

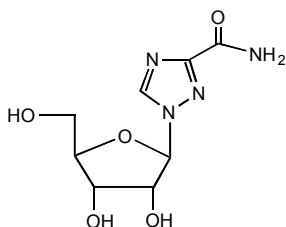
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**PRODUCT
INFORMATION****REBETOL[®] (ribavirin, USP) Capsules**

- 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).
- THE PRIMARY TOXICITY OF RIBAVIRIN IS HEMOLYTIC ANEMIA. THE ANEMIA ASSOCIATED WITH REBETOL THERAPY MAY RESULT IN WORSENING OF CARDIAC DISEASE THAT HAS LEAD TO FATAL AND NONFATAL MYOCARDIAL INFARCTIONS. PATIENTS WITH A HISTORY OF SIGNIFICANT OR UNSTABLE CARDIAC DISEASE SHOULD NOT BE TREATED WITH REBETOL. (SEE WARNINGS, ADVERSE REACTIONS, AND DOSAGE AND ADMINISTRATION).
- SIGNIFICANT TERATOGENIC AND/OR EMBRYOCIDAL EFFECTS HAVE BEEN DEMONSTRATED IN ALL ANIMAL SPECIES EXPOSED TO RIBAVIRIN. IN ADDITION, RIBAVIRIN HAS A MULTIPLE-DOSE HALF-LIFE OF 12 DAYS, AND SO IT MAY PERSIST IN NONPLASMA COMPARTMENTS FOR AS LONG AS 6 MONTHS. THEREFORE, REBETOL THERAPY IS CONTRAINDICATED IN WOMEN WHO ARE PREGNANT AND IN THE MALE PARTNERS OF WOMEN WHO ARE PREGNANT. EXTREME CARE MUST BE TAKEN TO AVOID PREGNANCY DURING THERAPY AND FOR 6 MONTHS AFTER COMPLETION OF TREATMENT IN BOTH FEMALE PATIENTS AND IN FEMALE PARTNERS OF MALE PATIENTS WHO ARE TAKING REBETOL THERAPY. AT LEAST TWO RELIABLE FORMS OF EFFECTIVE CONTRACEPTION MUST BE UTILIZED DURING TREATMENT AND DURING THE 6-MONTH POSTTREATMENT FOLLOW-UP PERIOD. (SEE CONTRAINDICATIONS, WARNINGS, PRECAUTIONS-INFORMATION FOR PATIENTS AND PREGNANCY CATEGORY X).

DESCRIPTION*REBETOL[®]*

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



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

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

Mechanism of Action

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

CLINICAL PHARMACOLOGY

Pharmacokinetics

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

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

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. There are insufficient data to address the clinical relevance of these results. Clinical efficacy studies with REBETOL/INTRON A were conducted without instructions with respect to food consumption. During clinical studies with REBETOL/PEG-INTRON, all subjects were instructed to take REBETOL Capsules with food. (See **DOSAGE AND ADMINISTRATION**.)

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

TABLE 1. Mean (% CV) Pharmacokinetic Parameters for REBETOL When Administered Individually to Adults with Chronic Hepatitis C

Parameter	REBETOL (N=12)	
	Single Dose 600 mg	Multiple Dose 600 mg BID
T _{max} (hr)	1.7 (46) ***	3 (60)
C _{max} *	782 (37)	3680 (85)
AUC _{0-t} **	13400 (48)	228000 (25)
T _{1/2} (hr)	43.6 (47)	298 (30)
Apparent Volume of Distribution (L)	2825 (9) †	
Apparent Clearance (L/hr)	38.2 (40)	
Absolute Bioavailability	64% (44) ††	

* ng/mL

** ng.hr/mL

*** N = 11

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

†† N = 6

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.

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 ¹⁴C-ribavirin, approximately 61% and 12% of the radioactivity was eliminated in the urine and feces, respectively, in 336 hours. Unchanged ribavirin accounted for 17% of the administered dose.

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

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

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

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 >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 non-renal clearance in these patients. Phase III efficacy trials included subjects with creatinine clearance values > 50 mL/min. The multiple dose pharmacokinetics of ribavirin cannot be accurately predicted in patients with renal dysfunction. Ribavirin is not effectively removed by hemodialysis. Patients with creatinine clearance <50 mL/min should not be treated with REBETOL (See **WARNINGS**).

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.

Pediatric Patients Pharmacokinetic evaluations in pediatric subjects have not been performed.

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 eighteen male and eighteen female subjects.

*** In this section of the label, numbers in parenthesis indicate % coefficient of variation.**

INDICATIONS AND USAGE

REBETOL (ribavirin, USP) Capsules are indicated in combination with INTRON A (interferon alfa-2b, recombinant) Injection for the treatment of chronic hepatitis C in patients with compensated liver disease previously untreated with alpha interferon or who have relapsed following alpha interferon therapy.

REBETOL Capsules are indicated in combination with PEG-INTRON (peginterferon alfa-2b, recombinant) Injection for the treatment of chronic hepatitis C in patients with compensated liver disease who have not been previously treated with interferon alpha and are at least 18 years of age.

The safety and efficacy of REBETOL Capsules with interferons other than INTRON A or PEG-INTRON products have not been established.

Description of Clinical Studies

REBETOL/INTRON A Combination Therapy

Previously Untreated Patients

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 patients weighing ≤ 75 kg) plus INTRON A Injection 3 MIU TIW or INTRON A 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 patients 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 patients (65% male, 95% Caucasian, mean Knodell score 6.8, and 58% genotype 1).

Study results are summarized in **TABLE 2**.

TABLE 2. Virologic and Histologic Responses: Previously Untreated Patients*

	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 ¹	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 ²	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 patients.

1. Defined as HCV RNA below limit of detection using a research based RT-PCR assay at end of treatment and during follow-up period.

2. Defined as posttreatment (end of follow-up) minus pretreatment liver biopsy Knodell HAI score (I+II+III) improvement of ≥ 2 points.

Of patients 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 patients 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 patients with HCV nongenotype 1 randomized to REBETOL/INTRON A therapy for 48 weeks compared to 24 weeks.

Relapse Patients

Patients 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 patients weighing ≤ 75 kg) plus INTRON A 3 MIU TIW or INTRON A plus placebo for 24 weeks followed by 24 weeks of off-therapy follow-up. The US study enrolled 153 patients 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 patients (64% male, 95% Caucasian, mean Knodell score 6.6, and 56% genotype 1).

Study results are summarized in **TABLE 3**.

TABLE 3. Virologic and Histologic Responses: Relapse Patients*

	US Study		International Study	
	INTRON A plus REBETOL	INTRON A plus Placebo	INTRON A plus REBETOL	INTRON A plus Placebo

	N=77	N=76	N=96	N=96
Virologic Response				
-Responder ¹	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 ²	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 Patients.

1. Defined as HCV RNA below limit of detection using a research based RT-PCR assay at end of treatment and during follow-up period.
2. Defined as posttreatment (end of follow-up) minus pretreatment liver biopsy Knodell HAI score (I+II+III) improvement of ≥ 2 points.

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

REBETOL/PEG-INTRON Combination Therapy

A randomized study compared treatment with two PEG-INTRON/REBETOL regimens [PEG-INTRON 1.5 $\mu\text{g}/\text{kg}$ SC once weekly (QW)/REBETOL 800 mg PO daily (in divided doses); PEG-INTRON 1.5 $\mu\text{g}/\text{kg}$ SC QW for 4 weeks then 0.5 $\mu\text{g}/\text{kg}$ SC QW for 44 weeks/REBETOL 1000/1200 mg PO daily (in divided doses)] with INTRON A [3 MIU SC thrice weekly (TIW)/REBETOL 1000/1200 mg PO daily (in divided doses)] in 1530 adults with chronic hepatitis C. Interferon naïve patients were treated for 48 weeks and followed for 24 weeks post-treatment. Eligible patients had compensated liver disease, detectable HCV RNA, elevated ALT, and liver histopathology consistent with chronic hepatitis.

Response to treatment was defined as undetectable HCV RNA at 24 weeks posttreatment (See **Table 4**).

Table 4. Rates of Response to Combination Treatment

	PEG-INTRON 1.5 $\mu\text{g}/\text{kg}$ QW REBETOL 800 mg QD	INTRON A 3 MIU TIW REBETOL 1000/1200mg QD
Overall ^{1,2} response	52% (264/511)	46% (231/505)
Genotype 1	41% (141/348)	33% (112/343)
Genotype 2-6	75%(123/163)	73% (119/162)

¹Serum HCV RNA was measured with a research-based quantitative polymerase chain reaction assay by a central laboratory.

²Difference in overall treatment response (PEG-INTRON/REBETOL vs. INTRON A/REBETOL) is 6% with 95% confidence interval of (0.18, 11.63) adjusted for viral genotype and presence of cirrhosis at baseline.

The response rate to PEG-INTRON 1.5→0.5µg/kg/REBETOL was essentially the same as the response to INTRON A/REBETOL (data not shown).

Patients with viral genotype 1, regardless of viral load, had a lower response rate to PEG-INTRON (1.5 µg/kg)/REBETOL combination therapy compared to patients with other viral genotypes. Patients with both poor prognostic factors (genotype 1 and high viral load) had a response rate of 30% (78/256) compared to a response rate of 29% (71/247) with INTRON A/REBETOL combination therapy.

Patients with lower body weight tended to have higher adverse event rates (see **ADVERSE REACTIONS**) and higher response rates than patients with higher body weights. Differences in response rates between treatment arms did not substantially vary with body weight.

Treatment response rates with PEG-INTRON/REBETOL combination therapy were 49% in men and 56% in women. Response rates were lower in African American and Hispanic patients and higher in Asians compared to Caucasians. Although African Americans had a higher proportion of poor prognostic factors compared to Caucasians the number of non-Caucasians studied (11% of the total) was insufficient to allow meaningful conclusions about differences in response rates after adjusting for prognostic factors.

Liver biopsies were obtained before and after treatment in 68% of patients. Compared to baseline approximately 2/3 of patients in all treatment groups were observed to have a modest reduction in inflammation.

CONTRAINDICATIONS

Pregnancy

REBETOL Capsules may cause birth defects and/or death of the exposed fetus. REBETOL therapy is contraindicated for use in women who are pregnant or in men whose female partners are pregnant. (See **WARNINGS, PRECAUTIONS-Information for Patients and Pregnancy Category X**).

REBETOL Capsules are contraindicated in patients with a history of hypersensitivity to ribavirin or any component of the capsule.

