F-XXXXXXXX

PRODUCT INFORMATION

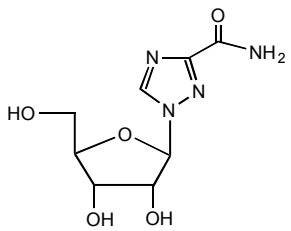
REBETOL® (ribavirin, USP) Capsules

- 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-1*H*-1,2,4-triazole-3-carboxamide and has the following structural formula:



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

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

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 $AUC12_{hr}$, 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_{tf} **	13400 (48)	228000 (25)
$T_{1/2}$ (hr)	43.6 (47)	298 (30)
Apparent Volume of Distribution (L)	2825 (9) †	
Apparent Clearance (L/hr)	38.2 (40)	
Absolute Bioavailability	64% (44) ††	

* ng/mL
** ng.hr/mL
*** N = 11
† data obtained from a single-dose pharmacokinetic study using ^{14}C labeled ribavirin; N = 5
†† N = 6

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

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 µg/kg SC once weekly (QW)/REBETOL 800 mg PO daily (in divided doses); PEG-INTRON 1.5 µg/kg SC QW for 4 weeks then 0.5 µg/kg SC QW for 44 weeks/REBETOL 1000/1200 mg PO daily (in divided doses)] with INTRON A [3 MIU SC thrice weekly (TIW)/REBETOL 1000/1200 mg PO daily (in divided doses)] in 1530 adults with chronic hepatitis C. Interferon naïve patients were treated for 48 weeks and followed for 24 weeks 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 1.5µg/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)

[1]Serum HCV RNA was measured with a research-based quantitative polymerase chain reaction assay by a central laboratory.
[2] Difference in overall treatment response (PEG-INTRON/REBETOL vs. INTRON A/REBETOL) is 6% with 95% confidence interval of (0.18, 11.63) adjusted for viral genotype and presence of cirrhosis at baseline.

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 coinfected 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.

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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 ≥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

	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

* 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

	*PERCENTAGE OF PATIENTS REPORTING ADVERSE EVENTS**			*PERCENTAGE OF PATIENTS REPORTING ADVERSE EVENTS**	
ADVERSE EVENTS	**PEG-INTRON 1.5µg/kg/ REBETOL** (n=511)	**INTRON A/ REBETOL** (n=505)	ADVERSE EVENTS	**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 ($x10^9$/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 ($x10^9$/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 ($x10^9$/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

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	5
8.0-9.4	3	3	50-69	3	0.8
6.5-7.9	0.2	0.2	30-49	0.2	0.2
<6.5	0	0	<30	0	0
Leukocytes ($x10^9$/L)			Total Bilirubin (mg/dL)		
2.0-2.9	46	41	1.5 -3.0	10	13
1.5-1.9	24	8	3.1-6.0	0.6	0.2
1.0-1.4	5	1	6.1-12.0	0	0.2
<1.0	0	0	>12.0	0	0
Neutrophils ($x10^9$/L)			ALT (SGPT)		
1.0-1.49	33	37	2 x Baseline	0.6	0.2
0.75-0.99	25	13	2.1-5 x Baseline	3	1
0.5-0.74	18	7	5.1-10 x Baseline	0	0
<0.5	4	2	>10 x Baseline	0	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.

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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

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.

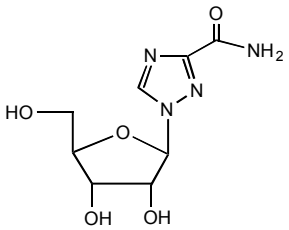
REBETOL MONOTHERAPY IS NOT EFFECTIVE FOR THE TREATMENT OF CHRONIC HEPATITIS C AND SHOULD NOT BE USED FOR THIS INDICATION. SEE WARNINGS.

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-ß-D-ribofuranosyl-1*H*-1,2,4-triazole-3-carboxamide and has the following structural formula:



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

REBETOL Capsules consist of a white powder in a white, opaque, gelatin capsule. Each capsule contains 200 mg ribavirin and the inactive ingredients microcrystalline cellulose, lactose monohydrate, croscarmellose sodium, and magnesium stearate. The capsule shell consists of gelatin, 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.

INTRON® A

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

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

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

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

Mechanism of Action

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

CLINICAL PHARMACOLOGY

Pharmacokinetics

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

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

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 $AUC12_{hr}$, 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 were conducted without instructions with respect to food consumption. (See **DOSAGE AND ADMINISTRATION**.)

