function tests and TSH.
- Pregnancy - including monthly monitoring for women of childbearing potential.
- ECG *[see Warnings and Precautions (5.2)].*

2.4 Dose Modifications

If severe adverse reactions or laboratory abnormalities develop during combination REBETOL/INTRON A therapy or REBETOL/PegIntron therapy, modified, or discontinue the dose until the adverse reaction abates or decreases in severity *[see Warnings and Precautions (5)].* If intolerance persists after dose adjustment, combination therapy should be discontinued. Dose reduction of PegIntron in adult patients on REBETOL/PegIntron combination therapy is accomplished in a two-step process from the original starting dose of 1.5 mcg/kg/week, to 1 mcg/kg/week, then to 0.5 mcg/kg/week, if needed. Dose reduction of PegIntron in adults may be accomplished by utilizing a lower dose strength or administering a lesser volume as shown in **Table 4.**

In the adult combination therapy study 2 dose reductions occurred in 42% of subjects receiving PegIntron 1.5 mcg/kg plus REBETOL 800 mg daily including 57% of those subjects weighing 60 kg or less. In Study 4, 16% of subjects had a dose reduction of PegIntron to 1 mcg/kg in combination with REBETOL, with an additional 4% requiring the second dose reduction of PegIntron to 0.5 mcg/kg due to adverse events *[see Adverse Reactions (6.1)].*

Table 4: Two-Step Dose Reduction of PegIntron in Combination Therapy in Adults

First Dose Reduction to PegIntron 1 mcg/kg				Second Dose Reduction to PegIntron 0.5 mcg/kg			
Body Weight kg (lbs)	**PegIntron REDIPEN/Vial Strength to Use**	**Amount of PegIntron (mcg) to Administer**	**Volume (mL) † of PegIntron to Administer**	**Body Weight kg (lbs)**	**PegIntron REDIPEN/Vial Strength to Use**	**Amount of PegIntron (mcg) to Administer**	**Volume (mL) † of PegIntron to Administer**
<40 (<88)	50 mcg per 0.5 mL	35	0.35	<40 (<88)	50 mcg per 0.5 mL*	20	0.2
40-50 (88-111)		45	0.45	40-50 (88-111)		25	0.25
51-60 (112-133)		50	0.5	51-60 (112-133)	50 mcg per 0.5 mL	30	0.3
61-75 (134-166)	80 mcg per 0.5 mL	64	0.4	61-75 (134-166)		35	0.35
76-85 (167-187)		80	0.5	76-85 (167-187)		45	0.45
86-104 (188-230)	120 mcg per 0.5 mL	96	0.4	86-104 (188-230)		50	0.5
105-125 (231-275)		108	0.45	105-125 (231-275)	80 mcg per 0.5 mL	64	0.4
>125 (>275)	150 mcg per 0.5 mL	135	0.45	>125 (>275)		72	0.45

* Must use vial. Minimum delivery for REDIPEN 0.3 mL.
† When reconstituted as directed.

Dose reduction in pediatric patients is accomplished by modifying the recommended PegIntron dose in a two-step process from the original starting dose of 60 mcg/m^2/week, to 40 mcg/m^2/week, then to 20 mcg/m^2/week, if needed (see **Table 5**). In the pediatric combination therapy trial, dose reductions occurred in 25% of subjects receiving PegIntron 60 mcg/m^2 weekly plus REBETOL 15 mg/kg daily. Dose reduction in pediatric patients is accomplished by modifying the recommended REBETOL dose from the original starting dose of 15 mg/kg daily in a two-step process to 12 mg/kg/day, then to 8 mg/kg/day, if needed (see **Table 5**).

REBETOL should not be used in patients with creatinine clearance less than 50 mL/min. Subjects with impaired renal function and those over the age of 50 should be carefully monitored with respect to development of anemia *[see Warnings and Precautions (5.2)*, *Use in Specific Populations (8.5)*, *and Clinical Pharmacology (12.3)*].

REBETOL should be administered with caution to patients with pre-existing cardiac disease. Patients should be assessed before commencement of therapy and should be appropriately monitored during therapy. If there is any deterioration of cardiovascular status, therapy should be stopped *[see Warnings and Precautions (5.2)].*

For patients with a history of stable cardiovascular disease, a permanent dose reduction is required if the hemoglobin decreases by greater than or equal to 2 g/dL during any 4-week period. In addition, for these cardiac history patients, if the hemoglobin remains less than 12 g/dL after 4 weeks on a reduced dose, the patient should discontinue combination therapy.

It is recommended that a patient whose hemoglobin level falls below 10 g/dL have his/her REBETOL dose modified or discontinued per **Table 5** *[see Warnings and Precautions (5.2)].*

Table 5: Guidelines for Dose Modification and Discontinuation of PegIntron, INTRON A or PegIntron/REBETOL Based on Laboratory Parameters in Adults and Pediatrics

Laboratory Values	**Adults**	**Pediatrics**		**Adults**	**Pediatrics**
	PegIntron/INTRON A	**PegIntron**	**INTRON A**	**REBETOL**	
Hgb <10 g/dL	For patients with cardiac disease, reduce by 50%*	See footnote*	See footnote*	Adjust Dose†	1st reduction to 12 mg/kg/day 2nd reduction to 8 mg/kg/day
WBC <1.5 x 10^9/L Neutrophils <0.75 x 10^9/L Platelets <50 x 10^9/L (Adults) <70 x 10^9/L (Pediatrics)	Adjust Dose‡	1st reduction to 40 mcg/m^2/week 2nd reduction to 20 mcg/m^2/week	Reduce by 50%	No Dose Change	No Dose Change
Hgb <8.5 g/dL WBC <1 x 10^9/L Neutrophils <0.5 x 10^9/L Creatinine >2 mg/dL (Pediatrics) Platelets <25 x 10^9/L (Adults) <50 x 10^9/L (Pediatrics)	Permanently Discontinue	Permanently Discontinue	Permanently Discontinue	Permanently Discontinue	Permanently Discontinue

* For adult patients with a history of stable cardiac disease receiving PegIntron or INTRON A in combination with ribavirin, the PegIntron or INTRON A dose should be reduced by half and the REBETOL dose by 200 mg/day if a greater than 2 g/dL decrease in hemoglobin is observed during any 4-week period. Both PegIntron and REBETOL or INTRON A and REBETOL should be permanently discontinued if patients have hemoglobin levels less than 12 g/dL after this REBETOL dose reduction. Pediatric patients who have pre-existing cardiac conditions and experience a hemoglobin decrease greater than or equal to 2 g/dL during any 4-week period during treatment should have weekly evaluations and hematology testing.
† 1st dose reduction of REBETOL is by 200 mg/day, except in patients receiving the 1400 mg dose it is by 400 mg/day; 2nd dose reduction of REBETOL (if needed) is by an additional 200 mg/day.

‡ For patients on REBETOL/PegIntron combination therapy: 1st dose reduction of PegIntron is to 1 mcg/kg/week, 2nd dose reduction (if needed) of PegIntron is to 0.5 mcg/kg/week. For patients on REBETOL/INTRON A combination therapy, reduce INTRON A dose by 50%.

Refer to the INTRON A Package Insert or PegIntron Powder for Injection Package Insert for additional information about how to reduce an INTRON A or PegIntron dose.

2.5 Discontinuation of Dosing

Adults It is recommended that HCV genotype 1 interferon-alfa-naïve patients receiving PegIntron in combination with ribavirin, be discontinued from therapy if there is not at least a 2 $\log_{10}$ drop or loss of HCV-RNA at 12 weeks of therapy, or whose HCV-RNA levels remain detectable (greater than 10-20 IU/mL) after 24 weeks of therapy. Regardless of genotype, previously treated patients who have detectable HCV-RNA at week 12 or 24 are highly unlikely to achieve SVR and discontinuation of therapy should be considered.

Pediatrics (3-17 years of age) It is recommended that patients receiving PegIntron/REBETOL combination (excluding HCV Genotype 2 and 3) be discontinued from therapy at 12 weeks if their treatment Week 12 HCV-RNA dropped less than 2 $\log_{10}$ compared to a pretreatment or at 24 weeks if they have detectable HCV-RNA (greater than 10-20 IU/mL) at treatment Week 24.

3 DOSAGE FORMS AND STRENGTHS

REBETOL 200 mg Capsules
REBETOL Oral Solution 40 mg per mL

4 CONTRAINDICATIONS

REBETOL combination therapy is contraindicated in:

- women who are pregnant. REBETOL may cause fetal harm when administered to a pregnant women. REBETOL is contraindicated in women who are or may become pregnant. If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to a fetus *[see Warnings and Precautions (5.1)*, *Use in Specific Populations (8.1), and Patient Counseling Information (17.2)]*
- men whose female partners are pregnant
- patients with known hypersensitivity reactions such as Stevens-Johnson syndrome, toxic, epidermal necrolysis, and erythema multiforme to ribavirin or any component of the product
- patients with autoimmune hepatitis
- patients with hemoglobinopathies (e.g., thalassemia major, sickle-cell anemia)
- patients with creatinine clearance less than 50 mL/min. *[see Use in Specific Populations (8.5) and Clinical Pharmacology (12.3)]*
- Coadministration of REBETOL and didanosine is contraindicated as because exposure to the active metabolite of didanosine (dideoxyadenosine 5'-triphosphate) are increased. Fatal hepatic failure, as well as peripheral neuropathy, pancreatitis, and symptomatic hyperlactatemia/lactic acidosis have been reported in patients receiving both didanosine and ribavirin *[see Drug Interactions (7.1)].*

5 WARNINGS AND PRECAUTIONS

5.1 Pregnancy

REBETOL Capsules and Oral Solution may cause birth defects and 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 during treatment and during the 6-month period after treatment has been stopped. Extreme care must be taken to avoid pregnancy in female patients and in female partners of male patients. REBETOL has demonstrated significant teratogenic and 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 *[see Boxed Warning, Contraindications (4), Use in Specific Populations (8.1), and Patient Counseling Information (17.2)].*

5.2 Anemia

The primary toxicity of ribavirin is hemolytic anemia, which was observed in approximately 10% of REBETOL/INTRON A-treated subjects in clinical trials. The anemia associated with REBETOL capsules occurs within 1 to 2 weeks of initiation of therapy. Because the initial drop in hemoglobin may be significant, it is advised that hemoglobin or hematocrit 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 *[see Dosage and Administration (2.4, 2.5)].*

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 ribavirin 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 (2.4, 2.5)].* Because cardiac disease may be worsened by drug-induced anemia, patients with a history of significant or unstable cardiac disease should not use REBETOL.

