

**CENTER FOR DRUG EVALUATION AND RESEARCH**

*APPLICATION NUMBER:*

**20-903/S-008, S-011, S-012, S-016**

**APPROVED LABELING**

F-XXXXXXXX

**PRODUCT  
INFORMATION**

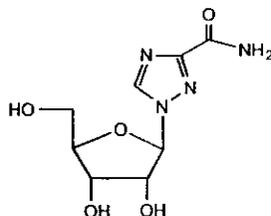
**REBETOL® (ribavirin, USP) Capsules**

- 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 led to fatal and nonfatal myocardial infarctions. Patients with a history of significant or unstable cardiac disease should not be treated with REBETOL. (See WARNINGS, ADVERSE REACTIONS and DOSAGE AND ADMINISTRATION).
- 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 non plasma compartments for as long as six 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<sub>8</sub>H<sub>12</sub>N<sub>4</sub>O<sub>5</sub> 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**

*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**

*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<sub>0-t</sub> (AUC from time zero to last measurable concentration) following single doses of 200-1200 mg ribavirin. The relationship between dose and C<sub>max</sub> was curvilinear, tending to asymptote above single doses of 400-600 mg.

Upon multiple oral dosing, based on AUC<sub>12hr</sub>, 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<sub>0-t</sub> and C<sub>max</sub> 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<sup>®</sup>) resulted in a 14% decrease in mean ribavirin AUC<sub>0-t</sub>. 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 <sub>max</sub> (hr)	1.7 (46) ***	3 (60)
C <sub>max</sub> *	782 (37)	3680 (85)
AUC <sub>0-t</sub> **	13400 (48)	228000 (25)
T <sub>1/2</sub> (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 <sup>14</sup>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<sub>s</sub>-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.

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

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 <sup>14</sup>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 non HCV-infected subjects with varying degrees of renal dysfunction. The mean AUC<sub>0-t</sub> 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<sub>0-∞</sub> was twofold greater when compared to control subjects. The increased AUC<sub>0-∞</sub> 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<sub>0-∞</sub> 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<sub>max</sub> 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 only 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.

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

### *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 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)
<b>Virologic Response</b>							
-Responder <sup>1</sup>	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)
<b>Histologic Response</b>							
-Improvement <sup>2</sup>	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  $\geq 2$  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 non-genotype 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  $\leq 75$  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 N=77	INTRON A plus Placebo N=76	INTRON A plus REBETOL N=96	INTRON A plus Placebo N=96
<b>Virologic Response</b>				
-Responder <sup>1</sup>	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)
<b>Histologic Response</b>				
-Improvement <sup>2</sup>	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

### Pregnancy

REBETOL 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.

## 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.**

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

The safety and efficacy of oral ribavirin 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 coinfectd with HBV or HIV.

#### **Pregnancy**

**REBETOL 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 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.)**

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

REBETOL 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.**)

## PRECAUTIONS

### Information for Patients

Patients must be informed that REBETOL 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 post therapy. Women of childbearing potential must be counseled about use of effective contraception (two reliable forms) prior to initiating therapy. Patients (male and female) must be advised of the teratogenic/embryocidal risks and must be instructed to practice effective contraception during REBETOL and for 6 months post therapy. Patients (male and female) should be advised to notify the physician immediately in the event of a pregnancy. (See **CONTRAINDICATIONS 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 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 is anemia, which may be severe. (See **ADVERSE REACTIONS.**) Patients should be advised that laboratory evaluations are required prior to starting therapy and periodically thereafter. (See **Laboratory Tests.**) It is advised that patients be well hydrated, especially during the initial stages of treatment.

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

**Carcinogenesis and Mutagenesis** Adequate studies to assess the carcinogenic potential of ribavirin in animals have not been conducted. However, ribavirin is a nucleoside analogue that has produced positive findings in multiple *in vitro* and animal *in vivo* genotoxicity assays, and should be considered a potential carcinogen. Further studies to assess the carcinogenic potential of ribavirin in animals are ongoing.

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 post therapy (e.g., 15 half-lives of clearance for ribavirin).

REBETOL should be used with caution in fertile men. In studies in mice to evaluate the time course and reversibility of ribavirin-induced testicular degeneration at doses of 15 to 150 mg/kg/day (estimated human equivalent of 1.25 - 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 post therapy period (e.g., 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 REBETOL 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 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 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.**

**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 elderly patients with creatinine clearance <50 mL/min (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.)**

In clinical trials, 19% and 6% of previously untreated and relapse patients, respectively, discontinued therapy due to adverse events in the combination arms compared to 13% and 3% in the interferon arms. Selected treatment-emergent adverse events that occurred in the US studies with  $\geq 5\%$  incidence are provided in **TABLE 4** 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 4. Selected Treatment-Emergent Adverse Events: Previously Untreated and Relapse Patients**

Patients Reporting Adverse Events *	Percentage of Patients					
	US Previously Untreated Study				US Relapse Study	
	24 weeks of treatment		48 weeks of treatment		24 weeks of treatment	
	INTRON A plus REBETOL (N=228)	INTRON A plus Placebo (N=231)	INTRON A plus REBETOL (N=228)	INTRON A plus Placebo (N=225)	INTRON A plus REBETOL (N=77)	INTRON A plus Placebo (N=76)
<b>Application Site Disorders</b>						
injection site inflammation	13	10	12	14	6	8
injection site reaction	7	9	8	9	5	3
<b>Body as a Whole - General Disorders</b>						
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
<b>Central &amp; Peripheral Nervous System Disorders</b>						
Dizziness	17	15	23	19	26	21
<b>Gastrointestinal System Disorders</b>						
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
<b>Musculoskeletal System Disorders</b>						
Myalgia	61	57	64	63	61	58
Arthralgia	30	27	33	36	29	29
musculoskeletal pain	20	26	28	32	22	28
<b>Psychiatric Disorders</b>						
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
<b>Respiratory System Disorders</b>						
Dyspnea	19	9	18	10	17	12
Sinusitis	9	7	10	14	12	7
<b>Skin and Appendages Disorders</b>						
Alopecia	28	27	32	28	27	26

Rash	20	9	28	8	21	5
Pruritus	21	9	19	8	13	4
<b>Special Senses, Other Disorders</b>						
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.

### Laboratory Values

Changes in selected hematologic values (hemoglobin, white blood cells, neutrophils, and platelets) during REBETOL are described below. (See TABLE 5.)

**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 5. 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)	
<b>Hemoglobin (g/dL)</b>						
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
<b>Leukocytes (x10<sup>9</sup>/L)</b>						
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
<b>Neutrophils (x10<sup>9</sup>/L)</b>						
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 <sup>9</sup> /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

In combination REBETOL/INTRON A clinical trials, the maximum overdose reported was a dose of 39 million units of INTRON A (13 subcutaneous injections of 3 million IU each) taken with 10 g of REBETOL (fifty 200-mg capsules) in an investigator-initiated trial. The patient was observed for 2 days in the emergency room during which time no adverse event from the overdose was noted.

## DOSAGE AND ADMINISTRATION (See CLINICAL PHARMACOLOGY, Special Populations; See WARNINGS).

The recommended dose of REBETOL Capsules depends on the patient's body weight. The recommended doses of REBETOL is provided in TABLE 6.