Patients with autoimmune hepatitis must not be treated with combination REBETOL/INTRON A therapy because using these medicines can make the hepatitis worse.

Patients with hemoglobinopathies (eg, thalassemia major, sickle-cell anemia) should not be treated with REBETOL Capsules.

WARNINGS

Based on results of clinical trials ribavirin monotherapy is not effective for the treatment of chronic hepatitis C virus infection; therefore, REBETOL Capsules must not be used alone. The safety and efficacy of REBETOL Capsules have only been established when used together with INTRON A (interferon alfa-2b, recombinant) as REBETRON Combination Therapy or with PEG-INTRON Injection.

There are significant adverse events caused by REBETOL/INTRON A or PEG-INTRON therapy, including severe depression and suicidal ideation, hemolytic anemia, suppression of bone marrow function, autoimmune and infectious disorders, pulmonary dysfunction, pancreatitis, and diabetes. The REBETRON Combination Therapy and PEG-INTRON package inserts should be reviewed in their entirety prior to initiation of combination treatment for additional safety information.

Pregnancy

REBETOL CAPSULES MAY CAUSE BIRTH DEFECTS AND/OR DEATH OF THE EXPOSED FETUS. EXTREME CARE MUST BE TAKEN TO AVOID PREGNANCY IN FEMALE PATIENTS AND IN FEMALE PARTNERS OF MALE PATIENTS. REBETOL HAS DEMONSTRATED SIGNIFICANT TERATOGENIC AND/OR EMBRYOCIDAL EFFECTS IN ALL ANIMAL SPECIES IN WHICH ADEQUATE STUDIES HAVE BEEN CONDUCTED. THESE EFFECTS OCCURRED AT DOSES AS LOW AS ONE TWENTIETH OF THE RECOMMENDED HUMAN DOSE OF RIBAVIRIN. REBETOL therapy should not be started until a report of a negative pregnancy test has been obtained immediately prior to planned initiation of therapy. PATIENTS SHOULD BE INSTRUCTED TO USE AT LEAST TWO FORMS OF EFFECTIVE CONTRACEPTION DURING TREATMENT AND DURING THE SIX MONTH PERIOD AFTER TREATMENT HAS BEEN STOPPED BASED ON MULTIPLE DOSE HALF-LIFE OF RIBAVIRIN OF 12 DAYS. PREGNANCY TESTING SHOULD OCCUR MONTHLY DURING REBETOL THERAPY AND FOR SIX MONTHS AFTER THERAPY HAS STOPPED (SEE CONTRAINDICATIONS AND PRECAUTIONS: INFORMATION FOR PATIENTS AND PREGNANCY CATEGORY X).

Anemia

The primary toxicity of ribavirin is hemolytic anemia, which was observed in approximately 10% of REBETOL/INTRON A-treated patients in clinical trials (See adverse reactions laboratory values - *hemoglobin*). The anemia associated with REBETOL capsules occurs within 1 - 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.

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: Guidelines for Dose Modification.) Because cardiac disease may be worsened by drug induced anemia, patients with a history of significant or unstable cardiac disease should not use REBETOL. (See ADVERSE REACTIONS.)

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

REBETOL should not be used in patients with creatinine clearance <50 mL/min. (See **Clinical Pharmacology, Special populations.**)

Pulmonary

Pulmonary symptoms, including dyspnea, pulmonary infiltrates, pneumonitis and pneumonia, have been reported during therapy with REBETOL/INTRON A; 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 REBETOL/INTRON A treatment should be discontinued.

PRECAUTIONS

The safety and efficacy of REBETOL/INTRON A and PEG-INTRON 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.

The safety and efficacy of REBETOL/INTRON A therapy has not been established in liver or other organ transplant patients, patients with decompensated liver disease due to hepatitis C infection, patients who are nonresponders to interferon therapy, or patients coinfecting with HBV or HIV.

Information for Patients

Patients must be informed that REBETOL Capsules may cause birth defects and/or death of the exposed fetus. 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 posttherapy. Women of childbearing potential must be counseled about use

of effective contraception (two reliable forms) prior to initiating therapy. Patients (male and female) must be advised of the teratogenic/embryocidal risks and must be instructed to practice effective contraception during REBETOL and for 6 months posttherapy. Patients (male and female) should be advised to notify the physician immediately in the event of a pregnancy. (See **CONTRAINDICATIONS and WARNINGS.**)

If pregnancy does occur during treatment or during 6 months posttherapy, the patient must be advised of the teratogenic risk of REBETOL therapy to the fetus. Patients, or partners of patients, should immediately report any pregnancy that occurs during treatment or within 6 months after treatment cessation to their physician. Physicians should report such cases by calling 1-800-727-7064.

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.

The most common adverse experience occurring with REBETOL Capsules is anemia, which may be severe. (See **ADVERSE REACTIONS.**) Patients should be advised that laboratory evaluations are required prior to starting therapy and periodically thereafter. (See **Laboratory Tests.**) It is advised that patients be well hydrated, especially during the initial stages of treatment.

Laboratory Tests The following laboratory tests are recommended for all patients treated with REBETOL Capsules, 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**]), 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**)

Carcinogenesis and Mutagenesis Ribavirin did not cause an increase in any tumor type when administered for 6 months in the transgenic p53 deficient mouse model at doses up to 300 mg/kg (estimated human equivalent of 25 mg/kg based on body surface area adjustment for a 60 kg adult; approximately 1.9 times the maximum recommended human daily dose). Ribavirin was non-carcinogenic when administered for 2 years to rats at doses up to 40 mg/kg (estimated human equivalent of 5.71 mg/kg based on body surface area adjustment for a 60 kg adult). However, this dose was less than the maximum tolerated dose, and therefore the study was not adequate to fully characterize the carcinogenic potential of ribavirin. Ribavirin demonstrated increased incidences of mutation and cell transformation in multiple genotoxicity assays. Ribavirin was active in the Balb/3T3 *In Vitro* Cell Transformation Assay. Mutagenic activity was observed in the mouse lymphoma assay, and at doses of 20-200 mg/kg (estimated human equivalent of 1.67 - 16.7 mg/kg, based on body surface area adjustment for a 60 kg adult; 0.1 - 1 X the maximum recommended human 24-hour dose of ribavirin) in a mouse micronucleus assay. A dominant lethal assay in rats was negative, indicating that if mutations occurred in rats they were not transmitted through male gametes.

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

Fertile women and partners of fertile women should not receive 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 posttherapy (eg, 15 half-lives of clearance for ribavirin).

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

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

Pregnancy Category X (see CONTRAINDICATIONS)

Ribavirin produced significant embryocidal and/or teratogenic effects in all animal species in which adequate studies have been conducted. Malformations of the skull, palate, eye, jaw, limbs, skeleton, and gastrointestinal tract were noted. The incidence and severity of teratogenic effects increased with escalation of the drug dose. Survival of fetuses and offspring was reduced. In conventional embryotoxicity/teratogenicity studies in rats and rabbits, observed no effect dose levels were well below those for proposed clinical use (0.3 mg/kg/day for both the rat and rabbit; approximately 0.06 X the recommended human 24-hour dose of ribavirin). No maternal toxicity or effects on offspring were observed in a peri/postnatal toxicity study in rats dosed orally at up to 1 mg/kg/day (estimated human equivalent dose of 0.17 mg/kg based on body surface area adjustment for a 60 kg adult; approximately 0.01 X the maximum recommended human 24-hour dose of ribavirin).

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

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

Male patients and their female partners must practice effective contraception (two reliable forms) during treatment with REBETOL and for the 6-month posttherapy period (eg, 15 half-lives for ribavirin clearance from the body).

If pregnancy occurs in a patient or partner of a patient during treatment or during the 6 months after treatment cessation, physicians should report such cases by calling 1-800-727-7064.

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.

GERIATRIC USE CLINICAL STUDIES OF REBETOL/INTRON A OR PEG-INTRON 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 <50 mL/MIN. (SEE WARNINGS.)

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/OR 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.)

Pediatric Use Safety and effectiveness in pediatric patients have not been established.

ADVERSE REACTIONS

The primary toxicity of ribavirin is hemolytic anemia. Reductions in hemoglobin levels occurred within the first 1-2 weeks of oral therapy. (See WARNINGS.) Cardiac and

pulmonary events associated with anemia occurred in approximately 10% of patients. (See WARNINGS.)

REBETOL/INTRON A Combination Therapy

In clinical trials, 19% and 6% of previously untreated and relapse patients, respectively, discontinued therapy due to adverse events in the combination arms compared to 13% and 3% in the interferon arms. Selected treatment-emergent adverse events that occurred in the US studies with $\geq 5\%$ incidence are provided in **TABLE 5** by treatment group. In general, the selected treatment-emergent adverse events 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.

TABLE 5. Selected Treatment-Emergent Adverse Events: Previously Untreated and Relapse Patients

Patients Reporting Adverse Events*	Percentage of Patients					
	US Previously Untreated Study				US Relapse Study	
	24 weeks of treatment		48 weeks of treatment		24 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)
Application Site Disorders						
injection site inflammation	13	10	12	14	6	8
injection site reaction	7	9	8	9	5	3
Body as a Whole - General Disorders						
Headache	63	63	66	67	66	68
Fatigue	68	62	70	72	60	53
Rigors	40	32	42	39	43	37
Fever	37	35	41	40	32	36
influenza-like symptoms	14	18	18	20	13	13
Asthenia	9	4	9	9	10	4
chest pain	5	4	9	8	6	7
Central & Peripheral Nervous System Disorders						
Dizziness	17	15	23	19	26	21
Gastrointestinal System Disorders						
Nausea	38	35	46	33	47	33
Anorexia	27	16	25	19	21	14
Dyspepsia	14	6	16	9	16	9
Vomiting	11	10	9	13	12	8
Musculoskeletal System Disorders						
Myalgia	61	57	64	63	61	58
Arthralgia	30	27	33	36	29	29
musculoskeletal pain	20	26	28	32	22	28
Psychiatric Disorders						
Insomnia	39	27	39	30	26	25
Irritability	23	19	32	27	25	20
Depression	32	25	36	37	23	14
emotional lability	7	6	11	8	12	8
concentration impaired	11	14	14	14	10	12
nervousness	4	2	4	4	5	4
Respiratory System Disorders						
Dyspnea	19	9	18	10	17	12
Sinusitis	9	7	10	14	12	7
Skin and Appendages Disorders						
Alopecia	28	27	32	28	27	26
Rash	20	9	28	8	21	5
Pruritus	21	9	19	8	13	4
Special Senses, Other Disorders						
taste perversion	7	4	8	4	6	5

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

In addition, the following spontaneous adverse events have been reported during the marketing surveillance of REBETOL/INTRON A therapy: hearing disorder and vertigo.