5.3 Pancreatitis

REBETOL and INTRON A or PegIntron therapy should be suspended in patients with signs and symptoms of pancreatitis and discontinued in patients with confirmed pancreatitis.

5.4 Pulmonary Disorders

Pulmonary symptoms, including dyspnea, pulmonary infiltrates, pneumonitis, pulmonary hypertension, and pneumonia, have been reported during therapy with REBETOL with alpha interferon combination therapy**;** occasional cases of fatal pneumonia have occurred. In addition, sarcoidosis or the exacerbation of sarcoidosis has been reported. If there is evidence of pulmonary infiltrates or pulmonary function impairment, the patient should be closely monitored, and if appropriate, combination therapy should be discontinued.

5.5 Ophthalmologic Disorders

Ribavirin is used in combination therapy with alpha interferons. Decrease or loss of vision, retinopathy including macular edema, retinal artery or vein, thrombosis, retinal hemorrhages and cotton wool spots, optic neuritis, papilledema, and serous retinal detachment are induced or aggravated by

treatment with alpha interferons. All patients should receive an eye examination at baseline. Patients with pre-existing ophthalmologic disorders (e.g., diabetic or hypertensive retinopathy) should receive periodic ophthalmologic exams during combination therapy with alpha interferon treatment. Any patient who develops ocular symptoms should receive a prompt and complete eye examination. Combination therapy with alpha interferons should be discontinued in patients who develop new or worsening ophthalmologic disorders.

5.6 Laboratory Tests

PegIntron in combination with ribavirin may cause severe decreases in neutrophil and platelet counts, and hematologic, endocrine (e.g., TSH), and hepatic abnormalities.

Patients on PegIntron/REBETOL combination therapy should have hematology and blood chemistry testing before the start of treatment and then periodically thereafter. In the adult 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. In pediatric subjects the same laboratory parameters were evaluated with additional assessment of hemoglobin at treatment week 6. TSH levels were measured every 12 weeks during the treatment period. HCV-RNA should be measured periodically during treatment *[see Dosage and Administration (2)].*

5.7 Dental and Periodontal Disorders

Dental and periodontal disorders have been reported in patients receiving ribavirin and interferon or peginterferon 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 interferon alfa-2b or pegylated interferon alfa-2b. Patients should brush their teeth thoroughly twice daily and have regular dental examinations If vomiting occurs, they should be advised to rinse out their mouth thoroughly afterwards.

5.8 Concomitant Administration of Azathioprine

Pancytopenia (marked decreases in red blood cells, neutrophils, and platelets) and bone marrow suppression have been reported in the literature to occur within 3 to 7 weeks after the concomitant administration of pegylated interferon/ribavirin and azathioprine. In this limited number of patients (n=8), myelotoxicity was reversible within 4 to 6 weeks upon withdrawal of both HCV antiviral therapy and concomitant azathioprine and did not recur upon reintroduction of either treatment alone. PegIntron, Rebetol, and azathioprine should be discontinued for pancytopenia, and pegylated interferon/ribavirin should not be reintroduced with concomitant azathioprine *[see Drug Interactions (7.4)].*

5.9 Impact on Growth - Pediatric Use

Data on the effects of PegIntron plus REBETOL on growth come from an open-label study in subjects 3 through 17 years of age, and weight and height changes are compared to U.S. normative population data. In general, the weight and height gain of pediatric subjects treated with PegIntron plus REBETOL lags behind that predicted by normative population data for the entire length of treatment. After about 6 months posttreatment (Follow-Up Week 24), subjects had weight gain rebounds and regained their weight to 53rd percentile, above the average of the normative population and similar to that predicted by their average baseline weight (57th percentile). After about 6 months posttreatment, height gain stabilized and subjects treated with PegIntron plus REBETOL had an average height percentile of 44th percentile, which was less than the average of the normative population and less than their average baseline height (51st percentile). Severely inhibited growth velocity (less than 3rd percentile) was observed in 70% of the subjects while on treatment. Of the subjects experiencing severely inhibited growth, 20% had continued inhibited growth velocity (less than 3rd percentile) after 6 months of follow-up.

Among the boys studied, the age groups of 3-11 years old and 12-17 years old had similar height percentile decreases of approximately 5 percentiles after 6 months posttreatment; weight gain continued to be similar to their average baseline percentile. Girls who were 3-11 years old and treated for 48 weeks had the largest average drop in height and weight percentiles (13 percentiles and 7 percentiles, respectively), whereas girls 12-17 years old continued along their average baseline height and weight percentiles after 6 months posttreatment.

5.10 Usage Safeguards

Based on results of clinical trials, ribavirin monotherapy is not effective for the treatment of chronic hepatitis C virus infection; therefore, REBETOL Capsules or Oral Solution must not be used alone. The safety and efficacy of REBETOL Capsules and Oral Solution have only been established when used together with INTRON A or PegIntron (not other interferons) as a combination therapy.

The safety and efficacy of REBETOL/INTRON A and PegIntron therapy for the treatment of HIV infection, adenovirus, RSV, parainfluenza, or influenza infections have not been established. REBETOL Capsules should not be used for these indications. Ribavirin for inhalation has a separate package insert, which should be consulted if ribavirin inhalation therapy is being considered.

There are significant adverse reactions caused by REBETOL/INTRON A or PegIntron therapy, including severe depression and suicidal ideation, hemolytic anemia, suppression of bone marrow function, autoimmune and infectious disorders, pulmonary dysfunction, pancreatitis, and diabetes. Suicidal ideation or attempts occurred more frequently among pediatric patients, primarily adolescents, compared to adult patients (2.4% versus 1%) during treatment and off-therapy follow-up. The INTRON A and PegIntron package inserts should be reviewed in their entirety for additional safety information prior to initiation of combination treatment.

6 ADVERSE REACTIONS

Clinical trials with REBETOL in combination with PegIntron or INTRON A have been conducted in over 7800 subjects from 3 to 76 years of age.

The primary toxicity of ribavirin is hemolytic anemia. Reductions in hemoglobin levels occurred within the first 1 to 2 weeks of oral therapy. Cardiac and pulmonary reactions associated with anemia occurred in approximately 10% of patients *[see Warnings and Precautions (5.2)].*

Greater than 96% of all subjects in clinical trials experienced one or more adverse reactions. The most commonly reported adverse reactions in adult subjects receiving PegIntron or INTRON A in combination with REBETOL were injection site inflammation/reaction, fatigue/asthenia, headache, rigors, fevers, nausea, myalgia and anxiety/emotional lability/irritability. The most common adverse reactions in pediatric subjects, ages 3 and older, receiving REBETOL in combination with PegIntron or INTRON A were pyrexia, headache, neutropenia, fatigue, anorexia, injection site erythema, and vomiting.

The Adverse Reactions section references the following clinical studies:

- REBETOL/PegIntron Combination therapy studies:
  - Clinical Study 1 – evaluated PegIntron monotherapy (not further described in this label; see PegIntron Powder for Injection Package Insert for information about this study).
  - Study 2 – evaluated REBETOL 800 mg/day flat dose in combination with 1.5 mcg/kg/week PegIntron or with INTRON A.
  - Study 3 – evaluated PegIntron/weight-based REBETOL in combination with PegIntron/flat dose REBETOL regimen.
  - Study 4 – compared two PegIntron (1.5 mcg/kg/week and 1 mcg/kg/week) doses in combination with REBETOL and a third treatment group receiving Pegasys® (180 mcg/week)/Copegus® (1000-1200 mg/day).

- Study 5 – evaluated PegIntron (1.5 mcg/kg/week) in combination with weight-based REBETOL in prior treatment failure subjects.

- PegIntron/REBETOL Combination Therapy in Pediatric Patients
- REBETOL/INTRON A Combination Therapy studies for adults and pediatrics

Serious adverse reactions have occurred in approximately 12% of subjects in clinical trials with PegIntron with or without REBETOL *[see BOXED WARNING, Warnings and Precautions (5)].* The most common serious events occurring in subjects treated with PegIntron and REBETOL were depression and suicidal ideation *[see Warnings and Precautions (5.2)],* each occurring at a frequency of less than 1%. Suicidal ideation or attempts occurred more frequently among pediatric patients, primarily adolescents, compared to adult patients (2.4% versus 1%) during treatment and off-therapy follow-up *[*see *Warnings and Precautions (5.10)].* The most common fatal reaction occurring in subjects treated with PegIntron and REBETOL was cardiac arrest, suicide ideation, and suicide attempt *[see Warnings and Precautions (5.10)],* all occurring in less than 1% of subjects.

Because clinical trials are conducted under widely varying conditions, adverse reactions rates observed in the clinical trials of a drug cannot be directly compared to rated in the clinical trials of another drug and may not reflect the rates observed in clinical practice.

6.1 Clinical Studies Experience – REBETOL/PegIntron Combination Therapy

Adult Subjects

Adverse reactions that occurred in the clinical trial at greater than 5% incidence are provided by treatment group from the REBETOL/PegIntron Combination Therapy (Study 2) in **Table 6**.

Table 6: Adverse Reactions Occurring in Greater Than 5% of Adult Subjects

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

* A subject may have reported more than one adverse reaction within a body system/organ class category.

Table 7 summarizes the treatment related adverse reactions in Study 4 that occurred at a greater than or equal to 10% incidence.