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 6. 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.
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REBETOL may be administered without regard to food, but should be administered in a consistent manner with respect to food intake. (See **CLINICAL PHARMACOLOGY**.)

***Dose Modifications (TABLE 7)***

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 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  $\geq 2$  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 7. 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	$\geq 2$ 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 84 capsules (NDC 0085-xxxx-xx).

## Storage Conditions

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



Schering Corporation  
Kenilworth, NJ 07033 USA

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B-XXXXXXX Rev. x/xx

## MEDICATION GUIDE

### REBETOL (ribavirin, USP) Capsules

Read this medication guide carefully before you begin taking REBETOL (REB-eh-tole) Capsules, and each time you refill your prescription in case new information has been included. This summary does not tell you everything about REBETOL Capsules. Your health care provider is the best source of information about this medicine. After reading this medication guide, talk with your health care provider if you have any questions about this medicine.

#### What is the most important information I should know about therapy with REBETOL Capsules?

- **REBETOL Capsules may cause birth defects and/or death of an unborn child. Therefore, if you are pregnant, you must not take REBETOL.** If you could become pregnant, you must not become pregnant during therapy and for six months after you have stopped therapy. During this time you must use two forms of birth control, and you must have pregnancy tests that show that you are not pregnant.

Female sexual partners of male patients being treated with REBETOL must not become pregnant during treatment and for six months after treatment has stopped. Therefore, two forms of birth control must be used during this time.

If pregnancy occurs, report the pregnancy to your healthcare provider right away.

- **REBETOL Capsules can cause a dangerous drop in your red blood cell count.** REBETOL Capsules can cause anemia, which is a decrease in the number of red blood cells. This can be dangerous, especially if you have heart or breathing problems. Tell your health care provider before taking REBETOL if you have ever had any of these problems. Your health care provider should check your red blood cell count before you start therapy and often during the first 4 weeks of therapy. Your red blood cell count may be checked more often if you have any heart or breathing problems.
- **You should not take REBETOL Capsules alone to treat Hepatitis C infection.** REBETOL Capsules should be used only in combination with interferon alfa-2b (INTRON A) for the treatment of chronic hepatitis C infection; the combination is called REBETRON Combination Therapy. Your health care provider or pharmacist should give you a copy of the REBETRON Combination Therapy Medication Guide. You should read the REBETRON Medication Guide because it has additional important information about combination therapy not covered in this guide.

### **What is REBETOL (ribavirin)?**

**“REBETOL” is the name given to the antiviral drug ribavirin made by Schering. It is used in combination with INTRON A, to treat chronic hepatitis C infection. It is not known how REBETOL and INTRON A work together to fight hepatitis C infection.**

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

You should use REBETOL (in combination with INTRON A) only if you have never been treated or your hepatitis C has returned after interferon therapy.

### **Who should not take REBETOL Capsules?**

**Do not use these medicines if:**

- You are a female and you are pregnant or plan to become pregnant at any time during your treatment with REBETOL or during the 6 months after your treatment has ended.
- You are a male patient with a female sexual partner who is pregnant or plans to become pregnant at any time while you are being treated with REBETOL or during the 6 months after your treatment has ended. **Please see “What is the most important information I should know about therapy with REBETOL Capsules?” at the beginning of this Medication Guide.**
- You are breast-feeding. REBETOL may pass through your milk and harm your baby. Talk with your health care provider about whether you should stop breast-feeding.
- You are allergic to any of the ingredients in REBETOL Capsules (See ingredients listed at the end of this Medication Guide).

Tell your health care provider before starting treatment with REBETOL Capsules in combination with Intron A (see also the Rebetrone Medication Guide) if you have any of the following medical conditions:

- **mental health problems, such as depression or anxiety.** REBETOL/INTRON A therapy may make them worse. Tell your health care provider if you are being treated for a mental illness or had treatment in the past for any mental problems, including depression, suicidal behavior, or psychosis. Psychosis is loss of contact with reality, such as hearing voices or seeing things that are not there.
- **high blood pressure, heart problems, or have had a heart attack.** REBETOL Capsules may worsen heart problems. Patients who have had certain heart problems should not take REBETOL Capsules.
- **blood disorders, including anemia (low red blood cell count), thalassemia (Mediterranean anemia), and sickle-cell anemia.** REBETOL Capsules can reduce the number of red blood cells you have. This may make you feel dizzy or weak and could worsen any heart problems you might have.

- **kidney problems.** If your kidneys do not work properly, you may experience worse side effects from REBETOL therapy and require a lower dose.
- **liver problems** (other than hepatitis C infection)
- **organ transplant**, and are taking medicine that keeps your body from rejecting your transplant (suppresses your immune system).
- **thyroid disease.** REBETOL/INTRON A therapy may make your thyroid disease worse or harder to treat. REBETOL/INTRON A therapy may be stopped if you develop thyroid abnormalities that cannot be controlled by medication.
- **alcoholism or drug abuse or addiction**
- **cancer**
- **infection with hepatitis B virus and/or human immunodeficiency virus** (the virus that causes AIDS).
- **diabetes.** REBETOL/INTRON A therapy may make your diabetes worse or harder to treat.
- **past interferon treatment for hepatitis C virus infection that did not work for you.**

**How should I take REBETOL Capsules?**

Your health care provider has determined the correct dose of REBETOL Capsules based on your weight. Your health care provider may lower your dose of REBETOL if you have side effects. The recommended dose of REBETOL Capsules is shown in the table below.

<b>If your weight is:</b>	<b>Take this many REBETOL Capsules each day:</b>
165 pounds or less	2 capsules in the AM 3 capsules in the PM
More than 165 pounds	3 capsules in the AM 3 capsules in the PM

- You can take your REBETOL Capsules with or without food, but you should take it the same way every day.
- It is important to follow your dosing schedule and your health care provider’s instructions on how to take your medicines.
- Take the medicine for as long as prescribed and do not take more than the recommended dose.
- If you miss a dose of REBETOL Capsules, take the missed dose as soon as possible during the same day. If an entire day has gone by, check with your health care provider about what to do. Do not double the next dose.
- Tell your health care provider if you are taking or planning to take other prescription or non-prescription medicines, including vitamin and mineral supplements, and herbal medicines.

**What should I avoid while taking REBETOL Capsules?**

- **Pregnancy:** If you or your sexual partner becomes pregnant, tell your health care provider right away. (See **“What is the most important information I should know about therapy with REBETOL Capsules?”** at the beginning of this Medication

Guide.).

Talk with your health care provider about how to avoid pregnancy. If you or your sexual partner becomes pregnant while on REBETOL or during the 6 months after your treatment ends, you must report the pregnancy to your health care provider right away. Your *health care provider* should call toll-free 1-800-727-7064. Your health care provider will be asked to give follow-up information about the pregnancy. Any information about your pregnancy that is reported about you will be confidential.

- Breastfeeding.
- Taking any medicines other than those prescribed or approved by your health care provider.
- Ask your health care provider if there are other things you should avoid, in addition to alcohol (beer, wine, liquor), prescription and nonprescription drugs, and alternative medications (herbal medicine).