REBETOL/PEG-INTRON Combination Therapy

Overall, in clinical trials, 14% of patients receiving REBETOL in combination with PEG-INTRON, discontinued therapy compared with 13% treated with REBETOL in combination with INTRON A. The most common reasons for discontinuation of therapy were related to psychiatric, systemic (e.g. fatigue, headache), or gastrointestinal adverse events. Adverse events that occurred in clinical trial at >5% incidence are provided in **Table 6** by treatment group.

Table 6. Adverse Events Occurring in > 5% of Patients

ADVERSE EVENTS	PERCENTAGE OF PATIENTS REPORTING ADVERSE EVENTS*		ADVERSE EVENTS	PERCENTAGE OF PATIENTS REPORTING ADVERSE EVENTS*	
	PEG-INTRON 1.5µg/kg/REBETOL (n=511)	INTRON A/REBETOL (n=505)		PEG-INTRON 1.5µg/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 Sys.			Musculoskeletal Pain	21	19
Mouth Dry	12	8	Psychiatric		
Sweating Increased	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 Decrease	29	20	Menstrual Disorder	7	6
RUQ Pain	12	6	Resistance Mechanism		
Chest Pain	8	7	Infection Viral	12	12
Malaise	4	6	Infection Fungal	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			

*PATIENTS REPORTING ONE OR MORE ADVERSE EVENTS. A PATIENT MAY HAVE REPORTED MORE THAN ONE ADVERSE EVENT WITHIN A BODY SYSTEM/ORGAN CLASS CATEGORY.

Laboratory Values

REBETOL/INTRON A Combination Therapy

Changes in selected hematologic values (hemoglobin, white blood cells, neutrophils, and platelets) during therapy are described below. (See **TABLE 7**.)

Hemoglobin Hemoglobin decreases among patients receiving REBETOL therapy began at Week 1, with stabilization by Week 4. In previously untreated patients 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 patients 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 - 8 weeks of cessation of therapy in most patients.

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 patients with a previous diagnosis of Gilbert's syndrome. This has not been associated with hepatic dysfunction or clinical morbidity.

TABLE 7. Selected Hematologic Values During Treatment with REBETOL plus INTRON A: Previously Untreated and Relapse Patients

	Percentage of Patients					
	US Previously Untreated Study				US Relapse Study	
	24 weeks of treatment		48 weeks of treatment		24 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)
Hemoglobin (g/dL)						
9.5-10.9	24	1	32	1	21	3
8.0-9.4	5	0	4	0	4	0
6.5-7.9	0	0	0	0.4	0	0
<6.5	0	0	0	0	0	0
Leukocytes (x10⁹/L)						
2.0-2.9	40	20	38	23	45	26
1.5-1.9	4	1	9	2	5	3
1.0-1.4	0.9	0	2	0	0	0
<1.0	0	0	0	0	0	0
Neutrophils (x10⁹/L)						
1.0-1.49	30	32	31	44	42	34
0.75-0.99	14	15	14	11	16	18
0.5-0.74	9	9	14	7	8	4
<0.5	11	8	11	5	5	8
Platelets (x10⁹/L)						
70-99	9	11	11	14	6	12
50-69	2	3	2	3	0	5
30-49	0	0.4	0	0.4	0	0
<30	0.9	0	1	0.9	0	0
Total Bilirubin (mg/dL)						
1.5 -3.0	27	13	32	13	21	7
3.1-6.0	0.9	0.4	2	0	3	0

6.1-12.0
>12.0

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REBETOL/PEG-INTRON Combination Therapy

Changes in selected hematologic values (hemoglobin, white blood cells, neutrophils, and platelets) during therapy are described below. (See **TABLE 8**.)

Hemoglobin.

REBETOL induced a decrease in hemoglobin levels in approximately two thirds of patients. Hemoglobin levels decreased to < 11g/dL in about 30% of patients. Severe anemia (<8 g/dl) occurred in < 1% of patients. Dose modification was required in 9 and 13% of patients in the PEG-INTRON/REBETOL and INTRON A/REBETOL groups.

Bilirubin and Uric

In the REBETOL/PEG-INTRON combination trial 10-14% of patients developed hyperbilirubenemia and 33-38% developed hyperuricemia in association with hemolysis. Six patients developed mild to moderate gout.

Table 8: Selected Hematologic Values During Treatment with REBETOL plus PEG-INTRON

Number (%) of Subjects				
	PEG-INTRON plus REBETOL (N=511)	INTRON A plus REBETOL (N=505)	PEG-INTRON plus REBETOL (N=511)	INTRON A plus REBETOL (N=505)
Hemoglobin (g/dL)			Platelets (x10 ⁹ /L)	
9.5-10.9	26	27	70-99	15
8.0-9.4	3	3	50-69	3
6.5-7.9	0.2	0.2	30-49	0.2
<6.5	0	0	<30	0
Leukocytes (x10 ⁹ /L)			Total Bilirubin (mg/dL)	
2.0-2.9	46	41	1.5 -3.0	10
1.5-1.9	24	8	3.1-6.0	0.6
1.0-1.4	5	1	6.1-12.0	0
<1.0	0	0	>12.0	0
Neutrophils (x10 ⁹ /L)			ALT (SGPT)	
1.0-1.49	33	37	2 x Baseline	0.6
0.75-0.99	25	13	2.1-5 x Baseline	3
0.5-0.74	18	7	5.1-10 x Baseline	0
<0.5	4	2	>10 x Baseline	0

OVERDOSAGE

There is limited experience with overdosage. Acute ingestion of up to 20 grams 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 events 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, and hemodialysis and peritoneal dialysis are not effective treatment of overdose of either agent.

DOSAGE AND ADMINISTRATION (see **CLINICAL PHARMACOLOGY, Special Populations**; see **WARNINGS**)**REBETOL/INTRON A Combination Therapy**

The recommended dose of REBETOL Capsules depends on the patient's body weight. The recommended dose of REBETOL is provided in **TABLE 9**.

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 **Description of Clinical Studies** and **ADVERSE REACTIONS**.) 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.

In patients who relapse following interferon therapy, the recommended duration of treatment is 24 weeks. There are no safety and efficacy data on treatment for longer than 24 weeks in the relapse patient population.

TABLE 9. Recommended Dosing

Body weight	REBETOL Capsules
≤ 75 kg	2 x 200- mg capsules AM, 3 x 200-mg capsules PM daily p.o.
> 75 kg	3 x 200 mg capsules AM, 3 x 200 mg capsules PM daily p.o.

REBETOL may be administered without regard to food, but should be administered in a consistent manner with respect to food intake. (See **CLINICAL PHARMACOLOGY**.)

REBETOL/PEG-INTRON Combination Therapy

The recommended dose of REBETOL Capsules is 800 mg/day in 2 divided doses: two capsules (400 mg) in the morning with food and two capsules (400 mg) with in the evening with food.

Dose Modifications (TABLE 10)

If severe adverse reactions or laboratory abnormalities develop during combination REBETOL/INTRON A therapy the dose should be modified, or discontinued if appropriate, until the adverse reactions abate. If intolerance persists after dose adjustment, REBETOL/INTRON A therapy should be discontinued.

REBETOL should not be used in patients with creatinine clearance <50 mL/min. (See **WARNINGS and CLINICAL PHARMACOLOGY, Special populations.**)

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.**)

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

It is recommended that a patient whose hemoglobin level falls below 10 g/dL have his/her REBETOL dose reduced to 600 mg daily (1 x 200- mg capsule *AM*, 2 x 200 mg capsules *PM*). A patient whose hemoglobin level falls below 8.5 g/dL should be permanently discontinued from REBETOL therapy. (See **WARNINGS.**)

TABLE 10. Guidelines for Dose Modifications and Discontinuation for Anemia

	Dose Reduction* REBETOL - 600 mg daily	Permanent Discontinuation of REBETOL Treatment
Hemoglobin		
No Cardiac History	<10 g/dL	<8.5 g/dL
Cardiac History Patients	≥2 g/dL decrease during any 4-week period during treatment	<12 g/dL after 4 weeks of dose reduction

HOW SUPPLIED

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 42 capsules (NDC 0085-1327-04), 56 capsules (NDC 0085-1351-05), 70 capsules (NDC 0085-1385-07), and 84 capsules (NDC 0085-1194-03).

Storage Conditions

The bottle of REBETOL Capsules should be stored at 25°C (77°F); excursions are permitted between 15° and 30°C (59° and 86°F).



Schering Corporation
Kenilworth, NJ 07033 USA

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**PRODUCT
INFORMATION**

REBETRON™

Combination Therapy**containing****REBETOL® (ribavirin, USP) Capsules****and****INTRON® A (interferon alfa-2b, recombinant) Injection****CONTRAINDICATIONS AND WARNINGS**

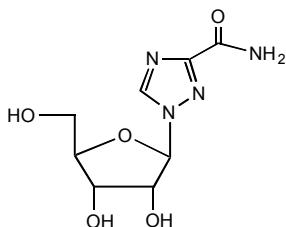
COMBINATION REBETOL/INTRON A THERAPY IS CONTRAINDICATED IN FEMALES WHO ARE PREGNANT AND IN THE MALE PARTNERS OF FEMALES WHO ARE PREGNANT. EXTREME CARE MUST BE TAKEN TO AVOID PREGNANCY DURING THERAPY AND FOR 6 MONTHS AFTER COMPLETION OF TREATMENT IN FEMALE PATIENTS, AND IN FEMALE PARTNERS OF MALE PATIENTS WHO ARE TAKING COMBINATION REBETOL/INTRON A THERAPY. FEMALES OF CHILDBEARING POTENTIAL AND MALES MUST USE TWO RELIABLE FORMS OF EFFECTIVE CONTRACEPTION DURING TREATMENT AND DURING THE 6-MONTH POSTTREATMENT FOLLOW-UP PERIOD. SIGNIFICANT TERATOGENIC AND/OR EMBRYOCIDAL EFFECTS HAVE BEEN DEMONSTRATED FOR RIBAVIRIN IN ALL ANIMAL SPECIES STUDIED. SEE CONTRAINDICATIONS AND WARNINGS.