Table 7: Summary of Treatment-Related Adverse Reactions (Greater Than or Equal to 10% Incidence) By Descending Frequency

	Study 4
	Percentage of Patients Reporting Treatment-Related Adverse Reactions

Adverse Reactions	PegIntron 1.5 mcg/kg with REBETOL (n=1019)	PegIntron 1 mcg/kg with REBETOL (n=1016)	Pegasys 180 mcg with Copegus (n=1035)
Fatigue	67	68	64
Headache	50	47	41
Nausea	40	35	34
Chills	39	36	23
Insomnia	38	37	41
Anemia	35	30	34
Pyrexia	35	32	21
Injection Site Reactions	34	35	23
Anorexia	29	25	21
Rash	29	25	34
Myalgia	27	26	22
Neutropenia	26	19	31
Irritability	25	25	25
Depression	25	19	20
Alopecia	23	20	17
Dyspnea	21	20	22
Arthralgia	21	22	22
Pruritus	18	15	19
Influenza-like Illness	16	15	15
Dizziness	16	14	13
Diarrhea	15	16	14
Cough	15	16	17
Weight Decreased	13	10	10
Vomiting	12	10	9
Unspecified Pain	12	13	9
Dry Skin	11	11	12
Anxiety	11	11	10
Abdominal Pain	10	10	10
Leukopenia	9	7	10

The incidence of serious adverse reactions was comparable in all studies. In Study 3, there was a similar incidence of serious adverse reactions reported for the weight-based REBETOL group (12%) and with the flat-dose REBETOL regimen. In Study 2, the incidence of serious adverse reactions was 17% in the PegIntron/REBETOL groups compared to 14% in the INTRON A/REBETOL group.

In many but not all cases, adverse reactions resolved after dose reduction or discontinuation of therapy. Some subjects experienced ongoing or new serious adverse reactions during the 6-month follow-up period. In Study 2, many subjects continued to experience adverse reactions several months after discontinuation of therapy. By the end of the 6-month follow-up period, the incidence of ongoing adverse reactions 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 to 15% of subjects' weight loss, fatigue, and headache had not resolved.

There have been 31 subject deaths which occurred during treatment or during follow-up in these clinical trials. In Study 1, there was 1 suicide in a subject receiving PegIntron monotherapy and 2 deaths among subjects receiving INTRON A monotherapy (1 murder/suicide and 1 sudden death). In Study 2, there was 1 suicide in a subject receiving PegIntron/REBETOL combination therapy; and 1 subject death in the INTRON A/REBETOL group (motor vehicle accident). There have been 31 subject deaths which occurred during treatment or during follow-up in the three clinical trials. In Study 3, there were 14 deaths, 2 of which were probable suicides and 1 was an unexplained death in a person with a relevant medical history of depression. In Study 4, there were 12 deaths, 6 of which occurred in subjects who received PegIntron/REBETOL combination therapy, 5 in the PegIntron 1.5 mcg/REBETOL arm (N=1019) and 1 in the PegIntron 1 mcg/REBETOL arm (N=1016), and 6 of which occurred in subjects receiving Pegasys/Copegus (N=1035). There were 3 suicides which occurred during the off treatment follow-up period in subjects who received PegIntron (1.5 mcg/kg)/REBETOL combination therapy.

In studies 1 and 2, 10 to 14% of subjects receiving PegIntron, alone or in combination with REBETOL, discontinued therapy compared with 6% treated with INTRON A alone and 13% treated with INTRON A in combination with REBETOL. Similarly in Study 3, 15% of subjects receiving PegIntron in combination with weight-based REBETOL and 14% of subjects receiving PegIntron and flat dose REBETOL discontinued therapy due to an adverse reaction. The most common reasons for discontinuation of therapy were related to known interferon effects of psychiatric, systemic (e.g., fatigue, headache), or gastrointestinal adverse reactions. In study 4, 13% of subjects in the PegIntron 1.5 mcg/REBETOL arm, 10% in the PegIntron 1 mcg/REBETOL arm and 13% in the Pegasys 180 mcg/Copegus arm discontinued due to adverse events.

In Study 2, dose reductions due to adverse reactions occurred in 42% of subjects receiving PegIntron (1.5 mcg/kg)/REBETOL and in 34% of those receiving INTRON A/REBETOL. The majority of subjects (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 greater than PegIntron 0.5 mcg/kg or INTRON A), 40%, 27%, 28%, respectively. Dose reduction for REBETOL was similar across all three groups, 33 to 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 reactions occurred more frequently with WBD compared to flat dosing (29% and 23%, respectively). In Study 4, 16% of subjects had a dose reduction of PegIntron to 1 mcg/kg in combination with REBETOL, with an additional 4% requiring the second dose reduction of PegIntron to 0.5 mcg/kg due to adverse events compared to 15% of subjects in the Pegasys/Copegus arm, who required a dose reduction to 135 mcg/week with Pegasys, with an additional 7% in the Pegasys/Copegus arm requiring second dose reduction to 90 mcg/week with Pegasys.

In the PegIntron/REBETOL combination trials the most common adverse reactions were psychiatric which occurred among 77% of subjects in Study 2 and 68% to 69% of subjects in Study 3. These psychiatric adverse reactions included most commonly depression, irritability, and insomnia, each reported by approximately 30% to 40% of subjects in all treatment groups. Suicidal behavior (ideation, attempts, and suicides) occurred in 2% of all subjects during treatment or during follow-up after treatment cessation [see *Warnings and Precautions (5)*]. In study 4 psychiatric adverse reactions

occurred in 58 % of subjects in the PegIntron 1.5 mcg/REBETOL arm, 55% of subjects in the PegIntron 1 mcg/REBETOL arm, 57% of subjects in the Pegasys 180 mcg/Copegus arm.

PegIntron induced fatigue or headache in approximately two-thirds of subjects, with fever or rigors in approximately half of the subjects. The severity of some of these systemic symptoms (e.g., fever and headache) tends to decrease as treatment continues. In Studies 1 and 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 subjects) compared with INTRON A. However, injection site pain was infrequent (2 to 3%) in all groups. In Study 3 there was a 23 to 24% incidence overall for injection site reactions or inflammation.

Subjects receiving REBETOL/PegIntron as re-treatment after failing a previous interferon combination regimen reported adverse reactions similar to those previously associated with this regimen during clinical trials of treatment-naïve subjects.

Pediatric Subjects

In general, the adverse-reaction profile in the pediatric population was similar to that observed in adults. In the pediatric study, the most prevalent adverse reactions in all subjects were pyrexia (80%), headache (62%), neutropenia (33%), fatigue (30%), anorexia (29%), injection-site erythema (29%) and vomiting (27%). The majority of adverse reactions reported in the study were mild or moderate in severity. Severe adverse reactions were reported in 7% (8/107) of all subjects and included injection site pain (1%), pain in extremity (1%), headache (1%), neutropenia (1%), and pyrexia (4%). Important adverse reactions that occurred in this subject population were nervousness (7%; 7/107), aggression (3%; 3/107), anger (2%; 2/107), and depression (1%; 1/107). Five subjects received levothyroxine treatment, 3 with clinical hypothyroidism and 2 with asymptomatic TSH elevations.

Dose modifications of PegIntron and/or ribavirin were required in 25% of subjects due to treatment-related adverse reactions, most commonly for anemia, neutropenia and weight loss. Two subjects (2%; 2/107) discontinued therapy as the result of an adverse reaction.

Adverse reactions that occurred with a greater than or equal to 10% incidence in the pediatric trial subjects are provided in **Table 8**.

Table 8: **Percentage (%) of Pediatric Subjects With Treatment-Related Adverse Reactions (in at Least 10% of All Subjects)**

System Organ Class Preferred Term	**All Subjects** (N=107)
Blood and Lymphatic System Disorders	
Neutropenia	33%
Anemia	11%
Leukopenia	10%
Gastrointestinal Disorders	
Abdominal Pain	21%
Abdominal Pain Upper	12%
Vomiting	27%
Nausea	18%
General Disorders and Administration Site Conditions	
Pyrexia	80%
Fatigue	30%
Injection-site Erythema	29%
Chills	21%
Asthenia	15%
Irritability	14%
Investigations	
Weight Loss	19%
Metabolism and Nutrition Disorders	
Anorexia	29%
Decreased Appetite	22%
Musculoskeletal and Connective Tissue Disorders	
Arthralgia	17%
Myalgia	17%
Nervous System Disorders	
Headache	62%
Dizziness	14%
Skin and Subcutaneous Tissue Disorders	
Alopecia	17%

Laboratory Values

Adult and Pediatric Subjects

The adverse reaction 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.

Changes in selected laboratory values during treatment in combination with REBETOL treatment are described below. **Decreases in hemoglobin, leukocytes, neutrophils, and platelets may require dose reduction or permanent discontinuation from therapy** [*see Dosage and Administration (2.4)*]. Changes in selected laboratory values during therapy are described in **Table 9**. Most of the changes in laboratory values in the PegIntron/REBETOL study with pediatric were mild or moderate.

Table 9: Selected Laboratory Values During Treatment With REBETOL Plus PegIntron or REBETOL Plus INTRON A in Previously Untreated Subjects

Laboratory Parameters*	Percent of Subjects		
	Adults (Study 2)		Pediatrics
	PegIntron plus REBETOL (N=511)	INTRON A plus REBETOL (N=505)	PegIntron plus REBETOL (N=107)*
Hemoglobin (g/dL)			
9.5 to <11.0	26	27	30
8.0 to <9.5	3	3	2
6.5-7.9	0.2	0.2	-
Leukocytes (x 10^9/L)			
2.0-2.9	46	41	39
1.5 to <2.0	24	8	3
1.0-1.4	5	1	-
Neutrophils (x 10^9/L)			
1.0-1.5	33	37	35
0.75 to <1.0	25	13	26
0.5 to <0.75	18	7	13
<0.5	4	2	3
Platelets (x 10^9/L)			
70-100	15	5	1
50 to <70	3	0.8	-
30-49	0.2	0.2	-
25 to <50	-	-	1
Total Bilirubin	**(mg/dL)**		**(µmole/L)**
1.5-3.0	10	13	-
1.26-2.59 x N†	-	-	7
3.1-6.0	0.6	0.2	-
2.6-5 x N†	-	-	-
6.1-12.0	0	0.2	-
ALT (U/L)			
2 x Baseline	0.6	0.2	1
2.1-5 x Baseline	3	1	5
5.1-10 x Baseline	0	0	3

* The table summarizes the worst category observed within the period per subject per laboratory test. Only subjects with at least one treatment value for a given laboratory test are included.
† N=Upper limit of normal.