#### What are the most common side effects of REBETOL Capsules?

- Feeling tired.
- Nausea and appetite loss.
- Rash and itching.
- **Trouble breathing.**
- **Cough**

This summary does not include all possible side effects of REBETOL therapy. You should talk to your health care provider, if you do not feel well while taking REBETOL. Your health care provider can give you more information about managing your side effects.

#### What should I know about hepatitis C infection?

Hepatitis C infection is a disease caused by a virus that infects the liver. This liver infection becomes a continuing (chronic) condition in most patients. Patients with chronic hepatitis C infection may develop cirrhosis, liver cancer, and liver failure. The virus is spread from one person to another by contact with the infected person's blood. You should talk to your health care provider about ways to prevent you from infecting others.

#### How do I store my medicine?

REBETOL Capsules should be stored in the refrigerator between 36° and 46°F (2° and 8°C) or at room temperature 77°F (25°C).

#### **General advice about prescription medicines**

Do not use REBETOL Capsules for conditions for which they were not prescribed. If you have any concern about REBETOL Capsules, ask your health care provider. Your health care provider or pharmacist can give you information about REBETOL Capsules that was written for health care professionals. Do not give this medicine to other people, even if they have the same condition you have.

**Ingredients:**

REBETOL capsules contain 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.

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

**Manufactured by:**

Schering Corporation  
Kenilworth, NJ 07033 USA

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Rev. X/XX

B-XXXXXXXX

## MEDICATION GUIDE

### REBETRON

*Combination Therapy*

containing

REBETOL (ribavirin, USP) Capsules

INTRON A (interferon alfa-2b, recombinant) Injection

REBETRON (REB-eh-tron) is the name for the combination of REBETOL (REB-eh-tole) and INTRON A (IN-tron aye). Read this medication guide carefully before you begin taking REBETRON Combination Therapy, and each time you refill your prescription in case there is new information. This summary does not tell you everything about REBETRON Combination Therapy. Your health care provider is the best source of information about these medicines. After reading this medication guide, talk with your health care provider if you have any questions about this treatment.

#### **What is the most important information I should know about REBETRON Combination Therapy?**

- **REBETRON Combination Therapy may cause birth defects and/or death of an unborn child. Therefore, if you are pregnant, you must not take REBETRON Combination Therapy.** If you could become pregnant, you must not become pregnant during therapy and for six months after you have stopped therapy. During this time you must use two forms of birth control, and you must have pregnancy tests that show that you are not pregnant.

Female sexual partners of male patients being treated with REBETOL must not become pregnant during treatment and for six months after treatment has stopped. Therefore, two forms of birth control must be used during this time.

If pregnancy occurs, report the pregnancy to your healthcare provider right away.

- **Treatment with REBETOL and INTRON A products can cause a dangerous drop in your blood cell counts.** REBETRON Combination Therapy can cause anemia, which is a decrease in the number of red blood cells. This can be dangerous, especially if you have heart or breathing problems. Tell your health care provider before taking REBETRON Combination Therapy if you have ever had any of these problems. Your health care provider should check your red blood cell count before starting therapy and often during the first 4 weeks of therapy. Your red blood cell count may be checked more often if you have heart or breathing problems.
- **REBETRON Combination Therapy can cause a dangerous drop in the number of cells that help fight infections and stop bleeding, which might cause you to have an infection or abnormal bleeding.**

- **Serious mental problems: REBETRON Combination Therapy may cause or worsen mood or behavioral problems.** These can include irritability (getting easily upset) and depression (feeling low, feeling bad about yourself). **Some patients think about hurting or killing themselves or other people, and some have killed themselves (suicide) or hurt themselves or others.** If you experience any of these thoughts or symptoms you should tell your health care provider right away. See **“What are the possible side effects of REBETRON Combination Therapy?”** for important information on signs of mental problems.
- **You should not take REBETOL Capsules alone to treat your hepatitis C virus infection.** REBETOL Capsules should be used only in combination with interferon alfa-2b (INTRON A) for the treatment of chronic hepatitis C infection; the combination is called REBETRON Combination Therapy.

### **What is REBETRON Combination Therapy?**

REBETRON Combination Therapy is a treatment for some people who have chronic hepatitis C infection. It consists of two separate medicines, REBETOL Capsules (ribavirin) and INTRON A Injection (interferon), used in combination. INTRON A helps the body’s immune system fight infections. “REBETOL” is the name given to the antiviral drug ribavirin made by Schering. It is not known how REBETOL and INTRON A work together to fight hepatitis C infection. REBETOL should not be used alone to treat chronic hepatitis C infection.

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

You should use REBETRON Combination Therapy only if you have never been treated or your hepatitis C has returned after interferon therapy.

### **Who should not take REBETRON Combination Therapy?**

**Do not use these medicines if:**

- You are a female and you are pregnant or plan to become pregnant at any time during your treatment with REBETRON Combination Therapy or during the 6 months after your treatment has ended.
- You are a male patient with a female sexual partner who is pregnant or plans to become pregnant at any time while you are being treated during treatment with REBETRON Combination Therapy or during the 6 months after your treatment has ended. **Please see “What is the most important information I should know about REBETRON Combination Therapy?” at the beginning of this Medication Guide.**
- You are breastfeeding. REBETOL and INTRON A products may pass through your milk and harm your baby. Talk with your health care provider about whether you should stop breast-feeding.

- You have autoimmune hepatitis (hepatitis caused by cells in your body attacking each other) because treatment with REBETOL and INTRON A can make this kind of liver problem worse.
- You are allergic to any of the ingredients in REBETOL Capsules or INTRON A Injection, or to any alpha interferon. (See ingredients listed at the end of this Medication Guide).

**Tell your health care provider before starting REBETRON Combination Therapy if you have any of the following medical conditions or other serious medical problems:**

- **mental health problems, such as depression or anxiety.** REBETRON Combination Therapy may make them worse. Tell your health care provider if you are being treated for a mental illness or had treatment in the past for any mental problems, including depression, suicidal behavior, or psychosis. Psychosis is loss of contact with reality, such as hearing voices or seeing things that are not there.
- **high blood pressure, other heart problems, or have had a heart attack.** The medicines in REBETRON Combination Therapy may worsen heart problems. Patients who have had certain heart problems should not take REBETRON Combination Therapy.
- **blood disorders, including anemia (low red blood cell count), thalassemia (Mediterranean anemia), and sickle-cell anemia.** REBETRON Combination Therapy can reduce the number of red blood cells you have. This may make you feel dizzy or weak and could worsen any heart problems you might have.
- **kidney problems.** If your kidneys do not work well, you may get worse side effects from REBETRON Combination Therapy and need a dose adjustment.
- **liver problems (other than hepatitis C infection)**
- **organ transplant, and are taking medicine that keeps your body from rejecting your transplant (suppresses your immune system)**
- **thyroid disease.** REBETRON Combination Therapy may make your thyroid disease worse or harder to treat. REBETRON Combination Therapy may be stopped if you develop thyroid abnormalities that cannot be controlled by medication.
- **alcoholism or drug abuse or addiction**
- **cancer**
- **infection with hepatitis B virus or human immunodeficiency virus (HIV), the virus that causes AIDS.**
- **diabetes.** REBETRON Combination Therapy may make your diabetes worse or harder to treat.
- **past interferon treatment for hepatitis C virus infection that did not work for you.**

**How should I take REBETRON Combination Therapy?**

- Your health care provider has determined the correct doses of REBETOL and INTRON A. Your doses of REBETOL and INTRON A may be lowered if you have side effects. The recommended dose of INTRON A Injection and REBETOL Capsules are shown in the table below.

