

NDA 20-903  
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## PRODUCT INFORMATION

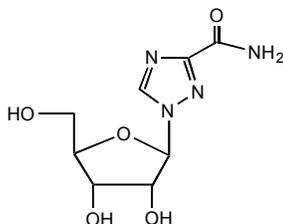
### REBETOL<sup>®</sup> (ribavirin, USP) Capsules and Oral Solution

- **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 nonplasma compartments for as long as 6 months. Therefore, REBETOL therapy is contraindicated in women who are pregnant and in the male partners of women who are pregnant. Extreme care must be taken to avoid pregnancy during therapy and for 6 months after completion of treatment in both female patients and in female partners of male patients who are taking REBETOL therapy. At least two reliable forms of effective contraception must be utilized during treatment and during the 6-month posttreatment follow-up period. (See CONTRAINDICATIONS, WARNINGS, PRECAUTIONS-Information for Patients and Pregnancy Category X).**

## DESCRIPTION

### REBETOL<sup>®</sup>

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.

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

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

### **Mechanism of Action**

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

### **CLINICAL PHARMACOLOGY**

#### **Pharmacokinetics**

*Ribavirin* Single- and multiple-dose pharmacokinetic properties in adults 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 with REBETOL/INTRON A were conducted without instructions with respect to food consumption. During clinical studies with REBETOL/PEG-INTRON, all subjects were instructed to take REBETOL Capsules with food. (See **DOSAGE AND ADMINISTRATION**.)

*Effect of Antacid on Absorption of Ribavirin* Coadministration of REBETOL Capsules with an antacid containing magnesium, aluminum, and simethicone (Mylanta<sup>®1</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.

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**TABLE 1. Mean (% CV) Pharmacokinetic Parameters for REBETOL When Administered Individually to Adults**

Parameter	REBETOL		
	Single Dose 600 mg Oral Solution (N=14)	Single Dose 600 mg Capsules (N=12)	Multiple Dose 600 mg BID Capsules (N=12)
T <sub>max</sub> (hr)	1.00(34)	1.7 (46) ***	3 (60)
C <sub>max</sub> *	872 (42)	782 (37)	3680 (85)
AUC <sub>0-t</sub> **	14098 (38)	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.

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.

### Drug Interactions

Ribavirin has been shown *in vitro* to inhibit phosphorylation of zidovudine and stavudine which could lead to decreased antiretroviral activity. Exposure to didanosine or its active metabolite (dideoxyadenosine 5'-triphosphate) is increased when didanosine is co-administered with ribavirin, which could cause or worsen clinical toxicities (see **PRECAUTIONS: Drug Interactions**).

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

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## 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>0-24</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>0-24</sub> was twofold greater when compared to control subjects. The increased AUC<sub>0-24</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>0-24</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.

**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.

**Pediatric Patients** Multiple-dose pharmacokinetic properties for REBETOL Capsules and INTRON A in pediatric patients with chronic hepatitis C between 5 and 16 years of age are summarized in TABLE 2. The pharmacokinetics of REBETOL and INTRON A (dose-normalized) are similar in adults and pediatric patients.

Complete pharmacokinetic characteristics of REBETOL Oral Solution have not been determined in pediatric patients. Ribavirin C<sub>min</sub> values were similar following administration of REBETOL Oral Solution or REBETOL Capsules during 48 weeks of therapy in pediatric patients (3 to 16 years of age).

**Table 2 Mean (% CV) Multiple-Dose Pharmacokinetic Parameters for INTRON A and REBETOL Capsules When Administered to Pediatric Patients With Chronic Hepatitis C**

Parameter	REBETOL 15mg/ kg/ day as 2 divided doses (n=17)	INTRON A 3MIU/m <sup>2</sup> TIW (n=54)
T <sub>max</sub> (hr)	1.9 (83)	5.9 (36)
C <sub>max</sub> (ng/ml)	3275 (25)	51(48)
AUC*	29774 (26)	622 (48)
Apparent clearance L/hr/kg	0.27 (27)	ND

\*AUC<sub>12</sub> (ng.hr/ml) for REBETOL; AUC<sub>0-24</sub> (IU.hr/ml) for INTRON A  
ND=not done

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

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## INDICATIONS AND USAGE

### Adult Use

REBETOL (ribavirin, USP) Capsules and Oral Solution are indicated in combination with INTRON A (interferon alfa-2b, recombinant) Injection for the treatment of chronic hepatitis C in patients 18 years of age and older with compensated liver disease previously untreated with alpha interferon and in patients 18 years of age and older who have relapsed following alpha interferon therapy.

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

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

### Pediatric Use

REBETOL (ribavirin, USP) Capsules are indicated in combination with INTRON A (interferon alfa-2b, recombinant) Injection for the treatment of chronic hepatitis C in patients 5 years of age and older with compensated liver disease previously untreated with alpha interferon and in patients who have relapsed following alpha interferon therapy.

REBETOL (ribavirin, USP) Oral Solution is indicated in combination with INTRON A (interferon alfa-2b, recombinant) Injection for the treatment of chronic hepatitis C in patients 3 years of age and older with compensated liver disease previously untreated with alpha interferon and in patients who have relapsed following alpha interferon therapy.

Evidence of disease progression, such as hepatic inflammation and fibrosis, as well as prognostic factors for response, HCV genotype and viral load, should be considered when deciding to treat a pediatric patient. The benefits of treatment should be weighed against the safety findings observed (see **PRECAUTIONS Pediatric Use**) for pediatric subjects in the clinical trials.

### Description of Clinical Studies

#### REBETOL/INTRON A Combination Therapy

##### *Adult Patients*

##### *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

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for patients weighing ≤75 kg) plus INTRON A Injection 3 MIU TIW or INTRON A Injection plus placebo for 24 or 48 weeks followed by 24 weeks of off-therapy follow-up. The International study did not contain a 24- week INTRON A plus placebo treatment arm. The US study enrolled 912 patients who, at baseline, were 67% male, 89% Caucasian with a mean Knodell HAI score (I+II+III) of 7.5, and 72% genotype 1. The International study, conducted in Europe, Israel, Canada, and Australia, enrolled 799 patients (65% male, 95% Caucasian, mean Knodell score 6.8, and 58% genotype 1). Study results are summarized in TABLE 3.

**TABLE 3. Virologic and Histologic Responses: Previously Untreated Patients\***

	US Study				International Study		
	24 weeks of treatment		48 weeks of treatment		24 weeks of treatment	48 weeks of treatment	
	INTRON A plus REBETOL (N=228)	INTRO N A plus Placebo (N=231)	INTRON A plus REBETOL (N=228)	INTRO N A plus Placebo (N=225)	INTRON A plus REBETOL (N=265)	INTRON A plus REBETOL (N=268)	INTRO N 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 ≥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

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

#### *Relapse Patients*

Patients with compensated chronic hepatitis C and detectable HCV RNA (assessed by a central laboratory using a research- based RT-PCR assay) who had relapsed following one or two courses of interferon therapy (defined as abnormal serum ALT levels) were enrolled into two multicenter, double-blind trials (US and International) and randomized to receive REBETOL 1200 mg/day (1000 mg/day for patients weighing  $\leq 75$  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 4**.