REBETOL MONOTHERAPY IS NOT EFFECTIVE FOR THE TREATMENT OF CHRONIC HEPATITIS C AND SHOULD NOT BE USED FOR THIS INDICATION. SEE WARNINGS.

ALPHA INTERFERONS, INCLUDING INTRON® A, CAUSE OR AGGRAVATE FATAL OR LIFE-THREATENING NEUROPSYCHIATRIC, AUTOIMMUNE, ISCHEMIC, AND INFECTIOUS DISORDERS. PATIENTS SHOULD BE MONITORED CLOSELY WITH PERIODIC CLINICAL AND LABORATORY EVALUATIONS. PATIENTS WITH PERSISTENTLY SEVERE OR WORSENING SIGNS OR SYMPTOMS OF THESE CONDITIONS SHOULD BE WITHDRAWN FROM THERAPY. IN MANY BUT NOT ALL CASES THESE DISORDERS RESOLVE AFTER STOPPING INTRON A THERAPY. SEE WARNINGS, AND ADVERSE REACTIONS.

DESCRIPTION**REBETOL®**

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



44 Ribavirin is a white, crystalline powder. It is freely soluble in water and slightly
45 soluble in anhydrous alcohol. The empirical formula is $C_8H_{12}N_4O_5$ and the molecular weight
46 is 244.21.

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

54

55 **INTRON[®] A**

56 INTRON A is Schering Corporation's brand name for interferon alfa-2b, recombinant, a
57 purified, sterile, recombinant interferon product.

58 Interferon alfa-2b, recombinant has been classified as an alpha interferon and is a
59 water-soluble protein composed of 165 amino acids with a molecular weight of 19,271
60 daltons produced by recombinant DNA techniques. It is obtained from the bacterial
61 fermentation of a strain of *Escherichia coli* bearing a genetically engineered plasmid
62 containing an interferon alfa-2b gene from human leukocytes. The fermentation is carried out
63 in a defined nutrient medium containing the antibiotic tetracycline hydrochloride at a
64 concentration of 5 to 10 mg/L; the presence of this antibiotic is not detectable in the final
65 product.

66 INTRON A Injection is a clear, colorless solution. The 3 million IU vial of INTRON
67 A Injection contains 3 million IU of interferon alfa-2b, recombinant per 0.5 mL. The 18
68 million IU multidose vial of INTRON A Injection contains a total of 22.8 million IU of
69 interferon alfa-2b, recombinant per 3.8 mL (3 million IU/0.5 mL) in order to provide the
70 delivery of six 0.5 mL doses, each containing 3 million IU of INTRON A (for a label
71 strength of 18 million IU). The 18 million IU INTRON A Injection multidose pen contains a
72 total of 22.5 million IU of interferon alfa-2b, recombinant per 1.5 mL (3 million IU/0.2 mL)
73 in order to provide the delivery of six 0.2-mL doses, each containing 3 million IU of
74 INTRON A (for a label strength of 18 million IU). Each mL also contains 7.5 mg sodium
75 chloride, 1.8 mg sodium phosphate dibasic, 1.3 mg sodium phosphate monobasic, 0.1 mg
76 edetate disodium, 0.1 mg polysorbate 80, and 1.5 mg m-cresol as a preservative.

77 Based on the specific activity of approximately 2.6×10^8 IU/mg protein as measured
78 by HPLC assay, the corresponding quantities of interferon alfa-2b, recombinant in the vials
79 and pen described above are approximately 0.012 mg, 0.088 mg, and 0.087 mg protein,
80 respectively.

81

82 **Mechanism of Action**

83 *Ribavirin/Interferon alfa-2b, recombinant* The mechanism of inhibition of hepatitis C virus
84 (HCV) RNA by combination therapy with REBETOL and INTRON A has not been
85 established.

86

87

CLINICAL PHARMACOLOGY

88 **Pharmacokinetics**

89 *Interferon alfa-2b, recombinant* Single- and multiple-dose pharmacokinetic properties of
90 INTRON A (interferon alfa-2b, recombinant) are summarized in **TABLE 1**. Following a
91 single 3 million IU (MIU) subcutaneous dose in 12 patients with chronic hepatitis C, mean

92 (% CV*) serum concentrations peaked at 7 (44%) hours. Following 4 weeks of
 93 subcutaneous dosing with 3 MIU three times a week (TIW), interferon serum concentrations
 94 were undetectable predose. However, a twofold increase in bioavailability was noted upon
 95 multiple dosing of interferon; the reason for this is unknown. Mean half-life values
 96 following single- and multiple-dose administrations were 6.8 (24%) hours and 6.5 (29%)
 97 hours, respectively.

98

99 *Ribavirin* Single- and multiple-dose pharmacokinetic properties in adults with chronic
 100 hepatitis C are summarized in **TABLE 1**. Ribavirin was rapidly and extensively absorbed
 101 following oral administration. However, due to first-pass metabolism, the absolute
 102 bioavailability averaged 64% (44%). There was a linear relationship between dose and
 103 AUC_{tf} (AUC from time zero to last measurable concentration) following single doses of 200-
 104 1200 mg ribavirin. The relationship between dose and C_{max} was curvilinear, tending to
 105 asymptote above single doses of 400-600 mg.

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

111

112 *Effect of Food on Absorption of Ribavirin* Both AUC_{tf} and C_{max} increased by 70% when
 113 REBETOL Capsules were administered with a high-fat meal (841 kcal, 53.8 g fat, 31.6 g
 114 protein, and 57.4 g carbohydrate) in a single-dose pharmacokinetic study. There are
 115 insufficient data to address the clinical relevance of these results. Clinical efficacy studies
 116 were conducted without instructions with respect to food consumption. (See **DOSAGE AND**
 117 **ADMINISTRATION**.)

118

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

122

TABLE 1. Mean (% CV) Pharmacokinetic Parameters for INTRON A and REBETOL When Administered Individually to Adults with Chronic Hepatitis C

Parameter	INTRON A (N=12)		REBETOL (N=12)	
	Single Dose 3 MIU	Multiple Dose 3 MIU TIW	Single Dose 600 mg	Multiple Dose 600 mg BID
T _{max} (hr)	7 (44)	5 (37)	1.7 (46)	3 (60)
C _{max} *	13.9 (32)	29.7 (33)	782 (37)	3680 (85)
AUC _{tf} **	142 (43)	333 (39)	13400 (48)	228000 (25)
T _{1/2} (hr)	6.8 (24)	6.5 (29)	43.6 (47)	298 (30)
Apparent Volume of Distribution (L)			2825 (9) [†]	
Apparent Clearance (L/hr)	14.3 (17)		38.2 (40)	
Absolute Bioavailability			64% (44) ^{††}	

123 * IU/mL for INTRON A and ng/mL for REBETOL

124 ** IU.hr/mL for INTRON A and ng.hr/mL for REBETOL

125 † data obtained from a single-dose pharmacokinetic study using ¹⁴C labeled ribavirin; N =

126 5

127 †† N = 6

128 *** N = 11

129

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

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

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

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

146

147 ***Special Populations***

148 ***Renal Dysfunction*** The pharmacokinetics of ribavirin were assessed after administration of a
149 single oral dose (400 mg) of ribavirin to subjects with varying degrees of renal dysfunction.
150 The mean AUC_{tf} value was threefold greater in subjects with creatinine clearance values
151 between 10 to 30 mL/min when compared to control subjects (creatinine clearance >90
152 mL/min). This appears to be due to reduction of apparent clearance in these patients.
153 Ribavirin was not removed by hemodialysis. Patients with creatinine clearance < 50mL/min
154 should not be treated with REBETOL (see **WARNINGS**).

155

156 ***Hepatic Dysfunction*** The effect of hepatic dysfunction was assessed after a single oral dose
157 of ribavirin (600 mg). The mean AUC_{tf} values were not significantly different in subjects
158 with mild, moderate, or severe hepatic dysfunction (Child-Pugh Classification A, B, or C),
159 when compared to control subjects. However, the mean C_{max} values increased with severity
160 of hepatic dysfunction and was twofold greater in subjects with severe hepatic dysfunction
161 when compared to control subjects.

162

163 ***Pediatric Patients*** Multiple-dose pharmacokinetic properties for ribavirin in pediatric
164 patients with chronic hepatitis C between 5 and 16 years of age are summarized in **TABLE**
165 **2**.

166

TABLE 2. Mean (% CV) Pharmacokinetic Parameters for REBETOL When Administered to Pediatric Patients with Chronic Hepatitis C		
Parameter	12 mg/kg/day as 2 divided doses (n=19)	15 mg/kg/day as 2 divided doses (n=19)
T _{max} (hr)	1.4 (60)	1.9 (81)

C _{max} (ng/mL)	2705 (17)	3243 (24)
AUC ₁₂ (ng*hr/mL)	25049 (16)	29620 (25)
Apparent Clearance (L/hr/kg)	0.25 (16)	0.27 (25)

167

168

169 *Elderly Patients* Pharmacokinetic evaluations for elderly subjects have not been performed.

170

171 *Gender* There were no clinically significant pharmacokinetic differences noted in a single-

172 dose study of eighteen male and eighteen female subjects.

173

174 * *In this section of the label, numbers in parenthesis indicate % coefficient of variation.*

175

176

INDICATIONS AND USAGE

177 REBETOL (ribavirin, USP) Capsules is indicated in combination with INTRON A

178 (interferon alfa-2b, recombinant) Injection for the treatment of chronic hepatitis C in patients

179 with compensated liver disease previously untreated with alpha interferon or who have

180 relapsed following alpha interferon therapy.

181

182 **Description of Clinical Studies**183 *Previously Untreated Patients* Adults with compensated chronic hepatitis C and184 *detectable HCV RNA (assessed by a central laboratory using a research-based RT-*185 *PCR assay) who were previously untreated with alpha interferon therapy were*186 *enrolled into two multicenter, double-blind trials (US and International) and*187 *randomized to receive REBETOL Capsules 1200 mg/day (1000 mg/day for patients*188 *weighing ≤75 kg) plus INTRON A Injection 3 MIU TIW or INTRON A Injection plus*189 *placebo for 24 or 48 weeks followed by 24 weeks of off-therapy follow-up. The*190 *International study did not contain a 24-week INTRON A plus placebo treatment arm.*191 *The US study enrolled 912 patients who, at baseline, were 67% male, 89% caucasian*192 *with a mean Knodell HAI score (I+II+III) of 7.5, and 72% genotype 1. The*193 *International study, conducted in Europe, Israel, Canada, and Australia, enrolled*194 *799 patients (65% male, 95% caucasian, mean Knodell score 6.8, and 58% genotype*195 *1).*

196

197 Study results are summarized in **TABLE 3.**

198

	US Study				International Study		
	24 weeks of treatment		48 weeks of treatment		24 weeks of treatment	48 weeks of treatment	
	INTRON A plus REBETO	INTRO N A plus	INTRON A plus REBET	INTRO N A plus	INTRON A plus REBETO	INTRON A plus REBETO	INTRO N A plus

	L (N=228)	Placebo (N=231)	OL (N=228)	Placebo (N=225)	L (N=265)	L (N=268)	Placebo (N=266)
Virologic Response							
-Responder ¹	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 ²	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)

199 * Number (%) of Patients.