<b>If your weight is:</b>	<b>Take this many REBETOL Capsules each day:</b>	<b>Inject this amount of INTRON A under your skin (subcutaneously)</b>
---------------------------	--	--

165 pounds or less	2 capsules in the AM 3 capsules in the PM	3 million international units 3times a week
More than 165 pounds	3 capsules in the AM 3 capsules in the PM	3 million international units 3times a week

- You can take your REBETOL Capsules with or without food, but you should take it the same way every day.
- It is important to follow your dosing schedule and your health care provider's instructions on how to take your medicines.
- Take the medicines for as long as they are prescribed, and do not take more than the recommended doses.
- If you miss a dose of REBETOL Capsules, take the missed dose as soon as possible during the same day. If an entire day has gone by, check with your health care provider about what to do. Do not double the next dose.
- If you miss a dose of INTRON A, take the missed dose as soon as possible during the same day or on the next day, and continue your regular dosing schedule. If several days go by without taking INTRON A, check with your health care provider about what to do. Do not double the next dose.
- Tell your health care provider if you are taking or planning to take other prescription or non-prescription medicines, including vitamin and mineral supplements and herbal medicines.

Instructions on how to inject INTRON A are at the end of this Medication Guide.

### **What should I avoid while taking REBETRON Combination Therapy?**

- **Pregnancy:** If you or your sexual partner becomes pregnant, tell your health care provider right away. (See "**What is the most important information I should know about therapy with Rebetrone Combination Therapy?**" at the beginning of this Medication Guide.)

Talk with your health care provider about how to avoid pregnancy. If you or your sexual partner becomes pregnant while being treated with REBETRON Combination Therapy or during the 6 months after treatment ends, you must report the pregnancy to your health care provider right away. Your *health care provider* should call toll-free 1-800-727-7064. Your health care provider will be asked to give follow-up information about the pregnancy. Any information about your pregnancy that is reported about you will be confidential.

- **Breastfeeding.** The medicine may pass through your milk and harm the baby.
- **Drinking alcohol,** including beer, wine and liquor because this may make your liver disease worse.
- **Do not inject yourself with Intron A** if it is discolored or contains particles.
- **Taking any medicines other than those prescribed or approved by your health care provider**
- **Ask your health care provider if there are other things you should avoid,** in addition to alcohol (beer, wine, liquor), prescription and nonprescription drugs, and alternative

medications (herbal medicine).

### **What are the possible side effects of REBETRON Combination Therapy?**

**Harm to unborn children.** REBETRON Combination Therapy can harm your unborn child. It can cause birth defects and may kill your unborn child. (For more details, see “**What is the most important information I should know about REBETRON Combination Therapy?**” at the beginning of this Medication Guide.)

- **Anemia.** REBETRON Combination Therapy causes anemia (a reduction in the number of red blood cells you have) which can be dangerous, especially if you have heart, or breathing problems. Tell your health care provider right away if you feel tired, have chest pain or shortness of breath. These may be signs of low red blood counts.
- **Infections.** INTRON A therapy may lower your white blood cell count, making it easier for you to get serious infections. You must have your blood tested regularly during treatment to check for this problem.
- **Mental Problems.** Tell your health care provider if you have ever had any mental illness, including depression, suicidal behavior, or psychosis (loss of contact with reality such as hearing voices or seeing things that are not there). Also, tell your health care provider if you are taking any medications for these problems. **Tell your health care provider right away if you have the following:**
  - **Start to feel unusually sad or have crying spells**
  - **Lose interest in your usual activities**
  - **Have changes in your normal sleep patterns**
  - **Become more irritable than usual**
  - **Lose your appetite**
  - **Become unusually tired**
  - **Have trouble concentrating**
  - **Withdraw from family and friends**
  - **Have thoughts about hurting yourself or others.**

**Tell your health care provider right away if you have any of the following symptoms. They may be signs of a serious side effect:**

- **trouble breathing, hives or swelling**
- **chest pain**
- **severe stomach or lower back pain**
- **bloody diarrhea or bloody stools (bowel movements). These may appear to be black and tarry.**
- **high fever**
- **bruising**
- **bleeding**
- **decreased vision**

### **What are the most common side effects of REBETRON Combination Therapy?**

- **“Flu-like” symptoms.** These include headache, feeling very tired (fatigue), muscle

aches, and fever. These get better as treatment continues. You can reduce some of these flu-like symptoms by injecting your INTRON A about 2 hours before bedtime. Some health care providers suggest taking non-prescription pain and fever reducers, such as acetaminophen or ibuprofen before taking INTRON A. This may be helpful to prevent or relieve the fever and headache.

- **Feeling tired**
- **Hair thinning**
- **Rash and itching**
- **Nausea and appetite loss**
- **Abdominal pain with nausea and vomiting**
- **Trouble breathing**
- **Trouble with your vision**
- **Trouble sleeping at night**

This summary does not include all possible side effects of combination therapy. You should talk to your health care provider, if you do not feel well while taking REBETOL and INTRON A. Your health care provider can give you more information about managing your side effects.

#### **What should I know about the hepatitis C virus?**

Hepatitis C infection is a disease caused by a virus that infects the liver. This liver infection becomes a continuing (chronic) condition in most patients. Patients with chronic hepatitis C infection may develop cirrhosis, liver cancer, and liver failure. The virus is spread from one person to another by contact with the infected person's blood. You should talk to your health care provider about ways to prevent you from infecting others.

#### **How do I Inject INTRON A?**

- When you have been trained to do it properly. If you have any questions, contact your health care provider before injecting INTRON A.
- Use the sterile technique taught by your health care provider. Use disposable needles after each use, and throw them away properly as directed by your health care provider, nurse, or pharmacist.
- If someone else gives you your injection, that person should be trained in the use of sterile technique and how to avoid an accidental needle stick.

*The INTRON A Injection multidose pen (INTRON A multidose pen) is a pre-filled multidose syringe containing six doses of INTRON A (interferon alfa-2b, recombinant). This multidose pen is specially designed to deliver six doses of 3 MIU of INTRON A. If necessary, it can also be used to deliver different doses (i.e. if your health care provider wants you to increase or decrease your dose). The different doses that it can deliver are 1.5 MIU, 3 MIU, 4.5 MIU and 6 MIU. Six MIU is the maximum dose that this pen can give at one time.*

*Please note the following important points BEFORE using your INTRON A multidose pen:*

- The INTRON A multidose pen should **ONLY** be used with the enclosed **Novofine\*** needles. The use of other needles may result in the pen not working properly and/or the wrong dose of INTRON A solution delivered.
- **ALWAYS** discard needles and used pens carefully; **NEVER** discard the pen with a needle attached.
- Use the INTRON A multidose pen **ONLY** in accordance with these instructions. **DO NOT** allow the INTRON A multidose pen to be handled roughly or otherwise misused.
- **KEEP** out of reach of children.
- When not in use you should **STORE** the INTRON A multidose pen in the **REFRIGERATOR** at **36°-46°F (2° to 8°C)** (not too near the freezer compartment).
- **ALWAYS** check that INTRON A **IS CLEAR** in appearance prior to use. If it **DOES NOT** have a clear uniform appearance **DO NOT USE**. Please consult your health care provider or pharmacist.
- **ALWAYS** check the expiration date; **NEVER** use after the expiration date.