Hemoglobin. Hemoglobin levels decreased to less than 11 g/dL in about 30% of subjects in Study 2. In Study 3, 47% of subjects receiving WBD REBETOL and 33% on flat dose REBETOL had decreases in hemoglobin levels less than 11 g/dl. Reductions in hemoglobin to less than 9 g/dL occurred more frequently in subjects receiving WBD compared to flat dosing (4% and 2%, respectively). In Study 2, dose modification was required in 9% and 13% of subjects in the PegIntron/REBETOL and INTRON A/REBETOL groups. In Study 4, patients receiving PegIntron (1.5 mcg/kg)/REBETOL had decreases in hemoglobin levels to between 8.5 to less than 10 g/dL (28%) and to less than 8.5 g/dL (3%), whereas in patients receiving Pegasys 180 mcg/Copegus these decreases occurred in 26% and 4% of subjects respectively. Hemoglobin levels become stable by treatment Weeks 4-6 on average. 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. In the PegIntron monotherapy trial, hemoglobin decreases were generally mild and dose modifications were rarely necessary *[see Dosage and Administration (2.4)].*

Neutrophils. Decreases in neutrophil counts were observed in a majority of adult subjects treated with combination therapy with REBETOL in Study 2 (85%) and INTRON A/REBETOL (60%). Severe potentially life-threatening neutropenia (less than 0.5 x 10^9/L) occurred in 2% of subjects

treated with INTRON A/REBETOL and in approximately 4% of subjects treated with PegIntron/REBETOL in Study 2. Eighteen percent of subjects receiving PegIntron/REBETOL in Study 2 required modification of interferon dosage. Few subjects (less than 1%) required permanent discontinuation of treatment. Neutrophil counts generally return to pre-treatment levels 4 weeks after cessation of therapy [see *Dosage and Administration (2.4)*].

Platelets. Platelet counts decreased to less than 100,000/mm^3 in approximately 20% of subjects treated with PegIntron alone or with REBETOL and in 6% of adult subjects treated with INTRON A/REBETOL. Severe decreases in platelet counts (less than 50,000/mm^3) occur in less than 4% of adult subjects. Subjects may require discontinuation or dose modification as a result of platelet decreases *[see Dosage and Administration (2.4)]*. In Study 2, 1% or 3% of subjects required dose modification of INTRON A or PegIntron, respectively. Platelet counts generally returned to pretreatment levels 4 weeks after the cessation of therapy.

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 subjects 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 to 14% of subjects developed hyperbilirubinemia and 33 to 38% developed hyperuricemia in association with hemolysis. Six subjects developed mild to moderate gout.

6.2 Clinical Studies Experience – REBETOL/INTRON A Combination Therapy

Adult Subjects

In clinical trials, 19% and 6% of previously untreated and relapse subjects, respectively, discontinued therapy due to adverse reactions in the combination arms compared to 13% and 3% in the interferon arms. Selected treatment-related adverse reactions that occurred in the US studies with ≥5% incidence are provided by treatment group (see **Table 10**). In general, the selected treatment-related adverse reactions were reported with lower incidence in the international studies as compared to the US studies with the exception of asthenia, influenza-like symptoms, nervousness, and pruritus.

Pediatric Subjects

In clinical trials of 118 pediatric subjects 3 to 16 years of age, 6% discontinued therapy due to adverse reactions. Dose modifications were required in 30% of subjects, most commonly for anemia and neutropenia. In general, the adverse-reaction profile in the pediatric population was similar to that observed in adults. Injection site disorders, fever, anorexia, vomiting, and emotional lability occurred more frequently in pediatric subjects compared to adult subjects. Conversely, pediatric subjects experienced less fatigue, dyspepsia, arthralgia, insomnia, irritability, impaired concentration, dyspnea, and pruritus compared to adult subjects. Selected treatment-related adverse reactions that occurred with greater than or equal to 5% incidence among all pediatric subjects who received the recommended dose of REBETOL/INTRON A combination therapy are provided in **Table 10**.

Table 10: Selected Treatment-Related Adverse Reactions: Previously Untreated and Relapse Adult Subjects and Previously Untreated Pediatric Subjects

	Percentage of Subjects						
	US Previously Untreated Study				US Relapse Study		Pediatric Subjects
	24 weeks of treatment		48 weeks of treatment		24 weeks of treatment		48 weeks of treatment
Patients Reporting Adverse Reactions*	**INTRON A plus REBETOL** (N=228)	**INTRON A plus Placebo** (N=231)	**INTRON A plus REBETOL** (N=228)	**INTRON A plus Placebo** (N=225)	**INTRON A plus REBETOL** (N=77)	**INTRON A plus Placebo** (N=76)	**INTRON A plus REBETOL** (N=118)
Application Site Disorders							
Injection Site Inflammation	13	10	12	14	6	8	14
Injection Site Reaction	7	9	8	9	5	3	19
Body as a Whole - General Disorders							
Headache	63	63	66	67	66	68	69
Fatigue	68	62	70	72	60	53	58
Rigors	40	32	42	39	43	37	25
Fever	37	35	41	40	32	36	61
Influenza-like Symptoms	14	18	18	20	13	13	31
Asthenia	9	4	9	9	10	4	5
Chest Pain	5	4	9	8	6	7	5
Central & Peripheral Nervous System Disorders							
Dizziness	17	15	23	19	26	21	20
Gastrointestinal System Disorders							
Nausea	38	35	46	33	47	33	33
Anorexia	27	16	25	19	21	14	51
Dyspepsia	14	6	16	9	16	9	<1
Vomiting	11	10	9	13	12	8	42
Musculoskeletal System Disorders							
Myalgia	61	57	64	63	61	58	32
Arthralgia	30	27	33	36	29	29	15
Musculoskeletal Pain	20	26	28	32	22	28	21
Psychiatric Disorders							
Insomnia	39	27	39	30	26	25	14
Irritability	23	19	32	27	25	20	10
Depression	32	25	36	37	23	14	13
Emotional Lability	7	6	11	8	12	8	16
Concentration Impaired	11	14	14	14	10	12	5
Nervousness	4	2	4	4	5	4	3
Respiratory System Disorders							
Dyspnea	19	9	18	10	17	12	5
Sinusitis	9	7	10	14	12	7	<1
Skin and Appendages Disorders							
Alopecia	28	27	32	28	27	26	23
Rash	20	9	28	8	21	5	17
Pruritus	21	9	19	8	13	4	12
Special Senses, Other Disorders							
Taste Perversion	7	4	8	4	6	5	<1

* Subjects reporting one or more adverse reactions. A patient may have reported more than one adverse reaction within a body system/organ class category.

Laboratory Values

Changes in selected hematologic values (hemoglobin, white blood cells, neutrophils, and platelets) during therapy are described below (see **Table 11)**.

Hemoglobin. Hemoglobin decreases among subjects receiving REBETOL therapy began at Week 1, with stabilization by Week 4. In previously untreated subjects treated for 48 weeks, the mean maximum decrease from baseline was 3.1 g/dL in the US study and 2.9 g/dL in the International study. In relapse subjects the mean maximum decrease from baseline was 2.8 g/dL in the US study and 2.6 g/dL in the International study. Hemoglobin values returned to pretreatment levels within 4 to 8 weeks of cessation of therapy in most subjects.

Bilirubin and Uric Acid. Increases in both bilirubin and uric acid, associated with hemolysis, were noted in clinical trials. Most were moderate biochemical changes and were reversed within 4 weeks after treatment discontinuation. This observation occurs most frequently in subjects with a previous diagnosis of Gilbert's syndrome. This has not been associated with hepatic dysfunction or clinical morbidity.

Table 11: Selected Hematologic Abnormalities During Treatment With REBETOL Plus INTRON A: Previously Untreated and Relapse Adult Subjects and Previously Untreated Pediatric Subjects

	Percentage of Subjects						
	US Previously Untreated Study				US Relapse Study		Pediatric Subjects
	24 weeks of treatment		48 weeks of treatment		24 weeks of treatment		48 weeks of treatment
	INTRON A plus REBETOL (N=228)	INTRON A plus Placebo (N=231)	INTRON A plus REBETOL (N=228)	INTRON A plus Placebo (N=225)	INTRON A plus REBETOL (N=77)	INTRON A plus Placebo (N=76)	INTRON A plus REBETOL (N=118)
Hemoglobin (g/dL)							
9.5 to 10.9	24	1	32	1	21	3	24
8.0 to 9.4	5	0	4	0	4	0	3
6.5 to 7.9	0	0	0	0.4	0	0	0
<6.5	0	0	0	0	0	0	0
Leukocytes (x 10^9/L)							
2.0 to 2.9	40	20	38	23	45	26	35
1.5 to 1.9	4	1	9	2	5	3	8
1.0 to 1.4	0.9	0	2	0	0	0	0
<1.0	0	0	0	0	0	0	0
Neutrophils (x 10^9/L)							
1.0 to 1.49	30	32	31	44	42	34	37
0.75 to 0.99	14	15	14	11	16	18	15
0.5 to 0.74	9	9	14	7	8	4	16
<0.5	11	8	11	5	5	8	3
Platelets (x 10^9/L)							
70 to 99	9	11	11	14	6	12	0.8
50 to 69	2	3	2	3	0	5	2
30 to 49	0	0.4	0	0.4	0	0	0
<30	0.9	0	1	0.9	0	0	0
Total Bilirubin (mg/dL)							
1.5 to 3.0	27	13	32	13	21	7	2
3.1 to 6.0	0.9	0.4	2	0	3	0	0
6.1 to 12.0	0	0	0.4	0	0	0	0
>12.0	0	0	0	0	0	0	0

6.3 Postmarketing Experiences

The following adverse reactions have been identified and reported during post approval use of REBETOL in combination with INTRON A or PegIntron. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Blood and Lymphatic System disorders
Pure red cell aplasia, aplastic anemia
Ear and Labyrinth disorders
Hearing disorder, vertigo
Respiratory, Thoracic and Mediastinal disorders
Pulmonary hypertension
Eye disorders
Serous retinal detachment
Endocrine disorders
Diabetes

7 DRUG INTERACTIONS

7.1 Didanosine

Exposure to didanosine or its active metabolite (dideoxyadenosine 5'-triphosphate) is increased when didanosine is coadministered with ribavirin, which could cause or worsen clinical toxicities; therefore, coadministration of REBETOL Capsules or Oral Solution and didanosine is contraindicated. Reports of fatal hepatic failure, as well as peripheral neuropathy, pancreatitis, and symptomatic hyperlactatemia/lactic acidosis have been reported in clinical trials.