200 ¹ Defined as HCV RNA below limit of detection using a research based RT-PCR assay at
201 end of treatment and during follow-up period.

202 ² Defined as posttreatment (end of follow-up) minus pretreatment liver biopsy Knodell
203 HAI score (I+II+III) improvement of ≥ 2 points.

204

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

208

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

215

216 *Relapse Patients Patients with compensated chronic hepatitis C and detectable HCV*
217 *RNA (assessed by a central laboratory using a research based RT-PCR assay) who*
218 *had relapsed following one or two courses of interferon therapy (defined as abnormal*
219 *serum ALT levels) were enrolled into two multicenter, double-blind trials (US and*
220 *International) and randomized to receive REBETOL 1200 mg/day (1000 mg/day for*
221 *patients weighing ≤ 75 kg) plus INTRON A 3 MIU TIW or INTRON A plus placebo for*
222 *24 weeks followed by 24 weeks of off-therapy follow-up. The US study enrolled 153*
223 *patients who, at baseline, were 67% male, 92% caucasian with a mean Knodell HAI*

224 *score (I+II+III) of 6.8, and 58% genotype 1. The International study, conducted in*
 225 *Europe, Israel, Canada, and Australia, enrolled 192 patients (64% male, 95%*
 226 *caucasian, mean Knodell score 6.6, and 56% genotype 1).*

227 Study results are summarized in **TABLE 4**.
 228

229

TABLE 4. Virologic and Histologic Responses: Relapse Patients*				
	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 ¹	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 ²	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)

230 * Number (%) of Patients.

231 ¹ Defined as HCV RNA below limit of detection using a research based RT-PCR assay at
 232 end of treatment and during follow-up period.

233 ² Defined as posttreatment (end of follow-up) minus pretreatment liver biopsy Knodell HAI
 234 score (I+II+III) improvement of ≥ 2 points.

235

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

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CONTRAINDICATIONS

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REBETOL Capsules in combination with INTRON A Injection is contraindicated in patients with a history of hypersensitivity to ribavirin and/or alpha interferon or any component of the capsule and/or injection.

258

259 Patients with autoimmune hepatitis must not be treated with combination
260 REBETOL/INTRON A therapy.

261

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WARNINGS

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Pregnancy

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264 **Category X, may cause birth defects. See boxed CONTRAINDICATIONS AND**
265 **WARNINGS. See CONTRAINDICATIONS.**

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Anemia

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268 **HEMOLYTIC ANEMIA (HEMOGLOBIN <10 G/DL) WAS OBSERVED IN**
269 **APPROXIMATELY 10% OF REBETOL/INTRON A-TREATED PATIENTS IN**
270 **CLINICAL TRIALS (SEE ADVERSE REACTIONS LABORATORY VALUES -**
271 **HEMOGLOBIN). ANEMIA OCCURRED WITHIN 1 - 2 WEEKS OF INITIATION OF**
272 **RIBAVIRIN THERAPY. BECAUSE OF THIS INITIAL ACUTE DROP IN**
273 **HEMOGLOBIN, IT IS ADVISED THAT COMPLETE BLOOD COUNTS (CBC)**
274 **SHOULD BE OBTAINED PRETREATMENT AND AT WEEK 2 AND WEEK 4 OF**
275 **THERAPY OR MORE FREQUENTLY IF CLINICALLY INDICATED. PATIENTS**
276 **SHOULD THEN BE FOLLOWED AS CLINICALLY APPROPRIATE.**

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278 The anemia associated with REBETOL/INTRON A therapy may result in
279 deterioration of cardiac function and/or exacerbation of the symptoms of coronary disease.
280 Patients should be assessed before initiation of therapy and should be appropriately
281 monitored during therapy. If there is any deterioration of cardiovascular status, therapy
282 should be suspended or discontinued. (See **DOSAGE AND ADMINISTRATION.**)
283 Because cardiac disease may be worsened by drug induced anemia, patients with a history of
284 significant or unstable cardiac disease should not use combination REBETOL/INTRON A
285 therapy. (See **ADVERSE REACTIONS.**)

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Psychiatric

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287 Similarly, patients with hemoglobinopathies (eg, thalassemia, sickle-cell anemia)
288 should not be treated with combination REBETOL/INTRON A therapy.

291 **Severe psychiatric adverse events, including depression, psychoses, aggressive behavior,**
292 **hallucinations, violent behavior (suicidal ideation, suicidal attempts, suicides) and rare**
293 **instances of homicidal ideation have occurred during combination Rebetol/Intron A**
294 **therapy, both in patients with and without a previous psychiatric disorder.**
295 **Rebetol/Intron A therapy should be used with extreme caution in patients with a**
296 **history of pre-existing psychiatric disorders, and all patients should be carefully**
297 **monitored for evidence of depression and other psychiatric symptoms. Suspension of**
298 **Rebetol/Intron A therapy should be considered if psychiatric intervention and/or dose**
299 **reduction is unsuccessful in controlling psychiatric symptoms. In severe cases, therapy**
300 **should be stopped immediately and psychiatric intervention sought. (See ADVERSE**
301 **REACTIONS.)**

303

Bone marrow toxicity:

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305

304 INTRON A therapy suppresses bone marrow function and may result in severe cytopenias
305 including very rare events of aplastic anemia. It is advised that complete blood counts (CBC)

306 be obtained pre-treatment and monitored routinely during therapy (see **PRECAUTIONS:**
307 **Laboratory Tests**). INTRON A therapy should be discontinued in patients who develop
308 severe decreases in neutrophil ($<0.5 \times 10^9/L$) or platelet counts ($<25 \times 10^9/L$) (see **DOSAGE**
309 **AND ADMINISTRATION: Guidelines for Dose Modifications**).

310

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313 **Pulmonary**

314 Pulmonary symptoms, including dyspnea, pulmonary infiltrates, pneumonitis and
315 pneumonia, have been reported during therapy with REBETOL/INTRON A; occasional
316 cases of fatal pneumonia have occurred. In addition, sarcoidosis or the exacerbation of
317 sarcoidosis has been reported. . If there is evidence of pulmonary infiltrates or pulmonary
318 function impairment, the patient should be closely monitored, and, if appropriate,
319 combination REBETOL/INTRON A treatment should be discontinued.

320

321 **Other**

322 • REBETOL Capsule monotherapy is not effective for the treatment of chronic hepatitis C
323 and should not be used for this indication.

324 • Fatal and nonfatal pancreatitis has been observed in patients treated with
325 REBETOL/INTRON A therapy. REBETOL/INTRON A therapy should be suspended in
326 patients with signs and symptoms of pancreatitis and discontinued in patients with
327 confirmed pancreatitis.

328 • Combination REBETOL/INTRON A therapy should not be used in patients with
329 creatinine clearance <50 mL/min.

330 • Diabetes mellitus and hyperglycemia have been observed in patients treated with
331 INTRON A.

332 • Ophthalmologic disorders have been reported with treatment with alpha interferons
333 (including INTRON A therapy). Investigators using alpha interferons have reported the
334 occurrence of retinal hemorrhages, cotton wool spots, and retinal artery or vein
335 obstruction in rare instances. Any patient complaining of loss of visual acuity or visual
336 field should have an eye examination. Because these ocular events may occur in
337 conjunction with other disease states, a visual exam prior to initiation of combination
338 REBETOL/INTRON A therapy is recommended in patients with diabetes mellitus or
339 hypertension.

340 • Acute serious hypersensitivity reactions (eg, urticaria, angioedema, bronchoconstriction,
341 anaphylaxis) have been observed in INTRON A-treated patients; if such an acute reaction
342 develops, combination REBETOL/INTRON A therapy should be discontinued immediately
343 and appropriate medical therapy instituted.

344 • Combination REBETOL/INTRON A therapy should be discontinued for patients
345 developing thyroid abnormalities during treatment whose thyroid function cannot be
346 controlled by medication.

347

348

348 PRECAUTIONS

349 Exacerbation of autoimmune disease has been reported in patients receiving alpha interferon
350 therapy (including INTRON A therapy). REBETOL/INTRON A therapy should be used with
351 caution in patients with other autoimmune disorders.

352 There have been reports of interferon, including INTRON A (interferon alfa-2b,
353 recombinant) exacerbating pre-existing psoriasis; therefore, combination

354 REBETOL/INTRON A therapy should be used in these patients only if the potential benefit
355 justifies the potential risk.

356 The safety and efficacy of REBETOL/INTRON A therapy has not been established in
357 liver or other organ transplant patients, decompensated hepatitis C patients, patients who are
358 nonresponders to interferon therapy, or patients coinfecting with HBV or HIV.

359 The safety and efficacy of REBETOL Capsule monotherapy for the treatment of HIV
360 infection, adenovirus, early RSV infection, parainfluenza, or influenza have not been
361 established and REBETOL Capsules should not be used for these indications.

362 There is no information regarding the use of REBETOL Capsules with other
363 interferons.

364

365 **TRIGLYCERIDES: ELEVATED TRIGLYCERIDE LEVELS HAVE BEEN OBSERVED IN PATIENTS**
366 **TREATED WITH INTERFERON INCLUDING REBETOL/INTRON A THERAPY. ELEVATED**
367 **TRIGLYCERIDE LEVELS SHOULD BE MANAGED AS CLINICALLY APPROPRIATE. SEVERE**
368 **HYPERTRIGLYCERIDEMIA (TRIGLYCERIDES >1000 MG/DL) MAY RESULT IN PANCREATITIS.**
369 **DISCONTINUATION OF REBETOL/INTRON A THERAPY SHOULD BE CONSIDERED FOR**
370 **PATIENTS WITH PERSISTENTLY ELEVATED TRIGLYCERIDES (TRIGLYCERIDES >1000 MG/DL)**
371 **ASSOCIATED WITH SYMPTOMS OF POTENTIAL PANCREATITIS, SUCH AS ABDOMINAL PAIN,**
372 **NAUSEA, OR VOMITING (SEE WARNINGS - OTHER).**

373

374 **Drug Interactions**

375 **Nucleoside Analogs:** Administration of nucleoside analogues has resulted in fatal and
376 nonfatal lactic acidosis. Coadministration of ribavirin and nucleoside analogues should be
377 undertaken with caution and only if the potential benefit outweighs the potential risks.