#### **Description of your INTRON A multidose pen**

**Diagrams A and B** show you all the different parts of the pen and the Novofine\* needle. The most important parts to note are as follows:

- The **push button scale** tells you what dose has been set.
- The **color coding strip** and the **push button** are at the bottom of the pen as it is held cap up. (The six doses of 3 MIU multidose pen have a brown coding strip)
- The INTRON A multidose pen can only be fully capped when the **triangle** on the **cap scale** is aligned with the **dosage indicator** on the barrel.

## INTRON A Pen

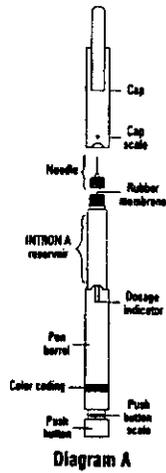


Diagram A

## Novofine\* Needle Assembly

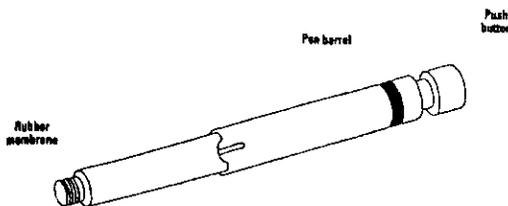


Diagram B

### HOW TO USE YOUR INTRON A Multidose Pen

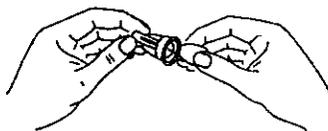
*When you are ready to give your injection prepare your pen as follows. (NOTE: **Boldface print indicates ACTION STEPS**):*

1. **First check that you have the correct INTRON A multidose pen as prescribed by your health care provider, (i.e. the six doses of 3 MIU INTRON A multidose pen which have a brown push button and a brown color coding strip).**
2. **Pull off the cap of the pen and disinfect the rubber membrane (see Diagram C) with one alcohol wipe.**



### Diagram C

3. **Remove the protective tab from the Novofine\* needle.** Note that the rear portion of the needle is revealed once the protective tab is removed (see Diagram D).



### Diagram D

4. **Gently push the Novofine\* needle onto the pen as shown in Diagram E.** (Notice that the rear portion of the needle described in Step 3 will pierce through the rubber membrane that you disinfected previously.) **Now screw the needle onto the INTRON A multidose pen securely by turning it in a clockwise direction** (see Diagram F).

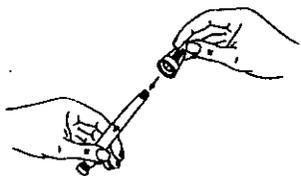


Diagram E

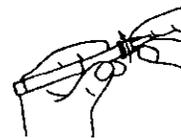
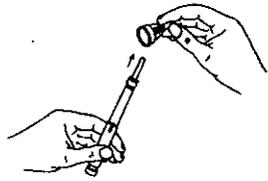
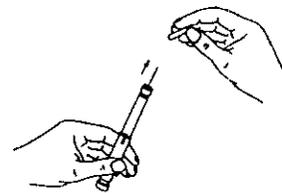


Diagram F

5. **First, pull off the outer needle cap** (Diagram G). **Then, pull off the inner needle cap carefully, bearing in mind that the needle will now be exposed** (Diagram H). **Keep the outer needle cap for later use.**



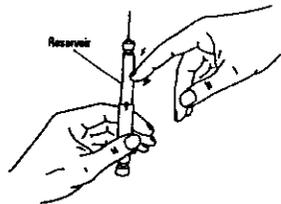
**Diagram G**



**Diagram H**

The pen is now ready to use. Since a small amount of air may collect in the needle and reservoir during storage, the next step is to remove any air bubbles.

6. **Hold the INTRON A multidose pen with the needle point upwards.**
7. **Tap the reservoir with your finger so that any air bubbles rise to the top of the reservoir, just below the needle (Diagram I).**



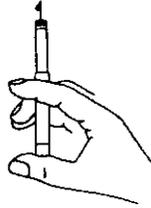
**Diagram I**

8. **Hold the pen by the barrel and turn the reservoir in the direction as indicated by the arrow in Diagram J (clockwise) until you feel it click.**



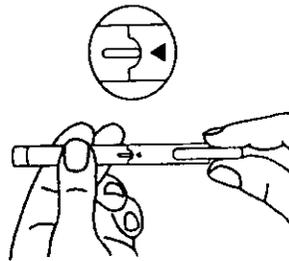
**Diagram J**

9. **Keeping the pen pointing upwards, press the push button up fully and see if a drop of INTRON A solution appears at the needle tip (notice the drop at the tip of needle in Diagram K).**



**Diagram K**

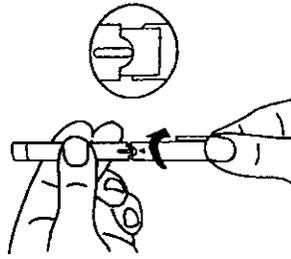
10. **If no drop appears then repeat Steps 7, 8, and 9 until a drop appears at the needle tip.** Note: Some air may still remain in the pen, but this is not important as you have removed the air from the needle and the dose will be accurate.
11. **Replace the INTRON A multidose pen cap with the ‘triangle’ opposite the dosage indicator as seen in Diagram L.**



**Diagram L**

The pen is now ready to set the dose. For the next step hold the pen in the middle of the barrel. This will allow the push button to move freely, ensuring that the correct dose is set.

12. **To set the required dose, hold the pen horizontally by the barrel with one hand. With the other hand, turn the cap in a clockwise direction indicated by the arrow in Diagram M.** You will observe the push button rising, indicating the dose set. To set a 3 MIU dose, turn the cap 2 full turns (10 clicks) = 3.0 MIU.



**Diagram M**

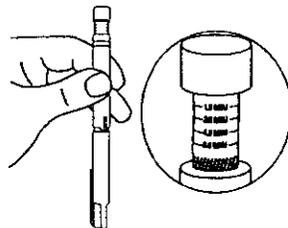
Note: If your health care provider has prescribed a dose other than 3 MIU, the correct dose can be set by turning the cap as many times as indicated as follows:

1 full turn (5 clicks) = 1.5 MIU

3 full turns (15 clicks) = 4.5 MIU

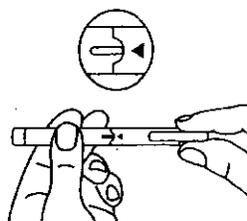
4 full turns (20 clicks) = 6.0 MIU

The push button scale will show you the dose set (see Diagram N). At that point check that you have the correct dose.