**TABLE 4. Virologic and Histologic Responses: Relapse Patients\***

	US Study		International Study	
	INTRON A plus REBETOL N=77	INTRON A plus Placebo N=76	INTRON A plus REBETOL N=96	INTRON A plus Placebo N=96
<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.

#### *Pediatric Patients*

Pediatric patients 3 to 16 years of age with compensated chronic hepatitis C and detectable HCV RNA (assessed by a central laboratory using a research-based RT-PCR assay) were treated with REBETOL 15 mg/kg per day plus INTRON A 3 MIU/m<sup>2</sup> TIW for 48 weeks followed by 24 weeks of off-therapy follow-up. A total of 118 patients received treatment who were 57% male, 80% Caucasian, and 78% genotype 1. Patients <5 years of age received REBETOL Oral Solution and those  $\geq 5$  years of age received either REBETOL Oral

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Solution or Capsules.

Study results are summarized in Table 5.

**Table 5: Virologic Response: Previously Untreated Pediatric Patients \***

	<b>INTRON A 3 MIU/m<sup>2</sup> TIW Plus REBETOL 15 mg/kg/day</b>
Overall Response <sup>1</sup> (n=118)	54 (46)
Genotype 1 (n=92)	33 (36)
Genotype non-1 (n=26)	21 (81)

\*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.

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

### **REBETOL/PEG-INTRON Combination Therapy**

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

Response to treatment was defined as undetectable HCV RNA at 24 weeks posttreatment (See **Table 6**).

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**Table 6 Rates of Response to Combination Treatment**

	PEG-INTRON 1.5µg/kg QW REBETOL 800 mg QD	INTRON A 3 MIU TIW REBETOL 1000/1200mg QD
Overall <sup>1,2</sup> response	52% (264/511)	46% (231/505)
Genotype 1	41% (141/348)	33% (112/343)
Genotype 2-6	75%(123/163)	73% (119/162)

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

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

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

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

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

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

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

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## CONTRAINDICATIONS

### **Pregnancy**

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

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

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

## WARNINGS

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

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

### **Pregnancy**

**REBETOL Capsules and Oral Solution 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**

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**CONTRAINDICATIONS and PRECAUTIONS: Information for Patients and Pregnancy Category X).**

**Anemia**

The primary toxicity of ribavirin is hemolytic anemia, which was observed in approximately 10% of REBETOL/INTRON A-treated patients in clinical trials (See adverse reactions laboratory values - *hemoglobin*). The anemia associated with REBETOL capsules occurs within 1 - 2 weeks of initiation of therapy. **BECAUSE THE INITIAL DROP IN HEMOGLOBIN MAY BE SIGNIFICANT, IT IS ADVISED THAT HEMOGLOBIN OR HEMATOCRIT BE OBTAINED PRETREATMENT AND AT WEEK 2 AND WEEK 4 OF THERAPY, OR MORE FREQUENTLY IF CLINICALLY INDICATED.** Patients should then be followed as clinically appropriate.

Fatal and nonfatal myocardial infarctions have been reported in patients with anemia caused by REBETOL. Patients should be assessed for underlying cardiac disease before initiation of ribavirin therapy. Patients with pre-existing cardiac disease should have electrocardiograms administered before treatment, and should be appropriately monitored during therapy. If there is any deterioration of cardiovascular status, therapy should be suspended or discontinued. (See **DOSAGE AND ADMINISTRATION: Guidelines for Dose Modification.**) Because cardiac disease may be worsened by drug induced anemia, patients with a history of significant or unstable cardiac disease should not use REBETOL. (See **ADVERSE REACTIONS.**)

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

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

**Pulmonary**

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

**PRECAUTIONS**

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

The safety and efficacy of REBETOL/INTRON A therapy has not been established in liver

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or other organ transplant patients, patients with decompensated liver disease due to hepatitis C infection, patients who are nonresponders to interferon therapy, or patients coinfecting with HBV or HIV.

### **Information for Patients**

Patients must be informed that REBETOL Capsules and Oral Solution may cause birth defects and/or death of the exposed fetus. REBETOL must not be used by women who are pregnant or by men whose female partners are pregnant. Extreme care must be taken to avoid pregnancy in female patients and in female partners of male patients taking REBETOL. REBETOL should not be initiated until a report of a negative pregnancy test has been obtained immediately prior to initiation of therapy. Patients must perform a pregnancy test monthly during therapy and for 6 months posttherapy. Women of childbearing potential must be counseled about use of effective contraception (two reliable forms) prior to initiating therapy. Patients (male and female) must be advised of the teratogenic/embryocidal risks and must be instructed to practice effective contraception during REBETOL and for 6 months posttherapy. Patients (male and female) should be advised to notify the physician immediately in the event of a pregnancy. (See **CONTRAINDICATIONS and WARNINGS**.)

If pregnancy does occur during treatment or during 6 months posttherapy, the patient must be advised of the teratogenic risk of REBETOL therapy to the fetus. Patients, or partners of patients, should immediately report any pregnancy that occurs during treatment or within 6 months after treatment cessation to their physician. Physicians should report such cases by calling 1-800-593-2214.

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

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

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

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

**Carcinogenesis and Mutagenesis** Ribavirin did not cause an increase in any tumor type when administered for 6 months in the transgenic p53 deficient mouse model at doses up to 300 mg/kg (estimated human equivalent of 25 mg/kg based on body surface area adjustment for a 60 kg adult; approximately 1.9 times the maximum recommended human daily dose).

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Ribavirin was non-carcinogenic when administered for 2 years to rats at doses up to 40 mg/kg (estimated human equivalent of 5.71 mg/kg based on body surface area adjustment for a 60 kg adult). However, this dose was less than the maximum tolerated dose, and therefore the study was not adequate to fully characterize the carcinogenic potential of ribavirin.

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

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

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

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

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

### **Pregnancy Category X (see CONTRAINDICATIONS)**

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

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

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

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

#### **Ribavirin Pregnancy Registry**

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

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

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

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

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

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### **Pediatric Use**

**Suicidal ideation or attempts occurred more frequently among pediatric patients, primarily adolescents, compared to adult patients (2.4% versus 1%) during treatment and off-therapy follow-up (see WARNINGS).** As in adult patients, pediatric patients experienced other psychiatric adverse events (eg, depression, emotional lability, somnolence), anemia, and neutropenia (see WARNINGS). During a 48-week course of therapy there was a decrease in the rate of linear growth (mean percentile assignment decrease of 9%) and a decrease in the rate of weight gain (mean percentile assignment decrease of 13%). A general reversal of these trends was noted during the 24-week post-treatment period.

### **Drug Interactions**

**Didanosine:** Co-administration of REBETOL Capsules or Oral Solution and didanosine is not recommended. Reports of fatal hepatic failure, as well as peripheral neuropathy, pancreatitis, and symptomatic hyperlactatemia/lactic acidosis have been reported in clinical trials (see **CLINICAL PHARMACOLOGY: Drug Interactions**).