378

379 **Information for Patients** Combination REBETOL/INTRON A therapy must not be used by
380 females who are pregnant or by males whose female partners are pregnant. Extreme care
381 must be taken to avoid pregnancy in female patients and in female partners of male patients
382 taking combination REBETOL/INTRON A therapy. Combination REBETOL/INTRON A
383 therapy should not be initiated until a report of a negative pregnancy test has been obtained
384 immediately prior to initiation of therapy. Patients must perform a pregnancy test monthly
385 during therapy and for 6 months posttherapy. Females of childbearing potential must be
386 counseled about use of effective contraception (two reliable forms) prior to initiating therapy.
387 Patients (male and female) must be advised of the teratogenic/embryocidal risks and must be
388 instructed to practice effective contraception during combination REBETOL/INTRON A
389 therapy and for 6 months posttherapy. Patients (male and female) should be advised to notify
390 the physician immediately in the event of a pregnancy. (See **CONTRAINDICATIONS.**)

391 If pregnancy does occur during treatment or during 6 months posttherapy, the patient
392 must be advised of the significant teratogenic risk of REBETOL therapy to the fetus.
393 Patients, or partners of patients, should immediately report any pregnancy that occurs during
394 treatment or within 6 months after treatment cessation to their physician. Physicians are
395 encouraged to report such cases by calling (800) 727-7064.

396 Patients receiving combination REBETOL/INTRON A treatment should be directed
397 in its appropriate use, informed of the benefits and risks associated with treatment, and
398 referred to the patient **MEDICATION GUIDE**. There are no data evaluating whether
399 REBETOL/INTRON A therapy will prevent transmission of infection to others. Also, it is
400 not known if treatment with REBETOL/INTRON A therapy will cure hepatitis C or prevent

401 cirrhosis, liver failure, or liver cancer that may be the result of infection with the hepatitis C
402 virus.

403 If home use is prescribed, a puncture-resistant container for the disposal of used
404 syringes and needles should be supplied to the patient. Patients should be thoroughly
405 instructed in the importance of proper disposal and cautioned against any reuse of needles
406 and syringes. The full container should be disposed of according to the directions provided
407 by the physician (see **MEDICATION GUIDE**). To avoid possible transmission of disease,
408 do not share your multidose pen with anyone; it is for you and you alone.

409 The most common adverse experiences occurring with combination
410 REBETOL/INTRON A therapy are "flu-like" symptoms, such as headache, fatigue, myalgia,
411 and fever (see **ADVERSE REACTIONS**) and appear to decrease in severity as treatment
412 continues. Some of these "flu-like" symptoms may be minimized by bedtime administration
413 of INTRON A therapy. Antipyretics should be considered to prevent or partially alleviate
414 the fever and headache. Another common adverse experience associated with INTRON A
415 therapy is thinning of the hair.

416 Patients should be advised that laboratory evaluations are required prior to starting
417 therapy and periodically thereafter (see **Laboratory Tests**). It is advised that patients be
418 well hydrated, especially during the initial stages of treatment.

419

420 **Laboratory Tests** The following laboratory tests are recommended for all patients on
421 combination REBETOL/INTRON A therapy, prior to beginning treatment and then
422 periodically thereafter.

423 •Standard hematologic tests - including hemoglobin (pretreatment, week 2 and week
424 4 of therapy, and as clinically appropriate [see **WARNINGS**]), complete and
425 differential white blood cell counts, and platelet count.

426 •Blood chemistries - liver function tests and TSH.

427 •Pregnancy - including monthly monitoring for females of childbearing potential.

428

429 **Carcinogenesis and Mutagenesis** Carcinogenicity studies with interferon alfa-2b,
430 recombinant have not been performed because neutralizing activity appears in the serum after
431 multiple dosing in all of the animal species tested.

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

440 Mutagenicity studies have demonstrated that interferon alfa-2b, recombinant is not
441 mutagenic. Ribavirin demonstrated increased incidences of mutation and cell transformation
442 in multiple genotoxicity assays. Ribavirin was active in the Balb/3T3 *In Vitro* Cell
443 Transformation Assay. Mutagenic activity was observed in the mouse lymphoma assay, and
444 at doses of 20-200 mg/kg (estimated human equivalent of 1.67 - 16.7 mg/kg, based on body
445 surface area adjustment for a 60 kg adult; 0.1 - 1 X the maximum recommended human 24-
446 hour dose of ribavirin) in a mouse micronucleus assay. A dominant lethal assay in rats was
447 negative, indicating that if mutations occurred in rats they were not transmitted through male
448 gametes.

449

450 **Impairment of Fertility** No reproductive toxicology studies have been performed using
451 interferon alfa-2b, recombinant in combination with ribavirin. However, evidence provided
452 below for interferon alfa-2b, recombinant and ribavirin when administered alone indicate that
453 both agents have adverse effects on reproduction. It should be assumed that the effects
454 produced by either agent alone will also be caused by the combination of the two agents.
455 Interferons may impair human fertility. In studies of interferon alfa-2b recombinant
456 administration in nonhuman primates, menstrual cycle abnormalities have been observed.
457 Decreases in serum estradiol and progesterone concentrations have been reported in females
458 treated with human leukocyte interferon. In addition, ribavirin demonstrated significant
459 embryocidal and/or teratogenic effects at doses well below the recommended human dose in
460 all animal species in which adequate studies have been conducted.

461 Fertile females and partners of fertile females should not receive combination
462 REBETOL/INTRON A therapy unless the patient and his/her partner are using effective
463 contraception (two reliable forms). Based on a multiple dose half-life ($t_{1/2}$) of ribavirin of 12
464 days, effective contraception must be utilized for 6 months posttherapy (eg, 15 half-lives of
465 clearance for ribavirin).

466 Combination REBETOL/INTRON A therapy should be used with caution in fertile
467 males. In studies in mice to evaluate the time course and reversibility of ribavirin-induced
468 testicular degeneration at doses of 15 to 150 mg/kg/day (estimated human equivalent of 1.25
469 - 12.5 mg/kg/day, based on body surface area adjustment for a 60 kg adult; 0.1 - 0.8 X the
470 maximum human 24-hour dose of ribavirin) administered for 3 or 6 months, abnormalities in
471 sperm occurred. Upon cessation of treatment, essentially total recovery from ribavirin-
472 induced testicular toxicity was apparent within 1 or 2 spermatogenesis cycles.

473

474 **Animal Toxicology** Long-term studies in the mouse and rat (18 - 24 months; doses of 20 -
475 75 and 10 - 40 mg/kg/day, respectively [estimated human equivalent doses of 1.67 - 6.25 and
476 1.43 - 5.71 mg/kg/day, respectively, based on body surface area adjustment for a 60 kg adult;
477 approximately 0.1 - 0.4 X the maximum human 24-hour dose of ribavirin]) have
478 demonstrated a relationship between chronic ribavirin exposure and increased incidences of
479 vascular lesions (microscopic hemorrhages) in mice. In rats, retinal degeneration occurred in
480 controls, but the incidence was increased in ribavirin-treated rats.

481

482 **Pregnancy Category X** (see **CONTRAINDICATIONS**) Interferon alfa-2b, recombinant
483 has been shown to have abortifacient effects in *Macaca mulatta* (rhesus monkeys) at 15 and
484 30 million IU/kg (estimated human equivalent of 5 and 10 million IU/kg, based on body
485 surface area adjustment for a 60 kg adult). There are no adequate and well-controlled studies
486 in pregnant females.

487 Ribavirin produced significant embryocidal and/or teratogenic effects in all animal
488 species in which adequate studies have been conducted. Malformations of the skull, palate,
489 eye, jaw, limbs, skeleton, and gastrointestinal tract were noted. The incidence and severity of
490 teratogenic effects increased with escalation of the drug dose. Survival of fetuses and
491 offspring was reduced. In conventional embryotoxicity/teratogenicity studies in rats and
492 rabbits, observed no effect dose levels were well below those for proposed clinical use (0.3
493 mg/kg/day for both the rat and rabbit; approximately 0.06 X the recommended human 24-
494 hour dose of ribavirin). No maternal toxicity or effects on offspring were observed in a
495 peri/postnatal toxicity study in rats dosed orally at up to 1 mg/kg/day (estimated human

496 equivalent dose of 0.17 mg/kg based on body surface area adjustment for a 60 kg adult;
497 approximately 0.01 X the maximum recommended human 24-hour dose of ribavirin).

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

507 Females of childbearing potential should not receive combination
508 REBETOL/INTRON A therapy unless they are using effective contraception (two reliable
509 forms) during the therapy period. In addition, effective contraception should be utilized for 6
510 months posttherapy based on a multiple dose half-life ($t_{1/2}$) of ribavirin of 12 days.

511 Male patients and their female partners must practice effective contraception (two
512 reliable forms) during treatment with combination REBETOL/INTRON A therapy and for
513 the 6-month posttherapy period (eg, 15 half-lives for ribavirin clearance from the body).

514 If pregnancy occurs in a patient or partner of a patient during treatment or during the
515 6 months after treatment cessation, physicians are encouraged to report such cases by calling
516 (800) 727-7064.

517 **Nursing Mothers** It is not known whether REBETOL and INTRON A are excreted in
518 human milk. However, studies in mice have shown that mouse interferons are excreted into
519 the milk. Because of the potential for serious adverse reactions from the drugs in nursing
520 infants, a decision should be made whether to discontinue nursing or to discontinue
521 combination REBETOL/INTRON A therapy, taking into account the importance of the
522 therapy to the mother.