**Diagram N**

13. **After each complete turn make sure that the triangle is opposite the dosage indicator (see Diagram O). If you have set a wrong dose, simply turn the cap back (counter-clockwise) as far as you can until the push button is fully home and start again. Once the correct dose is set, you are ready to give the injection.**



### Diagram O

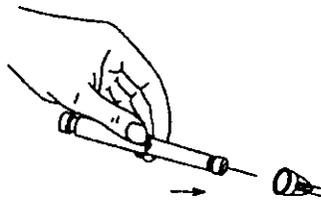
14. To give the injection, remove the pen cap from the needle. With one hand, pinch a 2-inch fold of loose skin.
15. With your other hand, pick up the pen and hold it as you would a pencil. Insert the needle into the pinched skin at an angle of approximately 45° (see Diagram P) then press the push button down fully.

If blood comes into the pen, do not inject. Withdraw the needle and consult your physician or pharmacist.



### Diagram P

16. Leave the needle in place for a few seconds, while holding down the push button, to allow the INTRON A Solution to distribute under the skin.
17. Slowly release the push button, then remove the needle.
18. Carefully replace the *outer* needle cap using a scooping motion (See Diagram Q).



### Diagram Q

19. Completely unscrew the needle assembly using a counter-clockwise turning motion as show in Diagram R. Then carefully lift it off the pen and discard the capped needle (see Diagram S).

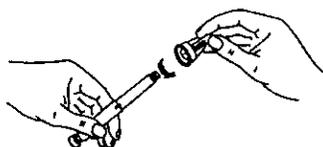


Diagram R

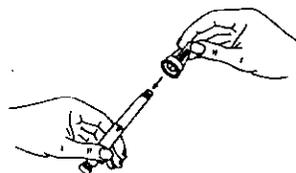


Diagram S

20. Replace the pen cap with the triangle once again opposite the dosage indicator as shown in Diagram T.

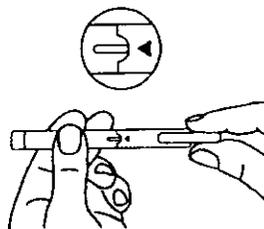


Diagram T

Instructional leaflet and video are available through your health care provider.

How do I store my medications?

**STORAGE OF REBETOL CAPSULES**

REBETOL capsules should be stored in the refrigerator between 36° and 46°F (2° and 8°C) or at room temperature 77°F (25°C).

**STORAGE OF INTRON A INJECTION MULTIDOSE PEN**

INTRON A Injection multidose pen should be stored in the refrigerator between 36° and 46°F (2° and 8°C), not in the freezer.

\* Novofine is a registered trademark of Novo Nordisk.

General advice about prescription medicines

Do not use REBETOL Capsules or INTRON A for conditions for which they were not prescribed. If you have any concern about REBETRON Combination Therapy, ask your health care provider. Your health care provider or pharmacist can give you information about

REBETRON Combination Therapy that was written for health care professionals. Do not give these medicines to other people, even if they have the same condition you have.

**Ingredients:**

REBETOL capsules contain 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 contains interferon alfa-2b recombinant, sodium chloride, dibasic sodium phosphate, monobasic sodium phosphate, edetate disodium, polysorbate 80, m-cresol (as a preservative).

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

Manufactured by:

Schering Corporation  
Kenilworth, NJ 07033 USA

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Rev. X/01

B-

## MEDICATION GUIDE

### REBETRON

*Combination Therapy*  
containing

REBETOL (ribavirin, USP) Capsules  
INTRON A (interferon alfa-2b, recombinant) Injection

REBETRON (REB-eh-tron) is the name for the combination of REBETOL (REB-eh-tole) and INTRON A (IN-tron aye). Read this medication guide carefully before you begin taking REBETRON Combination Therapy, and each time you refill your prescription in case there is new information. This summary does not tell you everything about REBETRON Combination Therapy. Your health care provider is the best source of information about these medicines. After reading this medication guide, talk with your health care provider if you have any questions about this treatment.

#### **What is the most important information I should know about REBETRON Combination Therapy?**

- **REBETRON Combination Therapy may cause birth defects and/or death of an unborn child. Therefore, if you are pregnant, you must not take REBETRON Combination Therapy.** If you could become pregnant, you must not become pregnant during therapy and for six months after you have stopped therapy. During this time you must use two forms of birth control, and you must have pregnancy tests that show that you are not pregnant.

Female sexual partners of male patients being treated with REBETOL must not become pregnant during treatment and for six months after treatment has stopped. Therefore, two forms of birth control must be used during this time.

If pregnancy occurs, report the pregnancy to your healthcare provider right away.

- **Treatment with REBETOL and INTRON A products can cause a dangerous drop in your blood cell counts.** REBETRON Combination Therapy can cause anemia, which is a decrease in the number of red blood cells. This can be dangerous, especially if you have heart or breathing problems. Tell your health care provider before taking REBETRON Combination Therapy if you have ever had any of these problems. Your health care provider should check your red blood cell count before starting therapy and often during the first 4 weeks of therapy. Your red blood cell count may be checked more often if you have heart or breathing problems.
- **REBETRON Combination Therapy can cause a dangerous drop in the number of cells that help fight infections and stop bleeding, which might cause you to have an infection or abnormal bleeding.**

- **Serious mental problems: REBETRON Combination Therapy may cause or worsen mood or behavioral problems.** These can include irritability (getting easily upset) and depression (feeling low, feeling bad about yourself). **Some patients think about hurting or killing themselves or other people, and some have killed themselves (suicide) or hurt themselves or others.** If you experience any of these thoughts or symptoms you should tell your health care provider right away. See **“What are the possible side effects of REBETRON Combination Therapy?”** for important information on signs of mental problems.
- **You should not take REBETOL Capsules alone to treat your hepatitis C virus infection.** REBETOL Capsules should be used only in combination with interferon alfa-2b (INTRON A) for the treatment of chronic hepatitis C infection; the combination is called REBETRON Combination Therapy.

### **What is REBETRON Combination Therapy?**

REBETRON Combination Therapy is a treatment for some people who have chronic hepatitis C infection. It consists of two separate medicines, REBETOL Capsules (ribavirin) and INTRON A Injection (interferon), used in combination. INTRON A helps the body’s immune system fight infections. “REBETOL” is the name given to the antiviral drug ribavirin made by Schering. It is not known how REBETOL and INTRON A work together to fight hepatitis C infection. REBETOL should not be used alone to treat chronic hepatitis C infection.

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

You should use REBETRON Combination Therapy only if you have never been treated or your hepatitis C has returned after interferon therapy.

### **Who should not take REBETRON Combination Therapy?**

**Do not use these medicines if:**

- You are a female and you are pregnant or plan to become pregnant at any time during your treatment with REBETRON Combination Therapy or during the 6 months after your treatment has ended.
- You are a male patient with a female sexual partner who is pregnant or plans to become pregnant at any time while you are being treated during treatment with REBETRON Combination Therapy or during the 6 months after your treatment has ended. **Please see “What is the most important information I should know about REBETRON Combination Therapy?” at the beginning of this Medication Guide.**
- You are breastfeeding. REBETOL and INTRON A products may pass through your milk and harm your baby. Talk with your health care provider about whether you should stop breast-feeding.
- You have autoimmune hepatitis (hepatitis caused by cells in your body attacking each

other) because treatment with REBETOL and INTRON A can make this kind of liver problem worse.

- You are allergic to any of the ingredients in REBETOL Capsules or INTRON A Injection, or to any alpha interferon. (See ingredients listed at the end of this Medication Guide).