**Stavudine and Zidovudine:** Ribavirin may antagonize the *in vitro* antiviral activity of stavudine and zidovudine against HIV. Therefore, concomitant use of ribavirin with either of these drugs should be used with caution (see **CLINICAL PHARMACOLOGY: Drug Interactions**).

## **ADVERSE REACTIONS**

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

### **REBETOL/INTRON A Combination Therapy**

In clinical trials, 19% and 6% of previously untreated and relapse patients, respectively, discontinued therapy due to adverse events in the combination arms compared to 13% and 3% in the interferon arms. Selected treatment-emergent adverse events that occurred in the US studies with  $\geq 5\%$  incidence are provided in **TABLE 7** by treatment group. In general, the selected treatment-emergent adverse events were reported with lower incidence in the international studies as compared to the US studies with the exception of asthenia, influenza-like symptoms, nervousness, and pruritus.

### **Pediatric Patients**

In clinical trials of 118 pediatric patients 3 to 16 years of age, 6% discontinued therapy due to adverse events. Dose modifications were required in 30% of patients, most commonly for anemia and neutropenia. In general, the adverse event profile in the pediatric population was similar to that observed in adults. Injection site disorders, fever, anorexia, vomiting, and emotional lability occurred more frequently in pediatric patients compared to adult patients. Conversely, pediatric patients experienced less fatigue, dyspepsia, arthralgia, insomnia, irritability, impaired concentration, dyspnea, and pruritus compared to adult patients. Selected treatment-emergent adverse events that occurred with  $\geq 5\%$  incidence among all pediatric patients who received the recommended dose of REBETOL/INTRON A

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combination therapy are provided in Table 7.

**TABLE 7. Selected Treatment-Emergent Adverse Events: Previously Untreated and Relapse Adult Patients and Previously Untreated Pediatric Patients**

Percentage of Patients							
US Previously Untreated Study				US Relapse Study		Pediatric Patients	
24 weeks of treatment			48 weeks of treatment		24 weeks of treatment		48 weeks of treatment
Patients Reporting Adverse Events*	INTRON A plus REBETOL (N=228)	INTRON A plus Placebo (N=231)	INTRON A plus REBETOL (N=228)	INTRON A plus Placebo (N=225)	INTRON A plus REBETOL (N=77)	INTRON A plus Placebo (N=76)	INTRON A Plus REBETOL (n=118)
<b>Application Site Disorders</b>							
Injection site inflammation	13	10	12	14	6	8	14
Injection site reaction	7	9	8	9	5	3	19
<b>Body as a Whole - General Disorders</b>							
Headache	63	63	66	67	66	68	69
Fatigue	68	62	70	72	60	53	58
Rigors	40	32	42	39	43	37	25
Fever	37	35	41	40	32	36	61
Influenza-like symptoms	14	18	18	20	13	13	31
Asthenia	9	4	9	9	10	4	5
Chest pain	5	4	9	8	6	7	5
<b>Central &amp; Peripheral Nervous System Disorders</b>							
Dizziness	17	15	23	19	26	21	20
<b>Gastrointestinal System Disorders</b>							
Nausea	38	35	46	33	47	33	33
Anorexia	27	16	25	19	21	14	51
Dyspepsia	14	6	16	9	16	9	<1
Vomiting	11	10	9	13	12	8	42
<b>Musculoskeletal System Disorders</b>							
Myalgia	61	57	64	63	61	58	32
Arthralgia	30	27	33	36	29	29	15

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Musculoskeletal pain	20	26	28	32	22	28	21
<b>Psychiatric Disorders</b>							
Insomnia	39	27	39	30	26	25	14
Irritability	23	19	32	27	25	20	10
Depression	32	25	36	37	23	14	13
Emotional lability	7	6	11	8	12	8	16
Concentration impaired	11	14	14	14	10	12	5
Nervousness	4	2	4	4	5	4	3
<b>Respiratory System Disorders</b>							
Dyspnea	19	9	18	10	17	12	5
Sinusitis	9	7	10	14	12	7	<1
<b>Skin and Appendages Disorders</b>							
Alopecia	28	27	32	28	27	26	23
Rash	20	9	28	8	21	5	17
Pruritus	21	9	19	8	13	4	12
<b>Special Senses, Other Disorders</b>							
Taste perversion	7	4	8	4	6	5	<1

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

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

#### **REBETOL/PEG-INTRON Combination Therapy**

Overall, in clinical trials, 14% of patients receiving REBETOL in combination with PEG-INTRON, discontinued therapy compared with 13% treated with REBETOL in combination with INTRON A. The most common reasons for discontinuation of therapy were related to psychiatric, systemic (e.g. fatigue, headache), or gastrointestinal adverse events. Adverse events that occurred in clinical trial at >5% incidence are provided in **Table 8** by treatment group. Safety and effectiveness of REBETOL in combination with PEG-INTRON has not been established in pediatric patients.

**Table 8. Adverse Events Occurring in > 5% of Patients**

Adverse Events	Percentage of Patients Reporting Adverse Events*		Adverse Events	Percentage of Patients Reporting Adverse Events*	
	PEG-INTRON 1.5µg/kg/REBETO	INTRON A/REBETO L		PEG-INTRON 1.5µg/kg/REBETO	INTRON A/REBETO L

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

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Hepatomegaly	4	4			

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

### Laboratory Values

#### REBETOL/INTRON A Combination Therapy

Changes in selected hematologic values (hemoglobin, white blood cells, neutrophils, and platelets) during therapy are described below. (See **TABLE 9**.)

**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 9. Selected Hematologic Values During Treatment with REBETOL plus INTRON A: Previously Untreated and Relapse Adult Patients and Previously Untreated Pediatric Patients<sup>17</sup>**

	Percentage of Patients						Pediatric Patients 48 weeks of treatment
	US Previously Untreated Study		US Relapse Study		INTRON A Plus REBETOL (n=118)		
	24 weeks of treatment	48 weeks of treatment	24 weeks of treatment	48 weeks of treatment			
	INTRO N A plus REBET OL (N=228)	INTRON A plus Placebo (N=228)	INTRON A plus Placebo (N=225)	INTRON A plus Placebo (N=76)	INTRON A plus Placebo (N=77)		
Hemoglobin (g/dL)							
9.5-10.9	24	1	32	1	21	3	24
8.0-9.4	5	0	4	0	4	0	3
6.5-7.9	0	0	0	0.4	0	0	0
<6.5	0	0	0	0	0	0	0
Leukocytes (x10 <sup>9</sup> /L)							