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

TABLE 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)††	

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

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

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

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

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.

Special Populations

Renal Dysfunction The pharmacokinetics of ribavirin were assessed after administration of a single oral dose (400 mg) of ribavirin to 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). This appears to be due to reduction of apparent clearance in these patients. Ribavirin was not removed by hemodialysis. Patients with creatinine clearance < 50mL/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 Multiple-dose pharmacokinetic properties for ribavirin in pediatric patients with chronic hepatitis C between 5 and 16 years of age are summarized in **TABLE 2**.

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

Elderly Patients Pharmacokinetic evaluations for 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 is 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.

Description of Clinical Studies

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 3**.

TABLE 3. 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 REBETO	**INTRON A plus**	**INTRON A plus REBET**	**INTRON A plus**	**INTRON A plus REBETO**	**INTRON A plus REBETO**	**INTRON 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) 16(7)	194(84) 24(10)	110(48) 33(14)	168(75) 30(13)	158(60) 21(8)	120(45) 35(13)	196(74) 24(9)
-Missing Data							
Histologic Response							
- Improvement[2]	102(45) 77(34)	77(33) 99(43)	96(42) 61(27)	65(29) 93(41)	103(39) 85(32)	102(38) 58(22)	69(26) 111(41)
-No improvement	49(21)	55(24)	71(31)	67(30)	77(29)	108(40)	86(32)
-Missing Data							

* 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 4**.

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)

* 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 $\geq$2 points.

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

CONTRAINDICATIONS

Combination REBETOL/INTRON A therapy must not be used by females who are pregnant or by males whose female partners are pregnant. Extreme care must be taken to avoid pregnancy in female patients and in female partners of male patients taking combination REBETOL/INTRON A therapy. Combination REBETOL/INTRON A therapy should not be initiated until a report of a negative pregnancy test has been obtained immediately prior to initiation of therapy. Females of childbearing potential and males must use two forms of effective contraception during treatment and during the 6 months after treatment has been concluded. Significant teratogenic and/or embryocidal effects have been demonstrated for ribavirin in all animal species in which adequate studies have been conducted. These effects occurred at doses as low as one twentieth of the recommended human dose of REBETOL Capsules. If pregnancy occurs in a patient or partner of a patient during treatment or during the 6 months after treatment stops, physicians are encouraged to report such cases by calling (800) 727-7064. **See boxed CONTRAINDICATIONS AND WARNINGS. See WARNINGS.**

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.

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

WARNINGS

Pregnancy

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

Anemia

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

The anemia associated with REBETOL/INTRON A therapy may result in deterioration of cardiac function and/or exacerbation of the symptoms of coronary disease. Patients should be assessed before initiation of therapy 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.**) Because cardiac disease may be worsened by drug induced anemia, patients with a history of significant or unstable cardiac disease should not use combination REBETOL/INTRON A therapy. (See **ADVERSE REACTIONS.**)

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

Psychiatric

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

Bone marrow toxicity:

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

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

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.

Other

- REBETOL Capsule monotherapy is not effective for the treatment of chronic hepatitis C and should not be used for this indication.
- Fatal and nonfatal pancreatitis has been observed in patients treated with REBETOL/INTRON A therapy. REBETOL/INTRON A therapy should be suspended in patients with signs and symptoms of pancreatitis and discontinued in patients with confirmed pancreatitis.
- Combination REBETOL/INTRON A therapy should not be used in patients with creatinine clearance <50 mL/min.
- Diabetes mellitus and hyperglycemia have been observed in patients treated with INTRON A.
- Ophthalmologic disorders have been reported with treatment with alpha interferons (including INTRON A therapy). Investigators using alpha interferons have reported the occurrence of retinal hemorrhages, cotton wool spots, and retinal artery or vein obstruction in rare instances. Any patient complaining of loss of visual acuity or visual field should have an eye examination. Because these ocular events may occur in conjunction with other disease states, a visual exam prior to initiation of combination REBETOL/INTRON A therapy is recommended in patients with diabetes mellitus or hypertension.
- Acute serious hypersensitivity reactions (eg, urticaria, angioedema, bronchoconstriction, anaphylaxis) have been observed in INTRON A-treated patients; if such an acute reaction develops, combination REBETOL/INTRON A therapy should be discontinued immediately and appropriate medical therapy instituted.
- Combination REBETOL/INTRON A therapy should be discontinued for patients developing thyroid abnormalities during treatment whose thyroid function cannot be controlled by medication.