**Tell your health care provider before starting REBETRON Combination Therapy if you have any of the following medical conditions or other serious medical problems:**

- **mental health problems, such as depression or anxiety.** REBETRON Combination Therapy may make them worse. Tell your health care provider if you are being treated for a mental illness or had treatment in the past for any mental problems, including depression, suicidal behavior, or psychosis. Psychosis is loss of contact with reality, such as hearing voices or seeing things that are not there.
- **high blood pressure, other heart problems, or have had a heart attack.** The medicines in REBETRON Combination Therapy may worsen heart problems. Patients who have had certain heart problems should not take REBETRON Combination Therapy.
- **blood disorders, including anemia (low red blood cell count), thalassemia (Mediterranean anemia), and sickle-cell anemia.** REBETRON Combination Therapy can reduce the number of red blood cells you have. This may make you feel dizzy or weak and could worsen any heart problems you might have.
- **kidney problems.** If your kidneys do not work well, you may get worse side effects from REBETRON Combination Therapy and need a dose adjustment.
- **liver problems (other than hepatitis C infection)**
- **organ transplant, and are taking medicine that keeps your body from rejecting your transplant (suppresses your immune system)**
- **thyroid disease.** REBETRON Combination Therapy may make your thyroid disease worse or harder to treat. REBETRON Combination Therapy may be stopped if you develop thyroid abnormalities that cannot be controlled by medication.
- **alcoholism or drug abuse or addiction**
- **cancer**
- **infection with hepatitis B virus or human immunodeficiency virus (HIV), the virus that causes AIDS.**
- **diabetes.** REBETRON Combination Therapy may make your diabetes worse or harder to treat.
- **past interferon treatment for hepatitis C virus infection that did not work for you.**

**How should I take REBETRON Combination Therapy?**

- Your health care provider has determined the correct doses of REBETOL and INTRON A. Your doses of REBETOL and INTRON A may be lowered if you have side effects. The recommended dose of INTRON A Injection and REBETOL Capsules are shown in the table below.

If your weight is:	Take this many REBETOL Capsules each day:	Inject this amount of INTRON A under your skin (subcutaneously)

165 pounds or less	2 capsules in the AM 3 capsules in the PM	3 million international units 3times a week
More than 165 pounds	3 capsules in the AM 3 capsules in the PM	3 million international units 3times a week

- You can take your REBETOL Capsules with or without food, but you should take it the same way every day.
- It is important to follow your dosing schedule and your health care provider's instructions on how to take your medicines.
- Take the medicines for as long as they are prescribed, and do not take more than the recommended doses.
- If you miss a dose of REBETOL Capsules, take the missed dose as soon as possible during the same day. If an entire day has gone by, check with your health care provider about what to do. Do not double the next dose.
- If you miss a dose of INTRON A, take the missed dose as soon as possible during the same day or on the next day, and continue your regular dosing schedule. If several days go by without taking INTRON A, check with your health care provider about what to do. Do not double the next dose.
- Tell your health care provider if you are taking or planning to take other prescription or non-prescription medicines, including vitamin and mineral supplements and herbal medicines.

Instructions on how to inject INTRON A are at the end of this Medication Guide.

**What should I avoid while taking REBETRON Combination Therapy?**

- **Pregnancy:** If you or your sexual partner becomes pregnant, tell your health care provider right away. (See "**What is the most important information I should know about therapy with Rebetrone Combination Therapy?**" at the beginning of this Medication Guide.)

Talk with your health care provider about how to avoid pregnancy. If you or your sexual partner becomes pregnant while being treated with REBETRON Combination Therapy or during the 6 months after treatment ends, you must report the pregnancy to your health care provider right away. Your *health care provider* should call toll-free 1-800-727-7064. Your health care provider will be asked to give follow-up information about the pregnancy. Any information about your pregnancy that is reported about you will be confidential.

- Breastfeeding. The medicine may pass through your milk and harm the baby.
- Drinking alcohol, including beer, wine and liquor because this may make your liver disease worse.
- Do not inject yourself with Intron A if it is discolored or contains particles.
- Taking any medicines other than those prescribed or approved by your health care provider
- Ask your health care provider if there are other things you should avoid, in addition to alcohol (beer, wine, liquor), prescription and nonprescription drugs, and alternative

medications (herbal medicine).

### **What are the possible side effects of REBETRON Combination Therapy?**

**Harm to unborn children.** REBETRON Combination Therapy can harm your unborn child. It can cause birth defects and may kill your unborn child. (For more details, see “**What is the most important information I should know about REBETRON Combination Therapy?**” at the beginning of this Medication Guide.)

- **Anemia.** REBETRON Combination Therapy causes anemia (a reduction in the number of red blood cells you have) which can be dangerous, especially if you have heart, or breathing problems. Tell your health care provider right away if you feel tired, have chest pain or shortness of breath. These may be signs of low red blood counts.
- **Infections.** INTRON A therapy may lower your white blood cell count, making it easier for you to get serious infections. You must have your blood tested regularly during treatment to check for this problem.
- **Mental Problems.** Tell your health care provider if you have ever had any mental illness, including depression, suicidal behavior, or psychosis (loss of contact with reality such as hearing voices or seeing things that are not there). Also, tell your health care provider if you are taking any medications for these problems. **Tell your health care provider right away if you have the following:**
  - **Start to feel unusually sad or have crying spells**
  - **Lose interest in your usual activities**
  - **Have changes in your normal sleep patterns**
  - **Become more irritable than usual**
  - **Lose your appetite**
  - **Become unusually tired**
  - **Have trouble concentrating**
  - **Withdraw from family and friends**
  - **Have thoughts about hurting yourself or others.**

**Tell your health care provider right away if you have any of the following symptoms. They may be signs of a serious side effect:**

- **trouble breathing, hives or swelling**
- **chest pain**
- **severe stomach or lower back pain**
- **bloody diarrhea or bloody stools (bowel movements). These may appear to be black and tarry.**
- **high fever**
- **bruising**
- **bleeding**
- **decreased vision**

### **What are the most common side effects of REBETRON Combination Therapy?**

- **“Flu-like” symptoms.** These include headache, feeling very tired (fatigue), muscle aches, and fever. These get better as treatment continues. You can reduce some of these

flu-like symptoms by injecting your INTRON A about 2 hours before bedtime. Some health care providers suggest taking non-prescription pain and fever reducers, such as acetaminophen or ibuprofen before taking INTRON A. This may be helpful to prevent or relieve the fever and headache.

- **Feeling tired**
- **Hair thinning**
- **Rash and itching**
- **Nausea and appetite loss**
- **Abdominal pain with nausea and vomiting**
- **Trouble breathing**
- **Trouble with your vision**
- **Trouble sleeping at night**

This summary does not include all possible side effects of combination therapy. You should talk to your health care provider, if you do not feel well while taking REBETOL and INTRON A. Your health care provider can give you more information about managing your side effects.

#### **What should I know about the hepatitis C virus?**

Hepatitis C infection is a disease caused by a virus that infects the liver. This liver infection becomes a continuing (chronic) condition in most patients. Patients with chronic hepatitis C infection may develop cirrhosis, liver cancer, and liver failure. The virus is spread from one person to another by contact with the infected person's blood. You should talk to your health care provider about ways to prevent you from infecting others.