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2.0-2.9	40	20	38	23	45	26	35
1.5-1.9	4	1	9	2	5	3	8
1.0-1.4	0.9	0	2	0	0	0	0
<1.0	0	0	0	0	0	0	0
<hr/>							
Neutrophils (x10 <sup>9</sup> /L)							
1.0-1.49	30	32	31	44	42	34	37
0.75-0.99	14	15	14	11	16	18	15
0.5-0.74	9	9	14	7	8	4	16
<0.5	11	8	11	5	5	8	3
<hr/>							
Platelets (x10 <sup>9</sup> /L)							
70-99	9	11	11	14	6	12	0.8
50-69	2	3	2	3	0	5	2
30-49	0	0.4	0	0.4	0	0	0
<30	0.9	0	1	0.9	0	0	0
<hr/>							
Total Bilirubin (mg/dL)							
1.5 -3.0	27	13	32	13	21	7	2
3.1-6.0	0.9	0.4	2	0	3	0	0
6.1-12.0	0	0	0.4	0	0	0	0
>12.0	0	0	0	0	0	0	0

### REBETOL/PEG-INTRON Combination Therapy

Changes in selected hematologic values (hemoglobin, white blood cells, neutrophils, and platelets) during therapy are described below. (See **TABLE 10.**)

#### *Hemoglobin.*

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

#### *Bilirubin and Uric Acid*

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

**Table 10: Selected Hematologic Values During Treatment with REBETOL plus PEG-INTRON**

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Number (%) of Subjects					
	PEG- INTRON plus REBETO L (N=511)	INTRON A plus REBETOL (N=505)		PEG- INTRON plus REBETOL (N=511)	INTRON A plus REBETOL (N=505)
Hemoglobin (g/dL)			Platelets (x10 <sup>9</sup> /L)		
9.5-10.9	26	27	70-99	15	5
8.0-9.4	3	3	50-69	3	0.8
6.5-7.9	0.2	0.2	30-49	0.2	0.2
<6.5	0	0	<30	0	0
Leukocytes (x10 <sup>9</sup> /L)			Total Bilirubin (mg/dL)		
2.0-2.9	46	41	1.5 -3.0	10	13
1.5-1.9	24	8	3.1-6.0	0.6	0.2
1.0-1.4	5	1	6.1-12.0	0	0.2
<1.0	0	0	>12.0	0	0
Neutrophils (x10 <sup>9</sup> /L)			ALT (SGPT)		
1.0-1.49	33	37	2 x Baseline	0.6	0.2
0.75-0.99	25	13	2.1-5 x Baseline	3	1
0.5-0.74	18	7	5.1-10 x Baseline	0	0
<0.5	4	2	>10 x Baseline	0	0

## OVERDOSAGE

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

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

**DOSAGE AND ADMINISTRATION** (see **CLINICAL PHARMACOLOGY, Special Populations**; see **WARNINGS**)

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## REBETOL/INTRON A Combination Therapy

### Adults

The recommended dose of REBETOL Capsules depends on the patient's body weight. The recommended dose of REBETOL is provided in **TABLE 11**.

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 non-pegylated interferon monotherapy, 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 11. 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.

### Pediatrics

The recommended dose of REBETOL is 15 mg/kg per day orally (divided dose AM and PM). For children weighing ≤25 kg or who cannot swallow capsules, REBETOL Oral Solution is supplied in a concentration of 40 mg/mL. For children weighing >25 kg, either the Oral Solution or 200-mg capsule may be administered Refer to Table 12 for dosing recommendations for the 200-mg capsule to achieve the recommended dose.

The recommended duration of treatment is 48 weeks for pediatric patients with genotype 1. After 24 weeks of treatment virologic response should be assessed. Treatment discontinuation should be considered in any patient who has not achieved an HCV RNA below the limit of detection of the assay by this time. The recommended duration of treatment for pediatric patients with genotype 2/3 is 24 weeks. There are no safety and efficacy data on treatment for longer than 48 weeks in pediatrics.

<b>Table 12. Pediatric Dosing</b>		
Body weight	REBETOL Capsules	INTRON A Injection

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25-36 kg	1 x 200 mg capsule AM 1 x 200 mg capsule PM daily p.o.	3 million IU/m <sup>2</sup> 3 times weekly s.c.
37-49 kg	1 x 200 mg capsule AM 2 x 200 mg capsules PM daily p.o.	3 million IU/m <sup>2</sup> 3 times weekly s.c.
50-61 kg	2 x 200 mg capsules AM 2 x 200 mg capsules PM daily p.o.	3 million IU/m <sup>2</sup> 3 times weekly s.c.
>61 kg	Refer to adult dosing table	Refer to adult dosing table

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

### **REBETOL/PEG-INTRON Combination Therapy**

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

#### ***Dose Modifications (TABLE 13)***

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) for adults and 7.5 mg/kg per day (divided dose AM and PM) for pediatric patients. A patient whose hemoglobin level falls below 8.5 g/dL should be permanently discontinued from REBETOL therapy. (See **WARNINGS**.)

**TABLE 13. Guidelines for Dose Modifications and Discontinuation for Anemia**

Dose Reduction <sup>*</sup> REBETOL –	Permanent Discontinuation of REBETOL Treatment
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600 mg daily adults  
7.5 mg/kg daily for  
pediatrics

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

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

## Storage Conditions

**The bottle of REBETOL Capsules should be stored—at 25°C (77°F); excursions permitted to 15°-30°C (59°-86°F) [See USP Controlled Room Temperature].**

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



Schering Corporation  
Kenilworth, NJ 07033 USA

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## MEDICATION GUIDE

### REBETOL (ribavirin, USP) Capsules and Oral Solution

Read this medication guide carefully before you or your child begin taking REBETOL [REB-eh-tol] Capsules or Oral Solution, and each time you refill your prescription in case new information has been included. This summary does not tell you everything about REBETOL Capsules or Oral Solution. 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 REBETOL.

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

- **REBETOL Capsules and Oral Solution may cause birth defects or death of an unborn child. Therefore, if you are pregnant or your sexual partner is pregnant, do not take REBETOL.** If you could become pregnant, you must not become pregnant during therapy and for 6 months after you have stopped therapy. During this time you must use 2 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 6 months after treatment has stopped. Therefore, you must use 2 forms of birth control during this time.

If you or a female sexual partner becomes pregnant, you should tell your healthcare provider. There is a Ribavirin Pregnancy Registry that collects information about pregnancy outcomes in female patients and female partners of male patients exposed to ribavirin. You or your healthcare provider are encouraged to contact the Registry at 1-800-593-2214.

Be assured that any information you tell the Registry will be kept confidential. (See “**What should I avoid while taking REBETOL Capsules and Oral Solution?**”)

- After each use of Rebetol Oral Solution, wash the measuring cup or spoon to avoid accidental swallowing of the medicine.
- **REBETOL Capsules and Oral Solution can cause a dangerous drop in your red blood cell count.**

REBETOL Capsules and Oral Solution 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.

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- **Do not take REBETOL Capsules or Oral Solution alone to treat hepatitis C infection.** REBETOL Capsules should be used in combination with interferon alfa-2b (INTRON A) or in combination with peginterferon alfa-2b (PEG-INTRON) for treating chronic hepatitis C infection in adults. In children, safety and effectiveness of REBETOL Capsules or Oral Solution has only been shown when used in combination with interferon alfa-2b (INTRON A). REBETOL Capsules and INTRON A when used together are called REBETRON Combination Therapy. Your health care provider or pharmacist should give you a copy of the REBETRON Combination Therapy or PEG-INTRON Medication Guide. They have additional important information about combination therapy not covered in this guide.