7.2 Nucleoside Analogues

Hepatic decompensation (some fatal) has occurred in cirrhotic HIV/HCV co-infected patients receiving combination antiretroviral therapy for HIV and interferon alpha and ribavirin. Adding treatment with alpha interferons alone or in combination with ribavirin may increase the risk in this patient subset. Patients receiving interferon with ribavirin and nucleoside reverse transcriptase inhibitors (NRTIs) should be closely monitored for treatment-associated toxicities, especially hepatic decompensation and anemia. Discontinuation of NRTIs should be considered as medically appropriate *(see Individual NRTI Product Information).* Dose reduction or discontinuation of interferon, ribavirin, or both should also be considered if worsening clinical toxicities are observed, including hepatic decompensation (e.g., Child-Pugh greater than 6).

Ribavirin may antagonize the *cell culture* antiviral activity of stavudine and zidovudine against HIV. Ribavirin has been shown in cell culture to inhibit phosphorylation of lamivudine, stavudine, and zidovudine, which could lead to decreased antiretroviral activity. 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 suppress) interaction was observed when ribavirin and lamivudine (n=18), stavudine (n=10), or zidovudine (n=6) were coadministered as part of a multidrug regimen to HIV/HCV co-infected subjects. Therefore, concomitant use of ribavirin with either of these drugs should be used with caution.

7.3 Drugs Metabolized by Cytochrome P-450

Results of *in vitro* studies using both human and rat liver microsome preparations indicated little or no cytochrome P-450 enzyme-mediated metabolism of ribavirin, with minimal potential for P-450 enzyme-based drug interactions.

No pharmacokinetic interactions were noted between INTRON A for Injection and REBETOL Capsules in a multiple-dose pharmacokinetic study.

7.4 Azathioprine

The use of ribavirin for the treatment of chronic hepatitis C in patients receiving azathioprine has been reported to induce severe pancytopenia and may increase the risk of azathioprine-related myelotoxicity. Inosine monophosphate dehydrogenase (IMDH) is required for one of the metabolic pathways of azathioprine. Ribavirin is known to inhibit IMDH, thereby leading to accumulation of an azathioprine metabolite, 6-methylthioinosine monophosphate (6-MTITP), which is associated with myelotoxicity (neutropenia, thrombocytopenia, and anemia). Patients receiving azathioprine with ribavirin should have complete blood counts, including platelet counts, monitored weekly for the first month, twice monthly for the second and third months of treatment, then monthly or more frequently if dosage or other therapy changes are necessary *[see Warnings and Precautions (5.8)].*

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category X

[See Contraindications (4), Warnings and Precautions (5.1), and Nonclinical Toxicology (13.1)].

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 to 28.6 mg/kg, based on body surface area adjustment for a 60 kg adult; up to 1.7 times 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 REBETOL unless they are using effective contraception (two reliable forms) during the therapy period. In addition, effective contraception should be utilized for 6 months post-therapy 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 REBETOL and for the 6-month post-therapy period (e.g., 15 half-lives for ribavirin clearance from the body).

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

8.3 Nursing Mothers

It is not known whether the REBETOL product is excreted in human milk. Because of the potential for serious adverse reactions from the drug in nursing infants, a decision should be made whether to discontinue nursing or to delay or discontinue REBETOL.

8.4 Pediatric Use

Safety and effectiveness of REBETOL in combination with PegIntron has not been established in pediatric patients below the age of 3 years. For treatment with REBETOL/INTRON A, evidence of disease progression, such as hepatic inflammation and fibrosis, as well as prognostic factors for response, HCV genotype and viral load should be considered when deciding to treat a pediatric patient. The benefits of treatment should be weighed against the safety findings observed.

Suicidal ideation or attempts occurred more frequently among pediatric patients, primarily adolescents, compared to adult patients (2.4% vs. 1%) during treatment and off-therapy follow-up *[see Warnings and Precautions (5.10)].* As in adult patients, pediatric patients experienced other psychiatric adverse reactions (e.g., depression, emotional lability, somnolence), anemia, and neutropenia *[see Warnings and Precautions (5.2)].*

8.5 Geriatric Use

Clinical studies of REBETOL/INTRON A or PegIntron therapy did not include sufficient numbers of subjects aged 65 and over to determine if they respond differently from younger subjects.

REBETOL is known to be substantially excreted by the kidney, and the risk of toxic reactions to this drug may be greater in patients with impaired renal function. Because elderly patients often have decreased renal function, care should be taken in dose selection. Renal function should be monitored and dosage adjustments should be made accordingly. REBETOL should not be used in patients with creatinine clearance less than 50 mL/min [see *Contraindications (4)*].

In general, REBETOL Capsules should be administered to elderly patients cautiously, starting at the lower end of the dosing range, reflecting the greater frequency of decreased hepatic and cardiac function, and of concomitant disease or other drug therapy. In clinical trials, elderly subjects had a higher frequency of anemia (67%) than did younger patients (28%) *[see Warnings and Precautions (5.2)].*

8.6 Organ Transplant Recipients

The safety and efficacy of INTRON A and PegIntron alone or in combination with REBETOL for the treatment of hepatitis C in liver or other organ transplant recipients have not been established. 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.

8.7 HIV or HBV Co-infection

The safety and efficacy of PegIntron/REBETOL and INTRON A/REBETOL for the treatment of patients with HCV co-infected with HIV or HBV have not been established.

10 OVERDOSAGE

There is limited experience with overdosage. Acute ingestion of up to 20 g of REBETOL Capsules, INTRON A ingestion of up to 120 million units, and subcutaneous doses of INTRON A up to 10 times the recommended doses have been reported. Primary effects that have been observed are increased incidence and severity of the adverse reactions related to the therapeutic use of INTRON A and REBETOL. However, hepatic enzyme abnormalities, renal failure, hemorrhage, and myocardial infarction have been reported with administration of single subcutaneous doses of INTRON A that exceed dosing recommendations.

There is no specific antidote for INTRON A or REBETOL overdose, and hemodialysis and peritoneal dialysis are not effective for treatment of overdose of these agents.

11 DESCRIPTION

REBETOL is Merck Sharp & Dohme Corp.'s brand name for ribavirin, a synthetic nucleoside analogue (purine analogue). The chemical name of ribavirin is 1-β-D-ribofuranosyl-1H-1,2,4-triazole-3-carboxamide and has the following structural formula (see **Figure 1**).

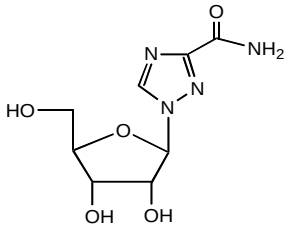

Figure 1: Structural Formula

Ribavirin is a white, crystalline powder. It is freely soluble in water and slightly soluble in anhydrous alcohol. The empirical formula is $C_8H_{12}N_4O_5$ 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.

REBETOL Oral Solution is a clear, colorless to pale or light yellow bubble gum-flavored liquid. Each milliliter of the solution contains 40 mg of ribavirin and the inactive ingredients sucrose, glycerin, sorbitol, propylene glycol, sodium citrate, citric acid, sodium benzoate, natural and artificial flavor for bubble gum #15864, and water.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Ribavirin is an antiviral agent *[see Clinical Pharmacology (12.4)].*

12.3 Pharmacokinetics

Single- and multiple-dose pharmacokinetic properties in adults are summarized in **Table 12.** 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 to 1200 mg ribavirin. The relationship between dose and C_{max} was curvilinear, tending to asymptote above single doses of 400 to 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 twice daily, steady-state was reached by approximately 4 weeks, with mean steady-state plasma concentrations of 2200 ng/mL (37%). Upon discontinuation of dosing, the mean half-life was 298 (30%) hours, which probably reflects slow elimination from nonplasma compartments.

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

Table 12: **Mean (% CV) Pharmacokinetic Parameters for REBETOL When Administered Individually to Adults**

Parameter	REBETOL		
	Single-Dose 600 mg Oral Solution (N=14)	**Single-Dose 600 mg Capsules** (N=12)	**Multiple-Dose 600 mg Capsules twice daily** (N=12)
T_{max} (hr)	1.00 (34)	1.7 (46)*****	3 (60)
C_{max} (ng/mL)	872 (42)	782 (37)	3680 (85)
AUC_{tf} (ng·hr/mL)	14,098 (38)	13,400 (48)	228,000 (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)[‡]	

***** N=11.
[†] Data obtained from a single-dose pharmacokinetic study using ^{14}C labeled ribavirin; N=5.
[‡] N=6.

Tissue Distribution: Ribavirin transport into nonplasma compartments has been most extensively studied in red blood cells, and has been identified to be primarily via an e_s-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.

Metabolism and Excretion: 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 of ^{14}C-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.

Special Populations:

Renal Dysfunction

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_{tf} value was threefold greater in subjects with creatinine clearance values between 10 to 30 mL/min when compared to control subjects (creatinine clearance greater than 90 mL/min). In subjects with creatinine clearance values between 30 to 60 mL/min, AUC_{tf} was twofold greater when compared to control subjects. The increased AUC_{tf} appears to be due to reduction of renal and nonrenal

clearance in these subjects. Phase III efficacy trials included subjects with creatinine clearance values greater than 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 less than 50 mL/min should not be treated with REBETOL [see *Contraindications (4)*].

Hepatic Dysfunction

The effect of hepatic dysfunction was assessed after a single oral dose of ribavirin (600 mg). The mean AUC_{tf} values were not 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.

Elderly Patients

Pharmacokinetic evaluations in elderly subjects have not been performed.

Gender

There were no clinically significant pharmacokinetic differences noted in a single-dose study of 18 male and 18 female subjects.

Pediatric Patients

Multiple-dose pharmacokinetic properties for REBETOL Capsules and INTRON A in pediatric subjects with chronic hepatitis C between 5 and 16 years of age are summarized in **Table 13.** The pharmacokinetics of REBETOL and INTRON A (dose-normalized) are similar in adults and pediatric subjects.

Complete pharmacokinetic characteristics of REBETOL Oral Solution have not been determined in pediatric subjects. Ribavirin C_{min} values were similar following administration of REBETOL Oral Solution or REBETOL Capsules during 48 weeks of therapy in pediatric patients (3 to 16 years of age).