523 **Pediatric Use**

524 One hundred twenty-five pediatric patients between three and sixteen years of age with
525 chronic hepatitis C virus infection (median duration 10.7 years) received REBETOL
526 Capsules with INTRON A for up to 48 weeks. The overall sustained response rate cannot be
527 calculated since all patients have not yet completed 24-weeks of off-therapy follow-up.
528

529 **Suicidal ideation or attempts occurred more frequently among pediatric patients**
530 **compared to adult patients (2.4% versus 1%) during treatment and off therapy follow-**
531 **up (see WARNINGS).** As in adult patients, pediatric patients experienced other psychiatric
532 adverse events (e.g., depression, emotional lability, somnolence), anemia, and neutropenia
533 (see WARNINGS). During a 48 week course of therapy there was a decrease in the rate of
534 linear growth (mean percentile assignment decrease of 7%) and a decrease in the rate of
535 weight gain (mean percentile assignment decrease of 9%). A general reversal of these trends
536 was noted during the 24 week post treatment period.

537
538 Injection site disorders, fever, anorexia, vomiting, and emotional lability occurred more
539 frequently in pediatric patients compared to adult patients. Conversely, pediatric patients
540 experienced less fatigue, dyspepsia, arthralgia, insomnia, irritability, impaired concentration,
541 dyspnea, and pruritis compared to adult patients.

542

543 **Geriatric Use** Clinical studies of REBETRON Combination Therapy did not include
 544 sufficient numbers of subjects aged 65 and over to determine if they respond differently from
 545 younger subjects. In clinical trials, elderly subjects had a higher frequency of anemia (67%)
 546 than did younger patients (28%) (see **WARNINGS**).

547 In general, REBETOL (ribavirin) should be administered to elderly patients
 548 cautiously, starting at the lower end of the dosing range, reflecting the greater frequency of
 549 decreased renal, hepatic and/or cardiac function, and of concomitant disease or other drug
 550 therapy.

551 REBETOL (ribavirin) is known to be substantially excreted by the kidney, and the
 552 risk of adverse reactions to ribavirin may be greater in patients with impaired renal function.
 553 Because elderly patients often have decreased renal function, care should be taken in dose
 554 selection. Renal function should be monitored and dosage adjustments of ribavirin should be
 555 made accordingly (see **DOSAGE AND ADMINISTRATION: Guidelines for Dose**
 556 **Modification**). REBETOL should not be used in elderly patients with creatinine clearance
 557 <50mL/min (see **WARNINGS**).

558 REBETRON Combination Therapy should be used very cautiously in elderly patients
 559 with a history of psychiatric disorders (see **WARNINGS**).

560

561

562

ADVERSE REACTIONS

563 The safety of combination REBETOL/INTRON A therapy was evaluated in controlled trials
 564 of 1010 HCV-infected adults who were previously untreated with interferon therapy and
 565 were subsequently treated for 24 or 48 weeks with combination REBETOL/INTRON A
 566 therapy and in 173 HCV-infected patients who had relapsed after interferon therapy and were
 567 subsequently treated for 24 weeks with combination REBETOL/INTRON A therapy. (See
 568 **Description of Clinical Studies**.) Overall, 19% and 6% of previously untreated and relapse
 569 patients, respectively, discontinued therapy due to adverse events in the combination arms
 570 compared to 13% and 3% in the interferon arms.

571 **The primary toxicity of ribavirin is hemolytic anemia. Reductions in**
 572 **hemoglobin levels occurred within the first 1-2 weeks of therapy (see WARNINGS).**
 573 **Cardiac and pulmonary events associated with anemia occurred in approximately 10%**
 574 **of patients treated with REBETOL/INTRON A therapy. (See WARNINGS.)**

575 The most common psychiatric events occurring in US studies of previously untreated
 576 and relapse patients treated with REBETOL/INTRON A therapy, respectively, were
 577 insomnia (39%, 26%), depression (34%, 23%), and irritability (27%, 25%). Suicidal
 578 behavior (ideation, attempts, and suicides) occurred in 1% of patients. (See **WARNINGS**.)
 579 In addition, the following spontaneous adverse events have been reported during the
 580 marketing surveillance of REBETOL/INTRON A therapy: hearing disorder and vertigo.
 581 Very rarely, combination REBETOL/INTRON A therapy may be associated with aplastic
 582 anemia.

583 Selected treatment-emergent adverse events that occurred in the US studies with $\geq 5\%$
 584 incidence are provided in **TABLE 5** by treatment group. In general, the selected treatment-
 585 emergent adverse events reported with lower incidence in the international studies as
 586 compared to the US studies with the exception of asthenia, influenza-like symptoms,
 587 nervousness, and pruritus.

588

TABLE 5. Selected Treatment-Emergent Adverse Events: Previously Untreated and Relapse Patients
 Percentage of Patients

	US Previously Untreated Study				US Relapse Study	
	24 weeks of treatment		48 weeks of treatment		24 weeks of treatment	
Patients Reporting Adverse Events*	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)
Application Site Disorders						
injection site inflammation	13	10	12	14	6	8
injection site reaction	7	9	8	9	5	3
Body as a Whole - General Disorders						
headache	63	63	66	67	66	68
fatigue	68	62	70	72	60	53
rigors	40	32	42	39	43	37
fever	37	35	41	40	32	36
influenza-like symptoms	14	18	18	20	13	13
asthenia	9	4	9	9	10	4
chest pain	5	4	9	8	6	7
Central & Peripheral Nervous System Disorders						
dizziness	17	15	23	19	26	21
Gastrointestinal System Disorders						
nausea	38	35	46	33	47	33
anorexia	27	16	25	19	21	14
dyspepsia	14	6	16	9	16	9
vomiting	11	10	9	13	12	8
Musculoskeletal System Disorders						
myalgia	61	57	64	63	61	58
arthralgia	30	27	33	36	29	29
musculoskeletal pain	20	26	28	32	22	28
Psychiatric Disorders						
insomnia	39	27	39	30	26	25
irritability	23	19	32	27	25	20
depression	32	25	36	37	23	14
emotional lability	7	6	11	8	12	8
concentration impaired	11	14	14	14	10	12

nervousness	4	2	4	4	5	4
Respiratory System Disorders						
dyspnea	19	9	18	10	17	12
sinusitis	9	7	10	14	12	7
Skin and Appendages Disorders						
alopecia	28	27	32	28	27	26
rash	20	9	28	8	21	5
pruritus	21	9	19	8	13	4
Special Senses, Other Disorders						
taste perversion	7	4	8	4	6	5

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

591

592 **Laboratory Values**

593 Changes in selected hematologic values (hemoglobin, white blood cells, neutrophils, and
594 platelets) during combination REBETOL/INTRON A treatment are described below (see
595 **TABLE 6**).

596

597 *Hemoglobin* Hemoglobin decreases among patients on combination therapy began at Week
598 1, with stabilization by Week 4. In previously untreated patients treated for 48 weeks the
599 mean maximum decrease from baseline was 3.1 g/dL in the US study and 2.9 g/dL in the
600 International study. In relapse patients the mean maximum decrease from baseline was 2.8
601 g/dL in the US study and 2.6 g/dL in the International study. Hemoglobin values returned to
602 pretreatment levels within 4 - 8 weeks of cessation of therapy in most patients.

603

604 *Neutrophils* There were decreases in neutrophil counts in both the combination
605 REBETOL/INTRON A and INTRON A plus placebo dose groups. In previously untreated
606 patients treated for 48 weeks the mean maximum decrease in neutrophil count in the US
607 study was 1.3×10^9 /L and in the International study was 1.5×10^9 /L. In relapse patients the
608 mean maximum decrease in neutrophil count in the US study was 1.3×10^9 /L and in the
609 International study was 1.6×10^9 /L. Neutrophil counts returned to pretreatment levels within
610 4 weeks of cessation of therapy in most patients.

611

612 *Platelets* In both previously untreated and relapse patients mean platelet counts generally
613 remained in the normal range in all treatment groups, however, mean platelet counts were
614 10% to 15% lower in the INTRON A plus placebo group than the REBETOL/INTRON A
615 group. Mean platelet counts returned to baseline levels within 4 weeks after treatment
616 discontinuation.

617

618 *Thyroid Function* Of patients who entered the previously untreated (24 and 48 week
619 treatment) and relapse (24 week treatment) studies without thyroid abnormalities,
620 approximately 3% to 6% and 1% to 2%, respectively, developed thyroid abnormalities
621 requiring clinical intervention.

622

623 *Bilirubin and Uric Acid* Increases in both bilirubin and uric acid, associated with hemolysis,

624 were noted in clinical trials. Most were moderate biochemical changes and were reversed

625 within 4 weeks after treatment discontinuation. This observation occurs most frequently in

626 patients with a previous diagnosis of Gilbert's syndrome. This has not been associated with

627 hepatic dysfunction or clinical morbidity.

628

628

TABLE 6. Selected Hematologic Values During Treatment with REBETOL plus INTRON A: Previously Untreated and Relapse Patients

	Percentage of Patients					
	US Previously Untreated Study		US Relapse Study			
	24 weeks of treatment	48 weeks of treatment	24 weeks of treatment			
	INTRO N A plus REBETOL (N=228)	INTRON A plus Placebo (N=231)	INTRON A plus Placebo (N=225)	INTRON A plus REBETOL (N=77)	INTRON A plus Placebo (N=76)	
Hemoglobin (g/dL)						
9.5-10.9	24	1	32	1	21	3
8.0-9.4	5	0	4	0	4	0
6.5-7.9	0	0	0	0.4	0	0
<6.5	0	0	0	0	0	0
Leukocytes (x10⁹/L)						
2.0-2.9	40	20	38	23	45	26
1.5-1.9	4	1	9	2	5	3
1.0-1.4	0.9	0	2	0	0	0
<1.0	0	0	0	0	0	0
Neutrophils (x10⁹/L)						
1.0-1.49	30	32	31	44	42	34
0.75-0.99	14	15	14	11	16	18
0.5-0.74	9	9	14	7	8	4
<0.5	11	8	11	5	5	8
Platelets (x10⁹/L)						
70-99	9	11	11	14	6	12
50-69	2	3	2	3	0	5
30-49	0	0.4	0	0.4	0	0
<30	0.9	0	1	0.9	0	0
Total Bilirubin (mg/dL)						

1.5 -3.0	27	13	32	13	21	7
3.1-6.0	0.9	0.4	2	0	3	0
6.1-12.0	0	0	0.4	0	0	0
>12.0	0	0	0	0	0	0

629

630

OVERDOSAGE

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

639

640 There is no specific antidote for INTRON A or REBETOL, and hemodialysis and peritoneal
 641 dialysis are not effective for treatment of overdose of either agent.