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

“REBETOL” is a form of the antiviral drug ribavirin. It is used in combination with interferon alfa-2b to treat some patients with chronic hepatitis C infection. It is not known how REBETOL and interferon alfa-2b work together to fight hepatitis C infection. (see the **REBETRON Combination Therapy or PEG-INTRON Medication Guide**).

It is not known if treatment with REBETOL and interferon alfa-2b 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 interferon alfa-2b will prevent an infected person from infecting another person with the hepatitis C virus.

### **Who should not take REBETOL Capsules or Oral Solution?**

#### **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. (See “**What is the most important information I should know about therapy with REBETOL Capsules or Oral Solution?**” and “**What should I avoid while taking REBETOL Capsules or Oral Solution?**”)
- You are breast-feeding. REBETOL may pass through your milk and harm your baby. Talk with your provider about whether you should stop breast-feeding.
- You are allergic to any of the ingredients in REBETOL Capsules or Oral Solution. See the ingredients listed at the end of this Medication Guide.

**Tell your health care provider before starting treatment with REBETOL Capsules or Oral Solution in combination with interferon alfa-2b if you have any of the following medical conditions:**

- **mental health problems, such as depression or anxiety.** REBETOL/interferon alfa-2b therapy may make them worse. Tell your health care provider if you are being treated or had treatment in the past for any mental problems, including depression, suicidal behavior, or a feeling of loss of contact with reality, such as hearing voices or seeing

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things that are not there (psychosis). Tell your health care provider if you take any medicines for these problems.

- **high blood pressure, heart problems, or have had a heart attack.** REBETOL Capsules and Oral Solution may worsen heart problems. Patients who have had certain heart problems should not take REBETOL Capsules or Oral Solution.
- **blood disorders**, including anemia (low red blood cell count), thalassemia (Mediterranean anemia), and sickle-cell anemia. REBETOL Capsules and Oral Solution 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/interferon alfa-2b therapy may make your thyroid disease worse or harder to treat. REBETOL/interferon alfa-2b therapy may be stopped if you develop thyroid problems that cannot be controlled by medicine.
- **lung problems.** REBETOL/interferon alfa-2b Therapy can cause breathing problems or worsen breathing problems you already have.
- **alcoholism or drug abuse or addiction**
- **cancer**
- **infection with hepatitis B virus and/or human immunodeficiency virus** (the virus that causes AIDS).
- **diabetes.** REBETOL/interferon alfa-2b therapy may make your diabetes worse or harder to treat.
- **past interferon treatment for hepatitis C virus infection that did not work for you.**

**For more information see the Rebetrone Combination Therapy or PEG-INTRON Medication Guides.**

### **How should I take REBETOL Capsules or Oral Solution?**

Your health care provider has determined the correct dose of REBETOL Capsules or Oral Solution based on your weight. Your health care provider may lower your dose of REBETOL if you have side effects.

- It is important to follow your dosing schedule and your health care provider's instructions on how to take your medicines.
- If you take REBETOL with PEG-INTRON, take it with food.
- If you take REBETOL with INTRON A, you can take it with or without food. However, you should **take it the same way every day.**
- 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 or Oral Solution, 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.

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- 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.
- Tell your provider before taking REBETOL Capsules or Oral Solution if you have ever had any heart or breathing problems. Your 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 frequently if you have had heart or breathing problems.
- Females taking REBETOL Capsules or Oral Solution or female sexual partners of male patients taking REBETOL Capsules or Oral Solution must have a pregnancy test before treatment begins, every month during treatment, and for 6 months after treatment ends to make sure there is no pregnancy.

### **What should I avoid while taking REBETOL Capsules or Oral Solution?**

Avoid the following during REBETOL Capsule or Oral Solution treatment:

- **Pregnancy:** If you or your sexual partner gets pregnant during treatment with REBETOL Capsules or Oral Solution or in the 6 months after treatment ends, tell your health care provider right away. (See “**What is the most important information I should know about therapy with REBETOL Capsules or Oral Solution?**”)

Talk with your health care provider about how to avoid pregnancy. If you or your sexual partner gets 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 1-800-593-2214. 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. This may make your liver disease worse.
- **Taking other medicines.** Take only medicines prescribed or approved by your health care provider. These include prescription and non-prescription medicines and herbal supplements.

### **What are the most common side effects of REBETOL Capsules and Oral Solution?**

**The most serious possible side effects of REBETOL Capsules and Oral Solution are:**

- **Harm to unborn children.** REBETOL Capsules and Oral Solution may cause birth defects or death of an unborn child. (For more details, see “**What is the most important information I should know about REBETOL Capsules or Oral Solution?**”)
- **Anemia.** Anemia is 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 cell counts.

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

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- **trouble breathing**
- **hives or swelling**
- **chest pain**
- **severe stomach or low back pain**
- **bloody diarrhea or bloody stools (bowel movements). These may appear black and tarry.**
- **bruising**
- **other bleeding**

**The most common side effects of REBETOL Capsules and Oral Solution are:**

- **feeling tired**
- **nausea and appetite loss**
- **rash and itching**
- **cough**

This summary does not include all possible side effects of REBETOL therapy. 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 REBETOL Capsules?**

Store REBETOL Capsules at room temperature 77°F (25°C).

### **How do I store my REBETOL Oral Solution?**

Store REBETOL Oral Solution at room temperature 77°F (25°C) or in the refrigerator 36° to 46°F (2° to 8°C).

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

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

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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.

REBETOL Oral Solution contains ribavirin and the inactive ingredients sodium citrate, citric acid, sodium benzoate, glycerin, sucrose, sorbitol, propylene glycol, and water.

*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

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## PRODUCT INFORMATION

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

### CONTRAINDICATIONS AND WARNINGS

Combination REBETOL/INTRON A therapy is contraindicated in females who are pregnant and in the male partners of females who are pregnant. Extreme care must be taken to avoid pregnancy during therapy and for 6 months after completion of treatment in female patients, and in female partners of male patients who are taking combination REBETOL/INTRON A therapy. Females of childbearing potential and males must use two reliable forms of effective contraception during treatment and during the 6-month posttreatment follow-up period. Significant teratogenic and/or embryocidal effects have been demonstrated for ribavirin in all animal species studied. See CONTRAINDICATIONS and WARNINGS.

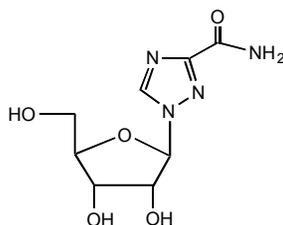
REBETOL monotherapy is not effective for the treatment of chronic hepatitis C and should not be used for this indication. See WARNINGS.