Table 13: **Mean (% CV) Multiple-dose Pharmacokinetic Parameters for INTRON A and REBETOL Capsules When Administered to Pediatric Subjects with Chronic Hepatitis C**

Parameter	REBETOL 15 mg/kg/day as 2 divided doses (N=17)	INTRON A 3 MIU/m^2 three times weekly (N=54)
T_{max} (hr)	1.9 (83)	5.9 (36)
C_{max} (ng/mL)	3275 (25)	51 (48)
AUC*	29,774 (26)	622 (48)
Apparent Clearance L/hr/kg	0.27 (27)	ND†

* AUC_{12} (ng·hr/mL) for REBETOL; $AUC_{0\text{-}24}$ (IU·hr/mL) for INTRON A.
† ND=not done.
Note: numbers in parenthesis indicate % coefficient of variation.

A clinical study in pediatric subjects with chronic hepatitis C between 3 and 17 years of age was conducted in which pharmacokinetics for PegIntron and REBETOL (Capsules and Oral Solution) were evaluated. In pediatric subjects receiving body surface area-adjusted dosing of PegIntron at 60 mcg/m^2/week, the log transformed ratio estimate of exposure during the dosing interval is predicted to be 58% [90% CI: 141%, 177%] higher than observed in adults receiving 1.5 mcg/kg/week. The pharmacokinetics of REBETOL (dose-normalized) in this trial were similar to those reported in a prior study of REBETOL in combination with INTRON A in pediatric subjects and in adults subjects.

Effect of Food on Absorption of Ribavirin

Both AUC_{tf} and C_{max} increased by 70% when REBETOL Capsules were administered with a high-fat meal (841 kcal, 53.8 g fat, 31.6 g protein, and 57.4 g carbohydrate) in a single-dose pharmacokinetic study *[see Dosage and Administration (2)].*

12.4 Microbiology

Mechanism of Action

The mechanism by which ribavirin contributes to its antiviral efficacy in the clinic is not fully understood. Ribavirin has direct antiviral activity in tissue culture against many RNA viruses. Ribavirin increases the mutation frequency in the genomes of several viruses and ribavirin triphosphate inhibits HCV polymerase in a biochemical reaction.

Antiviral Activity in Cell Culture

The anti-viral activity of ribavirin in the HCV-replicon is not well understood and has not been defined because of the cellular toxicity of ribavirin. Direct anti-viral activity has been observed in tissue culture of other RNA viruses. The anti-HCV activity of interferon was demonstrated in cell containing self-replicating HCV-RNS (HCV replicon cells) or HCV infection.

Resistance

HCV genotypes show wide variability in their response to pegylated recombinant human interferon/ribavirin therapy. Genetic changes associated with the variable response have not been identified.

Cross-resistance

There is no reported cross-resistance between pegylated/non-pegylated interferons and ribavirin.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis

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 noncarcinogenic 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).

Mutagenesis

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 to 200 mg/kg (estimated human equivalent of 1.67 to 16.7 mg/kg, based on body surface area adjustment for a 60 kg adult; 0.1 to 1 times 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.

Impairment of Fertility

Ribavirin demonstrated significant embryocidal and teratogenic effects at doses well below the recommended human dose 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 times 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 times the maximum recommended human 24-hour dose of ribavirin) *[see Contraindications (4), and Warnings and Precautions (5.1)].*

Fertile women and partners of fertile women should not receive REBETOL 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 post-therapy (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 to 12.5 mg/kg/day, based on body surface area adjustment for a 60-kg adult; 0.1-0.8 times 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.

13.2 Animal Toxicology and Pharmacology

Long-term studies in the mouse and rat [18 to 24 months; doses of 20 to 75 and 10 to 40 mg/kg/day, respectively {estimated human equivalent doses of 1.67 to 6.25 and 1.43 to 5.71 mg/kg/day, respectively, based on body surface area adjustment for a 60 kg adult; approximately 0.1 to 0.4 times 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.

In a study in which rat pups were dosed postnatally with ribavirin at doses of 10, 25, and 50 mg/kg/day, drug-related deaths occurred at 50 mg/kg (at rat pup plasma concentrations below human plasma concentrations at the human therapeutic dose) between study Days 13 and 48. Rat pups dosed from postnatal Days 7 through 63 demonstrated a minor, dose-related decrease in overall growth at all doses, which was subsequently manifested as slight decreases in body weight, crown-rump length, and bone length. These effects showed evidence of reversibility, and no histopathological effects on bone were observed. No ribavirin effects were observed regarding neurobehavioral or reproductive development.

14 CLINICAL STUDIES

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

14.1 REBETOL/PegIntron Combination Therapy

Adult Subjects

Study 2

A randomized study compared treatment with two PegIntron/REBETOL regimens [PegIntron 1.5 mcg/kg subcutaneously once weekly/REBETOL 800 mg orally daily (in divided doses); PegIntron 1.5 mcg/kg subcutaneously once weekly for 4 weeks then 0.5 mcg/kg subcutaneously once weekly for 44 weeks/REBETOL 1000 or 1200 mg orally daily (in divided doses)] with INTRON A [3 MIU subcutaneously three times weekly/REBETOL 1000 or 1200 mg orally daily (in divided doses)] in 1530 adults with chronic hepatitis C. Interferon-naïve subjects were treated for 48 weeks and followed for 24 weeks posttreatment. Eligible subjects 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 (see **Table 14**). 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 14**).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 14: Rates of Response to Combination Treatment

	PegIntron 1.5 mcg/kg once weekly REBETOL 800 mg once daily	INTRON A 3 MIU three times weekly REBETOL 1000/1200 mg once daily
Overall response*,†	52% (264/511)	46% (231/505)
Genotype 1	41% (141/348)	33% (112/343)
Genotype 2-6	75% (123/163)	73% (119/162)

* Serum HCV-RNA was measured with a research-based quantitative polymerase chain reaction assay by a central laboratory.

† 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 at 24 weeks posttreatment.

Subjects with viral genotype 1, regardless of viral load, had a lower response rate to PegIntron (1.5 mcg/kg)/REBETOL (800 mg) compared to subjects with other viral genotypes. Subjects 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 combination therapy.

Subjects with lower body weight tended to have higher adverse-reaction rates *[see Adverse Reactions (6.1)]* and higher response rates than subjects with higher body weights. Differences in response rates between treatment arms did not substantially vary with body weight.

Treatment response rates with PegIntron/REBETOL combination therapy were 49% in men and 56% in women. Response rates were lower in African American and Hispanic subjects 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 subjects. Compared to baseline approximately two-thirds of subjects in all treatment groups were observed to have a modest reduction in inflammation.

Study 3

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

Treatment with PegIntron 1.5 mcg/kg and REBETOL 800 to 1400 mg resulted in a higher sustained virologic response compared to PegIntron in combination with a flat 800 mg daily dose of REBETOL. Subjects weighing greater than 105 kg obtained the greatest benefit with WBD, although a modest benefit was also observed in subjects weighing greater than 85 to 105 kg (see **Table 15**). The benefit of WBD in subjects weighing greater than 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 (6.1)].*

Table 15: 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)

* *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 greater than 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.

Study 4

A large randomized study compared the safety and efficacy of treatment for 48 weeks with two PegIntron/REBETOL regimens [PegIntron 1.5 mcg/kg and 1 mcg/kg subcutaneously once weekly both in combination with REBETOL 800 to 1400 mg PO daily (in two divided doses)] and Pegasys 180 mcg subcutaneously once weekly in combination with Copegus 1000 to 1200 mg PO daily (in two divided doses) in 3070 treatment-naïve adults with chronic hepatitis C genotype 1. In this study, lack of early virologic response by treatment Week 12 (subjects who do not achieve undetectable HCV-RNA or greater than or equal to 2 $\log_{10}$ reduction from baseline) was the criteria for discontinuation of treatment. Sustained Virologic Response (SVR) to the treatment was defined as undetectable HCV-RNA (Roche COBAS TaqMan assay, a lower limit of quantitation of 27 IU/mL) at 24 weeks posttreatment (see **Table 16**).

Table 16: Response Rate by Treatment

Treatment Group	% (number) of Patients		
	PegIntron 1.5 mcg/kg/REBETOL	**PegIntron 1 mcg/kg/REBETOL**	**Pegasys 180 mcg/Copegus**
SVR	40 (406/1019)	38 (386/1016)	41 (423/1035)

In all three treatment groups, overall SVR rates were similar. In subjects with poor prognostic factors, subjects randomized to PegIntron (1.5 mcg/kg)/REBETOL or Pegasys/Copegus achieved higher SVR rates compared to those randomized to the PegIntron 1 mcg/kg/REBETOL arm. In all arms, SVR rates were lower in subjects with poor prognostic factors compared to those without. For the PegIntron 1.5 mcg/kg plus REBETOL dose, SVR rates for those with and without, respectively, the following baseline factors were as follows: cirrhosis (10% vs. 42%), normal ALT levels (32% vs. 42%), baseline viral load greater than 600,000 IU/mL (35% vs. 61%), older than 40 years of age (38% vs. 50%), and African American subjects (23% vs. 44%). In subjects with undetectable HCV-RNA at treatment week 12 who received PegIntron (1.5 mcg/kg)/REBETOL, the SVR rate was 81% (328/407).

Study 5 - REBETOL/PegIntron Combination Therapy in Prior Treatment Failures

In a noncomparative trial, 2293 patients with moderate to severe fibrosis who failed previous treatment with combination alpha interferon/ribavirin were re-treated with PegIntron, 1.5 mcg/kg subcutaneously, once weekly, in combination with weight adjusted ribavirin. Eligible patients included prior nonresponders (patients who were HCV-RNA positive at the end of a minimum 12 weeks of treatment) and prior relapsers (patients who were HCV-RNA negative at the end of a minimum 12 weeks of treatment and subsequently relapsed after posttreatment follow-up). Patients who were negative at Week 12 were treated for 48 weeks and followed for 24 weeks posttreatment. Response to treatment was defined as undetectable HCV-RNA at 24 weeks posttreatment (measured using a research-based test, limit of detection 125 IU/mL). The overall response rate was 22% (497/2293) (99% CI: 19.5, 23.9). Patients with the following characteristics were less likely to benefit from re-treatment: previous nonresponse, previous pegylated interferon treatment, significant bridging fibrosis or cirrhosis, and genotype 1 infection.