642

643

DOSAGE AND ADMINISTRATION

644 INTRON A Injection should be administered subcutaneously and REBETOL
 645 Capsules should be administered orally. REBETOL may be administered without regard to
 646 food, but should be administered in a consistent manner. (See **CLINICAL**
 647 **PHARMACOLOGY.**)

648

Adults

650 The recommended dose of REBETOL Capsules depends on the patient's body weight. The
 651 recommended doses of REBETOL and INTRON A for adults are given in **TABLE 7.**

652

653 The recommended duration of treatment for patients previously untreated with
 654 interferon is 24 to 48 weeks. The duration of treatment should be individualized to the
 655 patient depending on baseline disease characteristics, response to therapy, and tolerability of
 656 the regimen (see **Description of Clinical Studies** and **ADVERSE REACTIONS**). After 24
 657 weeks of treatment virologic response should be assessed. Treatment discontinuation should
 658 be considered in any patient who has not achieved an HCV-RNA below the limit of detection
 659 of the assay by 24 weeks. There are no safety and efficacy data on treatment for longer than
 660 48 weeks in the previously untreated patient population.

661

662 In patients who relapse following interferon therapy, the recommended duration of
 663 treatment is 24 weeks. There are no safety and efficacy data on treatment for longer than 24
 664 weeks in the relapse patient population.

663

Body weight	REBETOL Capsules	INTRON A Injection
≤ 75 kg	2 x 200 mg capsules AM, 3 x 200 mg capsules PM daily p.o.	3 million IU 3 times weekly s.c.
> 75 kg	3 x 200 mg capsules AM, 3 x 200 mg capsules PM daily p.o.	3 million IU 3 times weekly s.c.

664

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666

Pediatrics

667

668

Efficacy of REBETOL and INTRON A for pediatric patients has not been established.

669

Based on pharmacokinetic data, the following doses of REBETOL and INTRON A provide

670

similar exposures in pediatric patients as observed in adult patients treated with the approved

671

doses of REBETOL and INTRON A (see **TABLE 8**).

Table 8. Pediatric Dosing		
Body weight	REBETOL Capsules	INTRON A Injection
25-36 kg	1 x 200 mg capsule AM 1 x 200 mg capsule PM daily p.o.	3 million IU/m ² 3 times weekly s.c.
37-49 kg	1 x 200 mg capsule AM 2 x 200 mg capsules PM daily p.o.	3 million IU/m ² 3 times weekly s.c.
50-61 kg	2 x 200 mg capsules AM 2 x 200 mg capsules PM daily p.o.	3 million IU/m ² 3 times weekly s.c.
>61 kg	Refer to adult dosing table	Refer to adult dosing table

672

673

674

Under no circumstances should REBETOL capsules be opened, crushed or broken (see Contraindications and Warnings).

675

676

677

Dose Modifications (TABLE 9)

678

In clinical trials, approximately 26% of patients required modification of their dose of REBETOL Capsules, INTRON A Injection, or both agents. If severe adverse reactions or laboratory abnormalities develop during combination REBETOL/INTRON A therapy the dose should be modified, or discontinued if appropriate, until the adverse reactions abate. If intolerance persists after dose adjustment, REBETOL/INTRON A therapy should be discontinued.

682

683

684

REBETOL/INTRON A therapy 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**.)

687

688

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

689

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692

It is recommended that a patient whose hemoglobin level falls below 10 g/dL have his/her REBETOL dose reduced to 600 mg daily (1 x 200 mg capsule AM, 2 x 200 mg capsules PM). A patient whose hemoglobin level falls below 8.5 g/dL should be permanently discontinued from REBETOL/INTRON A therapy. (See **WARNINGS**.)

696

697

698

It is recommended that a patient who experiences moderate depression (persistent low mood, loss of interest, poor self image, and/or hopelessness) have his/her INTRON A dose temporarily reduced and/or be considered for medical therapy. A patient experiencing severe depression or suicidal ideation/attempt should be discontinued from REBETOL/INTRON A therapy and followed closely with appropriate medical management. (See **WARNINGS**.)

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701

702

TABLE 9. Guidelines for Dose Modifications

	Dose Reduction* REBETOL – Adults 600 mg daily Pediatrics: half the dose INTRON A – Adults 1.5 million IU TIW Pediatrics: 1.5 million IU/m ² TIW	Permanent Discontinuation of Treatment REBETOL and INTRON A
Hemoglobin	<10 g/dL (REBETOL)	<8.5 g/dL
	Cardiac History Patients only. ≥2 g/dL decrease during any 4- week period during treatment (REBETOL/INTRON A)	Cardiac History Patients only. <12 g/dL after 4 weeks of dose reduction
White blood count	<1.5 x 10 ⁹ /L (INTRON A)	<1.0 x 10 ⁹ /L
Neutrophil count	<0.75 x 10 ⁹ /L (INTRON A)	<0.5 x 10 ⁹ /L
Platelet count	Adults: <50 x 10 ⁹ /L (INTRON A) Pediatrics: <80 x 10 ⁹ /L (INTRON A)	Adults: <25 x 10 ⁹ /L Pediatrics: <50 x 10 ⁹ /L

*Study medication to be dose reduced is shown in parenthesis

703

704 *Administration of INTRON A Injection*

705 At the discretion of the physician, the patient may self-administer the INTRON A. (See illustrated
706 **MEDICATION GUIDE** for instructions.)

707 The Intron A Injection is supplied as a clear and colorless solution. The appropriate
708 INTRON A dose should be withdrawn from the vial or set on the multidose pen and injected
709 subcutaneously. The INTRON A Injection supplied with the B-D Safety Lok™ syringes
710 contain a plastic sleeve to be pulled over the needle after use. The syringe locks with an
711 audible click when the green stripe on the safety sleeve covers the red stripe on the needle.
712 After administration of INTRON A Injection, it is essential to follow the procedure for
713 proper disposal of syringes and needles. (See **MEDICATION GUIDE** for detailed
714 instructions.)

715

Vial/Pen Label Strength	Fill Volume	Concentration
3 million IU vial	0.5 mL	3 million IU/0.5 mL
18 million IU multidose vial†	3.8 mL	3 million IU/0.5 mL
18 million IU multidose	1.5 mL	3 million IU/0.2 mL

pen††

716 †This is a multidose vial which contains a total of 22.8 million IU of interferon alfa-2b,
717 recombinant per 3.8 mL in order to provide the delivery of six 0.5-mL doses, each containing
718 3 million IU of interferon alfa-2b, recombinant (for a label strength of 18 million IU).

719 †† This is a multidose pen which contains a total of 22.5 million IU of interferon alfa-2b,
720 recombinant per 1.5 mL in order to provide the delivery of six 0.2-mL doses, each containing
721 3 million IU of interferon alfa-2b, recombinant (for a label strength of 18 million IU).

722

723 Parenteral drug products should be inspected visually for particulate matter and discoloration
724 prior to administration, whenever solution and container permit. INTRON A Injection may
725 be administered using either sterilized glass or plastic disposable syringes.

726 *Stability* INTRON A Injection provided in vials is stable at 35°C (95°F) for up to 7 days and
727 at 30°C (86°F) for up to 14 days. INTRON A Injection provided in a multidose pen is stable
728 at 30°C (86°F) for up to 2 days. The solution is clear and colorless.

729

730

HOW SUPPLIED

731 REBETOL 200-mg Capsules are white, opaque capsules with REBETOL, 200 mg, and the
732 Schering Corporation logo imprinted on the capsule shell; the capsules are packaged in a
733 bottle.

734 INTRON A Injection is a clear, colorless solution packaged in single dose and multidose
735 vials, and a multidose pen.

736 INTRON A Injection and REBETOL Capsules are available in the following combination
737 package presentations:

738

	Each REBETRON Combination Package Consists of:	
For Patients ≤75 kg	A box containing 6 vials of INTRON A Injection (3 million IU in 0.5 mL per vial), 6 syringes, alcohol swabs and one bottle containing 70 REBETOL Capsules .	(NDC 0085-1241-02)
	One 18 million IU multidose vial of INTRON A Injection (22.8 million IU per 3.8 mL; 3 million IU/0.5 mL), 6 syringes, alcohol swabs and one bottle containing 70 REBETOL.	(NDC 0085-1236-02)
	One 18 million IU INTRON A Injection multidose pen (22.5 million IU per 1.5 mL; 3 million IU/0.2 mL), 6 disposable needles, alcohol swabs and one bottle containing 70 REBETOL Capsules.	(NDC 0085-1258-02)
For Patients >75 kg	A box containing 6 vials of INTRON A Injection (3 million IU in 0.5 mL per vial), 6 syringes, alcohol swabs and one bottle containing 84 REBETOL Capsules.	(NDC 0085-1241-01)
	One 18 million IU multidose vial of INTRON A Injection (22.8 million IU per 3.8 mL; 3 million IU/0.5 mL), 6 syringes, alcohol swabs and one bottle containing 84	(NDC 0085-1236-01)

	REBETOL Capsules.	
	One 18 million IU INTRON A Injection multidose pen (22.5 million IU per 1.5 mL; 3 million IU/0.2 mL), 6 disposable needles, alcohol swabs, and one bottle containing 84 REBETOL Capsules.	(NDC 0085-1258-01)
For REBETOL Dose Reduction	A box containing 6 vials of INTRON A Injection (3 million IU in 0.5 mL per vial), 6 syringes, alcohol swabs, and one bottle containing 42 REBETOL Capsules.	(NDC 0085-1241-03)
	One 18 million IU multidose vial of INTRON A Injection (22.8 million IU per 3.8 mL; 3 million IU/0.5 mL), 6 syringes, alcohol swabs and one bottle containing 42 REBETOL Capsules.	(NDC 0085-1236-03)
	One 18 million IU INTRON A Injection multidose pen (22.5 million IU per 1.5 mL; 3 million IU/0.2 mL), 6 disposable needles, alcohol swabs and one bottle containing 42 REBETOL Capsules.	(NDC 0085-1258-03)

739

740

STORAGE CONDITIONS

741

Store the REBETOL Capsules plus INTRON A Injection combination package refrigerated between 2°C and 8°C (36° and 46° F).

742

When separated, the individual bottle of REBETOL Capsules should be stored refrigerated between 2° and 8°C (36° and 46°F) or at 25°C (77°F); excursions are permitted between 15° and 30°C (59° and 86°F).

743

744

When separated, the individual vials of INTRON A Injection and the INTRON A Multidose Pen should be stored refrigerated between 2° and 8°C (36° and 46°F).

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