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

### DESCRIPTION

#### **REBETOL®**

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



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

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

### **INTRON<sup>®</sup> A**

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

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

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

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

### **Mechanism of Action**

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

## **CLINICAL PHARMACOLOGY**

### **Pharmacokinetics**

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

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

*Ribavirin* Single- and multiple-dose pharmacokinetic properties in adults with chronic hepatitis C are summarized in **TABLE 1**. Ribavirin was rapidly and extensively absorbed following oral administration. However, due to first-pass metabolism, the absolute bioavailability averaged 64% (44%). There was a linear relationship between dose and AUC<sub>tf</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>tf</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>tf</sub>. The clinical relevance of results from this single-dose study is unknown.

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

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

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

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

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

<sup>††</sup> N = 6

\*\*\* N = 11

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

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

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

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

### ***Special Populations***

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

***Hepatic Dysfunction*** The effect of hepatic dysfunction was assessed after a single oral dose of ribavirin (600 mg). The mean  $\text{AUC}_{\text{tr}}$  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  $C_{\text{max}}$  values increased with severity of hepatic dysfunction and was twofold greater in subjects with severe hepatic dysfunction when compared to control subjects.

**Pediatric Patients** Multiple-dose pharmacokinetic properties for REBETOL Capsules and INTRON A in pediatric patients with chronic hepatitis C between 5 and 16 years of age are summarized in **Table 2**. The pharmacokinetics of REBETOL and INTRON A (dose-normalized) are similar in adults and pediatric patients.

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

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**Table 2 Mean (% CV) Multiple-Dose Pharmacokinetic Parameters for INTRON A and REBETOL Capsules When Administered to Pediatric Patients With Chronic Hepatitis C**

Parameter	REBETOL 15mg/ kg/ day as 2 divided doses (n=17)	INTRON A 3MIU/m <sup>2</sup> TIW (n=54)
T <sub>max</sub> (hr)	1.9 (83)	5.9 (36)
C <sub>max</sub> (ng/ml)	3275 (25)	51(48)
AUC*	29774 (26)	622 (48)
Apparent clearance L/hr/kg	0.27 (27)	ND

\*AUC<sub>12</sub> (ng.hr/ml) for REBETOL; AUC<sub>0-24</sub> (IU.hr/ml) for INTRON A  
ND=not done

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

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

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

### Drug Interactions

Ribavirin has been shown *in vitro* to inhibit phosphorylation of zidovudine and stavudine which could lead to decreased antiretroviral activity. Exposure to didanosine or its active metabolite (dideoxyadenosine 5'-triphosphate) is increased when didanosine is co-administered with ribavirin, which could cause or worsen clinical toxicities (see **PRECAUTIONS:Drug Interactions**).

## INDICATIONS AND USAGE

### Adult Use

REBETOL (ribavirin, USP) Capsules and Oral Solution are indicated in combination with INTRON A (interferon alfa-2b, recombinant) Injection for the treatment of chronic hepatitis C in patients 18 years of age and older with compensated liver disease previously untreated with alpha interferon and in patients 18 years of age and older who have relapsed following alpha interferon therapy.

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

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

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### Pediatric Use

REBETOL (ribavirin, USP) Capsules are indicated in combination with INTRON A (interferon alfa-2b, recombinant) Injection for the treatment of chronic hepatitis C in patients 5 years of age and older with compensated liver disease previously untreated with alpha interferon and in patients who have relapsed following alpha interferon therapy.

REBETOL (ribavirin, USP) Oral Solution is indicated in combination with INTRON A (interferon alfa-2b, recombinant) Injection for the treatment of chronic hepatitis C in patients 3 years of age and older with compensated liver disease previously untreated with alpha interferon and in patients who have relapsed following alpha interferon therapy.

Evidence of disease progression, such as hepatic inflammation and fibrosis, as well as prognostic factors for response, HCV genotype and viral load, should be considered when deciding to treat a pediatric patient. The benefits of treatment should be weighed against the safety findings observed (see **PRECAUTIONS Pediatric Use**) for pediatric subjects in the clinical trials.

### Description of Clinical Studies

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

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

	US Study				International Study		
	24 weeks of treatment		48 weeks of treatment		24 weeks of treatment	48 weeks of treatment	
	<b>INTRON A plus REBETOL (N=228)</b>	<b>INTRON A plus Placebo (N=231)</b>	<b>INTRON A plus REBETOL (N=228)</b>	<b>INTRON A plus Placebo (N=225)</b>	<b>INTRON A plus REBETOL (N=265)</b>	<b>INTRON A plus REBETOL (N=268)</b>	<b>INTRON A plus Placebo (N=266)</b>
<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)

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\* Number (%) of Patients.

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

<sup>2</sup> 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 nongenotype 1 randomized to REBETOL/INTRON A therapy for 48 weeks compared to 24 weeks.

*Relapse Patients* Patients with compensated chronic hepatitis C and detectable HCV RNA (assessed by a central laboratory using a research based RT-PCR assay) who had relapsed following one or two courses of interferon therapy (defined as abnormal serum ALT levels) were enrolled into two multicenter, double-blind trials (US and International) and randomized to receive REBETOL 1200 mg/day (1000 mg/day for patients weighing  $\leq 75$  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 4**.

	US Study		International Study	
	<b>INTRON A plus REBETOL N=77</b>	<b>INTRON A plus Placebo N=76</b>	<b>INTRON A plus REBETOL N=96</b>	<b>INTRON A plus Placebo N=96</b>
<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.

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

<sup>2</sup> 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.

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

Study results are summarized in **Table 5**.

**Table 5: Virologic Response: Previously Untreated Pediatric Patients \***

	<b>INTRON A 3 MIU/m<sup>2</sup> TIW Plus REBETOL 15 mg/kg/day</b>
Overall Response <sup>1</sup> (n=118)	54 (46)
Genotype 1 (n=92)	33 (36)
Genotype non-1 (n=26)	21 (81)

\*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.

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

## **CONTRAINDICATIONS**

Combination REBETOL/INTRON A therapy must not be used by females who are pregnant or by males whose female partners are pregnant. Extreme care must be taken to avoid pregnancy in female patients and in female partners of male patients taking combination REBETOL/INTRON A therapy. Combination REBETOL/INTRON A therapy should not be initiated until a report of a negative pregnancy test has been obtained immediately prior to initiation of therapy. Females of childbearing potential and males must use two forms of effective contraception during treatment and during the 6 months after treatment has been concluded. Significant teratogenic and/or embryocidal effects have been demonstrated for ribavirin in all animal species in which adequate studies have been conducted. These effects occurred at doses as low as one twentieth of the recommended human dose of REBETOL Capsules. If pregnancy occurs in a patient or partner of a patient during treatment or during the 6 months after treatment stops, physicians are encouraged to report such cases by calling (800) 593-2214. See **boxed CONTRAINDICATIONS AND WARNINGS**. See **WARNINGS**.

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

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

## **WARNINGS**

### **Pregnancy**

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

### **Anemia**

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

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

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

### **Psychiatric**

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

### **Bone marrow toxicity:**

INTRON A therapy suppresses bone marrow function and may result in severe cytopenias including very rare events of aplastic anemia. It is advised that complete blood counts (CBC) be obtained pre-treatment and monitored routinely during therapy (see **PRECAUTIONS**:

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**Laboratory Tests).** INTRON A therapy should be discontinued in patients who develop severe decreases in neutrophil ( $<0.5 \times 10^9/L$ ) or platelet counts ( $<25 \times 10^9/L$ ) (see **DOSAGE AND ADMINISTRATION: Guidelines for Dose Modifications**).