#### **How do I Inject INTRON A?**

- When you have been trained to do it properly. If you have any questions, contact your health care provider before injecting INTRON A.
- Use the sterile technique taught by your health care provider. Use disposable needles after each use, and throw them away properly as directed by your health care provider, nurse, or pharmacist.
- If someone else gives you your injection, that person should be trained in the use of sterile technique and how to avoid an accidental needle stick.

### Preparing the INTRON A Dose

**IMPORTANT:** Before each use, the liquid in the vial (small bottle) should be clear, colorless to light yellow, and without particles. **Do not use the medicine if you see particles or the color is not correct.** Call your doctor, nurse, or pharmacist to find out what to do if this happens.

1. Check the date printed on the INTRON A carton to make sure that the expiration date has not passed.
2. Wash your hands well and remove the protective plastic cap from the top of the INTRON A vial.
3. Remove the protective plastic wrapper from the syringe provided (Figure A). The safety sleeve should be tight against the flange for use and moved over the needle only when ready for disposal, as instructed in step 6.

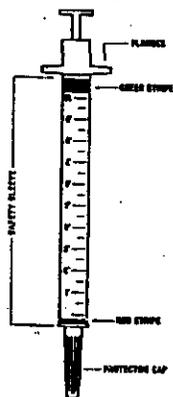


Figure A

4. Clean the rubber stopper on the top of the INTRON A vial with an alcohol swab.
5. Remove the protective cap from the syringe needle. Ensure safety sleeve is pushed firmly against the syringe flange so that the needle is fully exposed. Fill the syringe with air by pulling the plunger to the level that represents your correct dose. (Figure B).

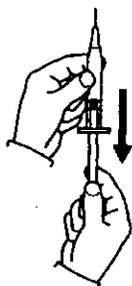
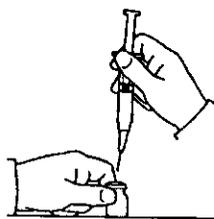


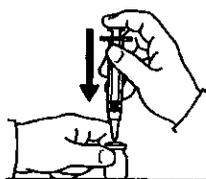
Figure B

6. Hold the INTRON A vial upright without touching the cleaned top of the vial with your hands (Figure C).



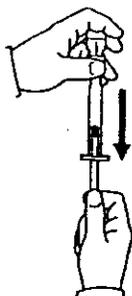
**Figure C**

7. Insert the needle into the vial containing the INTRON A solution and inject the air into the vial (**Figure D**).



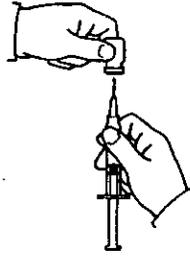
**Figure D**

8. Turn vial and syringe upside down in one hand. Be sure tip of needle is in the INTRON A solution. Your other hand will be free to move the plunger. Pull back on plunger slowly to draw the correct dose into syringe (**Figure E**).



**Figure E**

9. Remove the needle from the vial (**Figure F**) and check for air bubbles in the syringe. If you see any bubbles, tap the syringe gently. Then, with the needle pointing up, push the plunger slowly until the bubbles disappear.



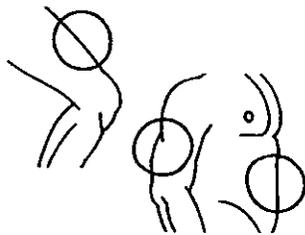
**Figure F**

10. Replace the needle cap. If the solution is cold, warm the syringe between your hands. Lay the syringe down on a flat surface so that needle does not touch anything.

**Subcutaneous (under the skin) Injection**

1. Select the site for injection

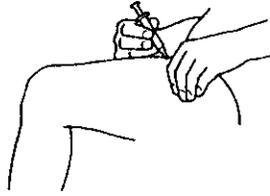
- The best sites for injection are tissues with a layer of fat between skin and muscle, such as the
  - thigh
  - outer surface of the upper arm
  - abdomen (stomach area), except the navel (belly button) or waistline
- If you are very thin, use only the thigh or outer surface of the arm for injection.
- Do not inject INTRON A solution in the same place repeatedly. Change your injection site in a regular pattern.



Use an alcohol swab to cleanse the skin where the injection is to be made. Wait for area to dry.

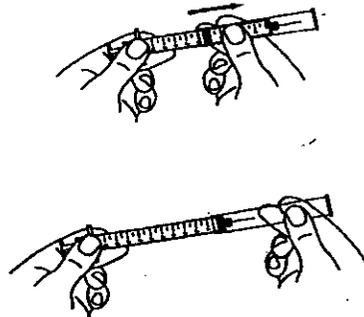
2. Remove the cap from the needle. Ensure the safety sleeve is pushed firmly against the syringe flange so that the needle is fully exposed. Hold the syringe with one hand, as you would hold a pencil. With the other hand, pinch approximately a 2-inch fold of loose skin.

With a quick dart-like motion, push the needle about 1/4 inch into the pinched skin at an angle of 45° to 90°.



After the needle is in, remove hand used to pinch skin and use it to hold syringe barrel. Pull back the plunger very slightly with one hand. If blood comes into the syringe, the needle has entered a blood vessel. Do not inject. Withdraw and discard needle and syringe as instructed in step 6 below. Prepare a new syringe and inject at a new site. (Follow steps 2 and 3.)

4. If blood does not appear in the syringe, gently push the plunger all the way down.
5. Hold an alcohol swab near the needle and pull the needle straight out of the skin. Press the alcohol swab over the injection site for several seconds. Do not massage (rub) the injection site. If there is bleeding, cover the area with an adhesive bandage.
6. After use, firmly grasp the safety sleeve and pull over the exposed needle until you hear a click, and the green stripe on the safety sleeve covers the red stripe on the needle.



7. Use disposable syringe only once to ensure sterility of syringe and needle. Dispose of syringe and needle as directed.

Your health care professional should tell you about the proper handling and disposal of all syringes and needles and the importance of not reusing any syringes or needles.

**Your health care professional should give you a container for throwing away used needles and syringes. Throw away the full container according to directions provided by your doctor.**

8. After 2 hours, check injection site for signs of inflammation, such as redness, swelling, or tenderness. If there are signs of inflammation, contact your doctor.

**Instructional leaflet and video are available through your health care provider.**

**How do I store my medications?**

**STORAGE OF REBETOL CAPSULES**

**REBETOL capsules should be stored in the refrigerator between 36° and 46°F (2° and 8°C) or at room temperature 77°F (25°C).**

**STORAGE OF INTRON A INJECTION VIAL**

**INTRON A Injection vial should be stored in the refrigerator between 36° and 46°F (2° and 8°C), not in the freezer.**

General advice about prescription medicines

Do not use REBETOL Capsules or INTRON A for conditions for which they were not prescribed. If you have any concern about REBETRON Combination Therapy, ask your health care provider. Your health care provider or pharmacist can give you information about REBETRON Combination Therapy that was written for health care professionals. Do not give these medicines to other people, even if they have the same condition you have.

**Ingredients:**

REBETOL capsules contain 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 contains interferon alfa-2b recombinant, sodium chloride, dibasic sodium phosphate, monobasic sodium phosphate, edetate disodium, polysorbate 80, m-cresol (as a preservative).

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

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