PRECAUTIONS

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

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

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

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

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

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

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

Drug Interactions

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

Information for Patients Combination REBETOL/INTRON A therapy must not be used by females who are pregnant or by males whose female partners are pregnant. Extreme care must be taken to avoid pregnancy in female patients and in female partners of male patients taking combination REBETOL/INTRON A therapy. Combination REBETOL/INTRON A therapy should not be initiated until a report of a negative pregnancy test has been obtained immediately prior to initiation of therapy. Patients must perform a pregnancy test monthly during therapy and for 6 months posttherapy. Females 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 combination REBETOL/INTRON A therapy 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.**)

If pregnancy does occur during treatment or during 6 months posttherapy, the patient must be advised of the significant 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 are encouraged to report such cases by calling (800) 727-7064.

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

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

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

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

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.

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Laboratory Tests The following laboratory tests are recommended for all patients on combination REBETOL/INTRON A therapy, 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 females of childbearing potential.

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

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.

Mutagenicity studies have demonstrated that interferon alfa-2b, recombinant is not mutagenic. 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 No reproductive toxicology studies have been performed using interferon alfa-2b, recombinant in combination with ribavirin. However, evidence provided below for interferon alfa-2b, recombinant and ribavirin when administered alone indicate that both agents have adverse effects on reproduction. It should be assumed that the effects produced by either agent alone will also be caused by the combination of the two agents. Interferons may impair human fertility. In studies of interferon alfa-2b recombinant administration in nonhuman primates, menstrual cycle abnormalities have been observed. Decreases in serum estradiol and progesterone concentrations have been reported in females treated with human leukocyte interferon. In addition, 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 females and partners of fertile females should not receive combination REBETOL/INTRON A therapy unless the patient and his/her partner are using effective contraception (two reliable forms). Based on a multiple dose half-life ($t_{1/2}$) of ribavirin of 12 days, effective contraception must be utilized for 6 months posttherapy (eg, 15 half-lives of clearance for ribavirin).

Combination REBETOL/INTRON A therapy should be used with caution in fertile males. 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)** Interferon alfa-2b, recombinant has been shown to have abortifacient effects in *Macaca mulatta* (rhesus monkeys) at 15 and 30 million IU/kg (estimated human equivalent of 5 and 10 million IU/kg, based on body surface area adjustment for a 60 kg adult). There are no adequate and well-controlled studies in pregnant females.

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.

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

Male patients and their female partners must practice effective contraception (two reliable forms) during treatment with combination REBETOL/INTRON A therapy 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 are encouraged to report such cases by calling (800) 727-7064.

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

Pediatric Use

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

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

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

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

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

REBETOL (ribavirin) is known to be substantially excreted by the kidney, and the risk of adverse reactions to ribavirin 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 of ribavirin should be made accordingly (see **DOSAGE AND ADMINISTRATION**: **Guidelines for Dose Modification**). REBETOL should not be used in elderly patients with creatinine clearance <50mL/min (see **WARNINGS**).

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

ADVERSE REACTIONS

The safety of combination REBETOL/INTRON A therapy was evaluated in controlled trials of 1010 HCV-infected adults who were previously untreated with interferon therapy and were subsequently treated for 24 or 48 weeks with combination REBETOL/INTRON A therapy and in 173 HCV-infected patients who had relapsed after interferon therapy and were subsequently treated for 24 weeks with combination REBETOL/INTRON A therapy. (See **Description of Clinical Studies**.) Overall, 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.

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

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

Selected treatment-emergent adverse events that occurred in the US studies with ≥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

	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

* 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

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

Hemoglobin Hemoglobin decreases among patients on combination 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.

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

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

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

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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

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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	
	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 ($x10^9$/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 ($x10^9$/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 ($x10^9$/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

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 for treatment of overdose of either agent.

DOSAGE AND ADMINISTRATION

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

Adults

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

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 7. Recommended Adult Dosing

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.

Pediatrics

Efficacy of REBETOL and INTRON A for pediatric patients has not been established. Based on pharmacokinetic data, the following doses of REBETOL and INTRON A provide similar exposures in pediatric patients as observed in adult patients treated with the approved 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

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

*Dose Modifications (**TABLE 9**)*

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.

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.**)

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/INTRON A therapy. (See **WARNINGS**.)

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**.)

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

Administration of INTRON A Injection

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

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

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††

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

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

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

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

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.

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

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

	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)

STORAGE CONDITIONS

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

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).

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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