The re-treatment sustained virologic response rates by baseline characteristics are summarized in **Table 17.**

Table 17: SVR Rates by Baseline Characteristics of Prior Treatment Failures

HCV Genotype/ Metavir Fibrosis Score	Overall SVR by Previous Response and Treatment			
	Nonresponder		Relapser	
	alfa interferon/ribavirin % (number of patients)	peginterferon (2a and 2b combined)/ribavirin % (number of patients)	alfa interferon/ribavirin % (number of patients)	peginterferon (2a and 2b combined)/ribavirin % (number of patients)
Overall	18 (158/903)	6 (30/476)	43 (130/300)	35 (113/344)
HCV 1	13 (98/761)	4 (19/431)	32 (67/208)	23 (56/243)
F2	18 (36/202)	6 (7/117)	42 (33/79)	32 (23/72)
F3	16 (38/233)	4 (4/112)	28 (16/58)	21 (14/67)
F4	7 (24/325)	4 (8/202)	26 (18/70)	18 (19/104)
HCV 2/3	49 (53/109)	36 (10/28)	67 (54/81)	57 (52/92)
F2	68 (23/34)	56 (5/9)	76 (19/25)	61 (11/18)
F3	39 (11/28)	38 (3/8)	67 (18/27)	62 (18/29)
F4	40 (19/47)	18 (2/11)	59 (17/29)	51 (23/45)
HCV 4	17 (5/29)	7 (1/15)	88 (7/8)	50 (4/8)

Achievement of an undetectable HCV-RNA at treatment week 12 was a strong predictor of sustained virologic response (SVR). In this trial, 1470 (64%) subjects did not achieve an undetectable HCV-RNA at treatment week 12, and were offered enrollment into long-term treatment trials, due to an inadequate treatment response. Of the 823 (36%) subjects who were HCV-RNA undetectable at treatment week 12, those infected with genotype 1 had an SVR of 48% (245/507), with a range of responses by fibrosis scores (F4-F2) of 39-55%. Subjects infected with genotype 2/3 who were HCV-RNA undetectable at treatment week 12 had an overall SVR of 70% (196/281), with a range of responses by fibrosis scores (F4-F2) of 60-83%. For all genotypes, higher fibrosis scores were associated with a decreased likelihood of achieving SVR.

Pediatric Subjects

Previously untreated pediatric subjects 3 to 17 years of age with compensated chronic hepatitis C and detectable HCV-RNA were treated with REBETOL 15 mg/kg per day plus PegIntron 60 mcg/m^2 once weekly for 24 or 48 weeks based on HCV genotype and baseline viral load. All subjects were to be followed for 24 weeks posttreatment. A total of 107 subjects received treatment of whom 52% were female, 89% were Caucasian, and 67% were infected with HCV Genotype 1. Subjects infected with Genotypes 1, 4 or Genotype 3 with HCV-RNA greater than or equal to 600,000 IU/mL received 48 weeks of therapy while those infected with Genotype 2 or Genotype 3 with HCV-RNA less than 600,000 IU/mL received 24 weeks of therapy. The study results are summarized in **Table 18**.

Table 18: Sustained Virologic Response Rates by Genotype and Assigned Treatment Duration – Pediatric Study

Genotype	All Subjects n=107	
	24 Weeks	48 Weeks
	Virologic Response n*,† (%)	Virologic Response n*,† (%)
All	26/27 (96.3)	44/80 (55.0)
1	-	38/72 (52.8)
2	14/15 (93.3)	-
3‡	12/12 (100)	2/3 (66.7)
4	-	4/5 (80.0)

* Response to treatment was defined as undetectable HCV-RNA at 24 weeks posttreatment.

† n=number of responders/number of subjects with given genotype, and assigned treatment duration.

‡ Subjects with genotype 3 low viral load (less than 600,000 IU/mL) were to receive 24 weeks of treatment while those with genotype 3 and high viral load were to receive 48 weeks of treatment.

14.2 REBETOL/INTRON A Combination Therapy

Adult Subjects

Previously Untreated Subjects

Adults with compensated chronic hepatitis C and detectable HCV-RNA (assessed by a central laboratory using a research-based RT-PCR assay) who were previously untreated with alpha interferon therapy were enrolled into two multicenter, double-blind trials (US and International) and randomized to receive REBETOL Capsules 1200 mg/day (1000 mg/day for subjects weighing less than or equal to 75 kg) plus INTRON A for Injection 3 MIU three times weekly or INTRON A for Injection plus placebo for 24 or 48 weeks followed by 24 weeks of off-therapy follow-up. The International study did not contain a 24-week INTRON A plus placebo treatment arm. The US study enrolled 912 subjects who, at baseline, were 67% male, 89%

Caucasian with a mean Knodell HAI score (I+II+III) of 7.5, and 72% genotype 1. The International study, conducted in Europe, Israel, Canada, and Australia, enrolled 799 subjects (65% male, 95% Caucasian, mean Knodell score 6.8, and 58% genotype 1).

Study results are summarized in **Table 19**.

Table 19: **Virologic and Histologic Responses: Previously Untreated Subjects***

	US Study				International Study		
	24 weeks of treatment		48 weeks of treatment		24 weeks of treatment	48 weeks of treatment	
	INTRON A plus REBETOL (N=228)	INTRON A plus Placebo (N=231)	INTRON A plus REBETOL (N=228)	INTRON A plus Placebo (N=225)	INTRON A plus REBETOL (N=265)	INTRON A plus REBETOL (N=268)	INTRON A plus Placebo (N=266)
Virologic Response							
Responder†	65 (29)	13 (6)	85 (37)	27 (12)	86 (32)	113 (42)	46 (17)
Nonresponder	147 (64)	194 (84)	110 (48)	168 (75)	158 (60)	120 (45)	196 (74)
Missing Data	16 (7)	24 (10)	33 (14)	30 (13)	21 (8)	35 (13)	24 (9)
Histologic Response							
Improvement‡	102 (45)	77 (33)	96 (42)	65 (29)	103 (39)	102 (38)	69 (26)
No improvement	77 (34)	99 (43)	61 (27)	93 (41)	85 (32)	58 (22)	111 (41)
Missing Data	49 (21)	55 (24)	71 (31)	67 (30)	77 (29)	108 (40)	86 (32)

* Number (%) of subjects.
† Defined as HCV-RNA below limit of detection using a research-based RT-PCR assay at end of treatment and during follow-up period.
‡ Defined as posttreatment (end of follow-up) minus pretreatment liver biopsy Knodell HAI score (I+II+III) improvement of greater than or equal to 2 points.

Of subjects who had not achieved HCV-RNA below the limit of detection of the research-based assay by Week 24 of REBETOL/INTRON A treatment, less than 5% responded to an additional 24 weeks of combination treatment.

Among subjects with HCV Genotype 1 treated with REBETOL/INTRON A therapy who achieved HCV-RNA below the detection limit of the research-based assay by 24 weeks, those randomized to 48 weeks of treatment had higher virologic responses compared to those in the 24-week treatment group. There was no observed increase in response rates for subjects with HCV nongenotype 1 randomized to REBETOL/INTRON A therapy for 48 weeks compared to 24 weeks.

Relapse Subjects

Subjects with compensated chronic hepatitis C and detectable HCV-RNA (assessed by a central laboratory using a research-based RT-PCR assay) who had relapsed following one or two courses of interferon therapy (defined as abnormal serum ALT levels) were enrolled into two multicenter, double-blind trials (US and International) and randomized to receive REBETOL 1200 mg/day (1000 mg/day for subjects weighing ≤75 kg) plus INTRON A 3 MIU three times weekly or INTRON A plus placebo for 24 weeks followed by 24 weeks of off-therapy follow-up. The US study enrolled 153 subjects who, at baseline, were 67% male, 92% Caucasian with a mean Knodell HAI score (I+II+III) of 6.8, and 58% genotype 1. The International study, conducted in Europe, Israel, Canada, and Australia, enrolled 192 subjects (64% male, 95% Caucasian, mean Knodell score 6.6, and 56% genotype 1). Study results are summarized in **Table 20.**

Table 20: **Virologic and Histologic Responses: Relapse Subjects***

	US Study		International Study	
	INTRON A plus REBETOL (N=77)	INTRON A plus Placebo (N=76)	INTRON A plus REBETOL (N=96)	INTRON A plus Placebo (N=96)
Virologic Response				
Responder†	33 (43)	3 (4)	46 (48)	5 (5)
Nonresponder	36 (47)	66 (87)	45 (47)	91 (95)
Missing Data	8 (10)	7 (9)	5 (5)	0 (0)
Histologic Response				
Improvement‡	38 (49)	27 (36)	49 (51)	30 (31)
No improvement	23 (30)	37 (49)	29 (30)	44 (46)
Missing Data	16 (21)	12 (16)	18 (19)	22 (23)

* Number (%) of subjects.
† Defined as HCV-RNA below limit of detection using a research-based RT-PCR assay at end of treatment and during follow-up period.
‡ Defined as posttreatment (end of follow-up) minus pretreatment liver biopsy Knodell HAI score (I+II+III) improvement of greater than or equal to 2 points.

Virologic and histologic responses were similar among male and female subjects in both the previously untreated and relapse studies.

Pediatric Subjects

Pediatric subjects 3 to 16 years of age with compensated chronic hepatitis C and detectable HCV-RNA (assessed by a central laboratory using a research-based RT-PCR assay) were treated with REBETOL 15 mg/kg per day plus INTRON A 3 MIU/m^2 three times weekly for 48 weeks followed by 24 weeks of off-therapy follow-up. A total of 118 subjects received treatment who were 57% male, 80% Caucasian, and 78% genotype 1. Subjects less than 5 years of age received REBETOL Oral Solution and those 5 years of age or older received either REBETOL Oral Solution or Capsules.

Study results are summarized in **Table 21.**

Table 21: **Virologic Response: Previously Untreated Pediatric Subjects***

	INTRON A 3 MIU/m^2 three times weekly plus REBETOL 15 mg/kg/day
Overall Response† (N=118)	54 (46)
Genotype 1 (N=92)	33 (36)
Genotype non-1 (N=26)	21 (81)

* Number (%) of subjects.
† Defined as HCV-RNA below limit of detection using a research-based RT-PCR assay at end of treatment and during follow-up period.

Subjects with viral genotype 1, regardless of viral load, had a lower response rate to INTRON A/REBETOL combination therapy compared to subjects with genotype non-1, 36% vs. 81%. Subjects with both poor prognostic factors (genotype 1 and high viral load) had a response rate of 26% (13/50).