### **Pulmonary**

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

### **Other**

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

### **PRECAUTIONS**

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

There have been reports of interferon, including INTRON A (interferon alfa-2b, recombinant) exacerbating pre-existing psoriasis; therefore, combination REBETOL/INTRON A therapy should be used in these patients only if the potential benefit justifies the potential risk.

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

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

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

**Triglycerides:** Elevated triglyceride levels have been observed in patients treated with interferon including REBETOL/INTRON A therapy. Elevated triglyceride levels should be managed as clinically appropriate. Severe hypertriglyceridemia (triglycerides >1000 mg/dL) may result in pancreatitis. Discontinuation of REBETOL/INTRON A therapy should be considered for patients with persistently elevated triglycerides (triglycerides >1000 mg/dL) associated with symptoms of potential pancreatitis, such as abdominal pain, nausea, or vomiting (see **WARNINGS - Other**).

### **Drug Interactions**

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

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

If pregnancy does occur during treatment or during 6 months posttherapy, the patient must be advised of the significant teratogenic risk of REBETOL therapy to the fetus. Patients, or partners of patients, should immediately report any pregnancy that occurs during treatment or within 6 months after treatment cessation to their physician. Physicians are encouraged to report such cases by calling (800) 593-2214.

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

If home use is prescribed, a puncture-resistant container for the disposal of used syringes and needles should be supplied to the patient. Patients should be thoroughly

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

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

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

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

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

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

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

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

**Impairment of Fertility** No reproductive toxicology studies have been performed using interferon alfa-2b, recombinant in combination with ribavirin. However, evidence provided below for interferon alfa-2b, recombinant and ribavirin when administered alone indicate that

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both agents have adverse effects on reproduction. It should be assumed that the effects produced by either agent alone will also be caused by the combination of the two agents. Interferons may impair human fertility. In studies of interferon alfa-2b recombinant administration in nonhuman primates, menstrual cycle abnormalities have been observed. Decreases in serum estradiol and progesterone concentrations have been reported in females treated with human leukocyte interferon. In addition, ribavirin demonstrated significant embryocidal and/or teratogenic effects at doses well below the recommended human dose in all animal species in which adequate studies have been conducted.

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

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

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

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

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

**Treatment and Posttreatment: Potential Risk to the Fetus** Ribavirin is known to accumulate in intracellular components from where it is cleared very slowly. It is not known whether ribavirin contained in sperm will exert a potential teratogenic effect upon fertilization of the

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ova. In a study in rats, it was concluded that dominant lethality was not induced by ribavirin at doses up to 200 mg/kg for 5 days (estimated human equivalent doses of 7.14 - 28.6 mg/kg, based on body surface area adjustment for a 60 kg adult; up to 1.7 X the maximum recommended human dose of ribavirin). However, because of the potential human teratogenic effects of ribavirin, male patients should be advised to take every precaution to avoid risk of pregnancy for their female partners.

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

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

If pregnancy occurs in a patient or partner of a patient during treatment or during the 6 months after treatment cessation, physicians are encouraged to report such cases by calling (800) 593-2214.

### **Ribavirin Pregnancy Registry**

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

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

### **Pediatric Use**

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

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

Injection site disorders, fever, anorexia, vomiting, and emotional lability occurred more frequently in pediatric patients compared to adult patients. Conversely, pediatric patients

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experienced less fatigue, dyspepsia, arthralgia, insomnia, irritability, impaired concentration, dyspnea, and pruritis compared to adult patients.

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

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

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

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

## **ADVERSE REACTIONS**

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

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

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

Selected treatment-emergent adverse events that occurred in the US studies with  $\geq 5\%$  incidence are provided in **TABLE 6** 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.

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<b>TABLE 6. Selected Treatment-Emergent Adverse Events: Previously Untreated and Relapse Adult Patients and Previously Untreated Pediatric Patients</b>							
Percentage of Patients							
US Previously Untreated Study				US Relapse Study		Pediatric Patients	
24 weeks of treatment		48 weeks of treatment		24 weeks of treatment		48 weeks of treatment	
<b>Patients Reporting Adverse Events*</b>	INTRON A plus REBETOL (N=228)	INTRON A plus Placebo (N=231)	INTRON A plus REBETOL (N=228)	INTRON A plus Placebo (N=225)	INTRON A plus REBETOL (N=77)	INTRON A plus Placebo (N=76)	INTRON A Plus REBETOL (n=118)
<b>Application Site Disorders</b>							
Injection site inflammation	13	10	12	14	6	8	14
Injection site reaction	7	9	8	9	5	3	19
<b>Body as a Whole - General Disorders</b>							
Headache	63	63	66	67	66	68	69
Fatigue	68	62	70	72	60	53	58
Rigors	40	32	42	39	43	37	25
Fever	37	35	41	40	32	36	61
Influenza like symptoms	14	18	18	20	13	13	31
Asthenia	9	4	9	9	10	4	5
Chest pain	5	4	9	8	6	7	5
<b>Central &amp; Peripheral Nervous System Disorders</b>							
Dizziness	17	15	23	19	26	21	20
<b>Gastrointestinal System Disorders</b>							
Nausea	38	35	46	33	47	33	33
Anorexia	27	16	25	19	21	14	51
Dyspepsia	14	6	16	9	16	9	<1
Vomiting	11	10	9	13	12	8	42
<b>Musculoskeletal System Disorders</b>							
Myalgia	61	57	64	63	61	58	32

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Arthralgia	30	27	33	36	29	29	15
Musculo-skeletal pain	20	26	28	32	22	28	21
<b>Psychiatric Disorders</b>							
Insomnia	39	27	39	30	26	25	14
Irritability	23	19	32	27	25	20	10
Depression	32	25	36	37	23	14	13
Emotional lability	7	6	11	8	12	8	16
Concentration impaired	11	14	14	14	10	12	5
Nervousness	4	2	4	4	5	4	3
<b>Respiratory System Disorders</b>							
Dyspnea	19	9	18	10	17	12	5
Sinusitis	9	7	10	14	12	7	<1
<b>Skin and Appendages Disorders</b>							
Alopecia	28	27	32	28	27	26	23
Rash	20	9	28	8	21	5	17
Pruritus	21	9	19	8	13	4	12
<b>Special Senses, Other Disorders</b>							
Taste perversion	7	4	8	4	6	5	<1

### Laboratory Values

Changes in selected hematologic values (hemoglobin, white blood cells, neutrophils, and platelets) during combination REBETOL/INTRON A treatment are described below (see TABLE 7).