16 HOW SUPPLIED/STORAGE AND HANDLING

REBETOL 200 mg Capsules are white, opaque capsules with REBETOL, 200 mg, and the Schering Corporation logo imprinted on the capsule shell; the capsules are packaged in a bottle containing 56 capsules (NDC 0085-1351-05), 70 capsules (NDC 0085-1385-07), and 84 capsules (NDC 0085-1194-03).

REBETOL Oral Solution 40 mg per mL is a clear, colorless to pale or light yellow bubble gum-flavored liquid and it is packaged in 4-oz amber glass bottles (100 mL/bottle) with child-resistant closures (NDC 0085-1318-01).

The 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].

REBETOL Oral Solution should be stored between 2-8°C (36-46°F) or at 25°C (77°F); excursions permitted to 15-30°C (59-86°F) [see USP Controlled Room Temperature].

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17 PATIENT COUNSELING INFORMATION

[See FDA-Approved Patient Labeling (Medication Guide).]

17.1 Anemia

The most common adverse experience occurring with REBETOL Capsules is anemia, which may be severe *[see Warnings and Precautions (5.2) and Adverse Reactions].* Patients should be advised that laboratory evaluations are required prior to starting therapy and periodically thereafter *[see Dosage and Administration (2.3)].* It is advised that patients be well hydrated, especially during the initial stages of treatment.

17.2 Pregnancy

Patients must be informed that REBETOL Capsules and Oral Solution may cause birth defects and 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 taking REBETOL. REBETOL 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 post therapy. 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 REBETOL and for 6 months post therapy. Patients (male and female) should be advised to notify the physician immediately in the event of a pregnancy *[see Contraindications (4), Warnings and Precautions (5.1), and Use in Specific Populations (8.1)].*

If pregnancy does occur during treatment or during 6 months post therapy, 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.

17.3 Risks versus Benefits

Patients receiving REBETOL Capsules should be informed of the benefits and risks associated with treatment, directed in its appropriate use, and referred to the patient **MEDICATION GUIDE**. Patients should be informed that the effect of treatment of hepatitis C infection on transmission is not known, and that appropriate precautions to prevent transmission of the hepatitis C virus should be taken.

Patients should be informed about what to do in the event they miss a dose of REBETOL; the missed dose should be taken as soon as possible during the same day. Patients should not double the next dose. Patients should be advised to contact their healthcare provider if they have questions.

Rebetol Oral Solution manufactured for:
Merck Sharp & Dohme Corp., a subsidiary of
MERCK & CO., INC.
Whitehouse Station, NJ 08889, USA

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Manufactured by:
Schering-Plough Canada, Inc.
Pointe Claire, Quebec, Canada

Rebetol Capsules manufactured by:
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MERCK & CO., INC.
Whitehouse Station, NJ 08889, USA

U.S. Patent No. 6,790,837.

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MEDICATION GUIDE

REBETOL® (REB-eh-tol)

(ribavirin)

Capsules and Oral Solution

Read this Medication Guide before you start taking REBETOL, and each time you get a refill. There may be new information. This information does not take the place of talking to your health care provider about your medical condition or your treatment.

What is the most important information I should know about REBETOL®?

1. **Do Not take REBETOL alone to treat chronic hepatitis C infection.** REBETOL should be used in combination with **either interferon alfa-2b (Intron® A) or peginterferon alfa-2b (PegIntron®)** to treat chronic hepatitis C infection.
2. **REBETOL may cause a significant drop in your red blood cell count and cause anemia in some cases. Anemia has been associated with worsening of Heart Problems, and in rare cases can cause a Heart Attack and Death.** Tell your health care provider if you have ever had any heart problems. REBETOL may not be right for you. **Seek medical attention right away if you experience chest pain**.
3. **REBETOL may cause Birth Defects or the Death of your unborn baby. Do Not Take REBETOL if you or your sexual partner is pregnant or plan to become pregnant. Do Not become Pregnant within 6 months after discontinuing REBETOL therapy.** You must use 2 forms of birth control when you take REBETOL and for the 6 months after treatment.
   - Females must have a pregnancy test before starting REBETOL, every month while taking REBETOL, and every month for the 6 months after the last dose of REBETOL.
   - **If you or your female sexual partner becomes pregnant while taking REBETOL, tell your health care provider right away. You or your health care provider should contact the REBETOL pregnancy registry by calling 1-800-593-2214. The REBETOL pregnancy registry collects information about what happens to mothers and their babies if the mother takes REBETOL while she is pregnant.**

What is REBETOL®?

REBETOL is a medicine used with either interferon alfa-2b (Intron A) or peginterferon alfa-2b (PegIntron) to treat chronic (lasting a long time) hepatitis C infection in people 3 years and older with liver disease.

It is not known if REBETOL use for longer than 1 year is safe and will work.

It is not known if REBETOL use in children younger than 3 years old is safe and will work.

Who should not take REBETOL®?

See "What is the most important information I should know about REBETOL?"

Do not take REBETOL if you have:

- or ever had serious allergic reactions to the ingredients in REBETOL. See the end of this Medication Guide for a complete list of ingredients.
- certain types of hepatitis (autoimmune hepatitis).
- certain blood disorders (hemoglobinopathies).
- severe kidney disease.
- taken or currently take didanosine (VIDEX®).

Talk to your health care provider before taking REBETOL if you have any of these conditions.

What should I tell my health care provider before taking REBETOL®?

Before you take REBETOL, tell your health care provider if you have or ever had:

- treatment for hepatitis C that did not work for you.
- breathing problems. REBETOL may cause or worsen breathing problems you already have.

- vision problems. REBETOL may cause eye problems or worsen eye problems you already have. You should have an eye exam before you start treatment with REBETOL.
- certain blood disorders such as anemia (low red blood cell count).
- high blood pressure, heart problems, or have had a heart attack. Your health care provider should check your blood and heart before you start treatment with REBETOL.
- thyroid problems.
- liver problems other than hepatitis C infection.
- human immunodeficiency virus (HIV) or any immunity problems.
- mental health problems, including depression or thoughts of suicide.
- kidney problems.
- an organ transplant.
- diabetes. REBETOL may make your diabetes worse or harder to treat.
- any other medical condition.
- are breastfeeding. It is not known if REBETOL passes into your breast milk. You and your health care provider should decide if you will take REBETOL or breastfeed.

Tell your health care provider about all the medicines you take, including prescription medicines, vitamins, and herbal supplements. REBETOL may affect the way other medicines work.

Especially tell your health care provider if you take didanosine (VIDEX®) or azathioprine (Imuran and Azasan).

Know the medicines you take. Keep a list of them to show your health care provider or pharmacist when you get a new medicine.

How should I take REBETOL®?

- Take REBETOL exactly as your health care provider tells you. Your health care provider will tell you how much REBETOL to take and when to take it.
- Take REBETOL with food.
- Take **REBETOL Capsules** whole. Do not open, break, or crush **REBETOL Capsules** before swallowing. If you cannot swallow **REBETOL Capsules** whole, tell your health care provider.
- If you miss a dose of REBETOL, take the missed dose as soon as possible during the same day. Do not double the next dose. If you have questions about what to do, call your health care provider.
- If you take too much REBETOL, call your health care provider or Poison Control Center at 1-800-222-1222, or go to the nearest hospital emergency room right away.

What are the possible side effects of REBETOL®?

REBETOL may cause serious side effects, including:
See "What is the most important information I should know about REBETOL?"

- **Swelling and irritation of your pancreas (pancreatitis).** You may have stomach pain, nausea, vomiting, or diarrhea.
- **Serious breathing problems.** Difficulty breathing may be a sign of a serious lung infection (pneumonia) that can lead to death.
- **Serious eye problems** that may lead to vision loss or blindness.
- **Dental problems.** Your mouth may be very dry, which can lead to problems with your teeth and gums.
- **Severe depression.**
- **Suicidal thoughts and attempts.** Adults and children who take REBETOL, especially teenagers, are more likely to have suicidal thoughts or attempt to hurt themselves while

taking REBETOL. Call your health care provider right away or go to the nearest hospital emergency room if you have new or worse depression or thoughts about suicide or dying.
- **Severe blood disorders.** An increased risk when used in combination with pegylated alpha interferons and azathioprine.
- **Weight loss and slowed growth in children.**

Tell your health care provider right away if you have any side effect that bothers you or that does not go away.

The most common side effects of REBETOL include:
- flu-like symptoms - feeling tired, headache, shaking along with high temperature (fever), nausea, and muscle aches.
- mood changes, feeling irritable.

The most common side effects of REBETOL in children include:
- a decrease in the blood cells that fight infection (neutropenia).
- a decrease in appetite.
- stomach pain and vomiting.

Tell your health care provider if you have any side effect that bothers you or that does not go away.

These are not all the possible side effects of REBETOL. For more information ask your health care provider or pharmacist.

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

How should I store REBETOL®?

- Store **REBETOL Capsules** between 59-86°F (15-30°C).
- Store **REBETOL Oral Solution** between 59-86°F (15-30°C) or in the refrigerator between 36-46°F (2-8°C).

Keep REBETOL and all medicines out of the reach of children.

GENERAL INFORMATION ABOUT THE SAFE AND EFFECTIVE USE OF REBETOL®.

It is not known if treatment with REBETOL will cure hepatitis C virus infections or prevent cirrhosis, liver failure, or liver cancer that can be caused by hepatitis C virus infections. It is not known if taking REBETOL will prevent you from infecting another person with the hepatitis C virus.

Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. Do not use REBETOL for a condition for which it was not prescribed. Do not give REBETOL to other people, even if they have the same symptoms that you have. It may harm them.

This Medication Guide summarizes the most important information about REBETOL. If you would like more information, talk with your health care provider. You can ask your pharmacist or health care provider for information about REBETOL that is written for health professionals.

What are the ingredients in REBETOL®?

Active ingredients: ribavirin

REBETOL Capsules

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.

REBETOL Oral Solution

Inactive ingredients: sucrose, glycerin, sorbitol, propylene glycol, sodium citrate, citric acid, sodium benzoate, natural and artificial flavor for bubble gum # 15864, and water.

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

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Manufactured by: Schering-Plough Canada, Inc., Pointe Claire, Quebec, Canada

Rebetol Capsules manufactured by:
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