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

*Neutrophils* There were decreases in neutrophil counts in both the combination REBETOL/INTRON A and INTRON A plus placebo dose groups. In previously untreated patients treated for 48 weeks the mean maximum decrease in neutrophil count in the US study was  $1.3 \times 10^9$  /L and in the International study was  $1.5 \times 10^9$  /L. In relapse patients the mean maximum decrease in neutrophil count in the US study was  $1.3 \times 10^9$  /L and in the

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International study was  $1.6 \times 10^9/L$ . Neutrophil counts returned to pretreatment levels within 4 weeks of cessation of therapy in most patients.

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

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

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

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

	Percentage of Patients						
	US Previously Untreated Study				US Relapse Study		Pediatric Patients
	24 weeks of treatment		48 weeks of treatment		24 weeks of treatment		48 weeks of treatment
	INTRON A plus REBETOL (N=228)	INTRON A plus Placebo (N=231)	INTRON A plus REBETOL (N=228)	INTRON A plus Placebo (N=225)	INTRON A plus REBETOL (N=77)	INTRON A plus Placebo (N=76)	INTRON A Plus REBETOL (n=118)
<b>Hemoglobin (g/dL)</b>							
9.5-10.9	24	1	32	1	21	3	24
8.0-9.4	5	0	4	0	4	0	3
6.5-7.9	0	0	0	0.4	0	0	0
<6.5	0	0	0	0	0	0	0
<b>Leukocytes (<math>\times 10^9/L</math>)</b>							
2.0-2.9	40	20	38	23	45	26	35
1.5-1.9	4	1	9	2	5	3	8
1.0-1.4	0.9	0	2	0	0	0	0
<1.0	0	0	0	0	0	0	0
<b>Neutrophils (<math>\times 10^9/L</math>)</b>							
1.0-1.49	30	32	31	44	42	34	37
0.75-0.99	14	15	14	11	16	18	15
0.5-0.74	9	9	14	7	8	4	16
<0.5	11	8	11	5	5	8	3

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<b>Platelets (x10<sup>9</sup>/L)</b>							
70-99	9	11	11	14	6	12	0.8
50-69	2	3	2	3	0	5	2
30-49	0	0.4	0	0.4	0	0	0
<30	0.9	0	1	0.9	0	0	0
<b>Total Bilirubin (mg/dL)</b>							
1.5 -3.0	27	13	32	13	21	7	2
3.1-6.0	0.9	0.4	2	0	3	0	0
6.1-12.0	0	0	0.4	0	0	0	0
>12.0	0	0	0	0	0	0	0

### OVERDOSAGE

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

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

### DOSAGE AND ADMINISTRATION

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

#### Adults

The recommended dose of REBETOL Capsules depends on the patient's body weight. The recommended doses of REBETOL and INTRON A for adults are given in **TABLE 8**.

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.

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<b>TABLE 8. Recommended Adult Dosing</b>		
Body weight	REBETOL Capsules	INTRON A Injection
≤ 75 kg	2 x 200 mg capsules AM, 3 x 200 mg capsules PM daily p.o.	3 million IU 3 times weekly s.c.
> 75 kg	3 x 200 mg capsules AM, 3 x 200 mg capsules PM daily p.o.	3 million IU 3 times weekly s.c.

### Pediatrics

Efficacy of REBETOL and INTRON A for pediatric patients has not been established. Based on pharmacokinetic data, the following doses of REBETOL and INTRON A provide similar exposures in pediatric patients as observed in adult patients treated with the approved doses of REBETOL and INTRON A (see **TABLE 9**).

<b>Table 9. Pediatric Dosing</b>		
Body weight	REBETOL Capsules	INTRON A Injection
25-36 kg	1 x 200 mg capsule AM 1 x 200 mg capsule PM daily p.o.	3 million IU/m <sup>2</sup> 3 times weekly s.c.
37-49 kg	1 x 200 mg capsule AM 2 x 200 mg capsules PM daily p.o.	3 million IU/m <sup>2</sup> 3 times weekly s.c.
50-61 kg	2 x 200 mg capsules AM 2 x 200 mg capsules PM daily p.o.	3 million IU/m <sup>2</sup> 3 times weekly s.c.
>61 kg	Refer to adult dosing table	Refer to adult dosing table

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

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

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

REBETOL/INTRON A therapy should be administered with caution to patients with pre-existing cardiac disease. Patients should be assessed before commencement of therapy and should be appropriately monitored during therapy. If there is any deterioration of cardiovascular status, therapy should be stopped. (See **WARNINGS**.)

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

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

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

**TABLE 10. Guidelines for Dose Modifications**

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

\*Study medication to be dose reduced is shown in parenthesis

***Administration of INTRON A Injection***

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

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

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

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

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

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

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

### HOW SUPPLIED

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

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

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

	Each REBETRON Combination Package Consists of:	
For Patients ≤75 kg	A box containing 6 vials of INTRON A Injection (3 million IU in 0.5 mL per vial), 6 syringes, alcohol swabs and one bottle containing 70 REBETOL Capsules .	(NDC 0085-1241-02)
	One 18 million IU multidose vial of INTRON A Injection (22.8 million IU per 3.8 mL; 3 million IU/0.5 mL), 6 syringes, alcohol swabs and one bottle containing 70 REBETOL.	(NDC 0085-1236-02)
	One 18 million IU INTRON A Injection multidose pen (22.5 million IU per 1.5 mL; 3 million IU/0.2 mL), 6 disposable needles, alcohol swabs and one bottle containing 70 REBETOL Capsules.	(NDC 0085-1258-02)
For Patients >75 kg	A box containing 6 vials of INTRON A Injection (3 million IU in 0.5 mL per vial), 6 syringes, alcohol swabs and one bottle containing 84 REBETOL Capsules.	(NDC 0085-1241-01)
	One 18 million IU multidose vial of INTRON A Injection (22.8 million IU per 3.8 mL; 3 million IU/0.5 mL), 6 syringes, alcohol swabs and one bottle containing 84 REBETOL Capsules.	(NDC 0085-1236-01)
	One 18 million IU INTRON A Injection multidose pen (22.5 million IU per 1.5 mL; 3 million IU/0.2 mL), 6 disposable needles, alcohol swabs, and one bottle containing 84 REBETOL Capsules.	(NDC 0085-1258-01)
For REBETOL Dose Reduction	A box containing 6 vials of INTRON A Injection (3 million IU in 0.5 mL per vial), 6 syringes, alcohol swabs, and one bottle containing 42 REBETOL Capsules.	(NDC 0085-1241-03)

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

**STORAGE CONDITIONS**

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

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

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



Schering Corporation  
Kenilworth, NJ 07033 USA

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## 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 you or a female sexual partner becomes pregnant, you should tell your healthcare provider. There is a Ribavirin Pregnancy Registry that collects information about pregnancy outcomes in female patients and female partners of male patients exposed to ribavirin. You or your healthcare provider are encouraged to contact the Registry at 1-800-593-2214.

- **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.

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- **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, including some children, 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.**

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- 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.
- **Under no circumstances should REBETOL capsules be opened, crushed or broken.**

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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

Ask your health care provider about the right amount of INTRON A Injection and REBETOL Capsules needed to treat a child with hepatitis C. This amount will depend on a child's weight.

- 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 1-800593-2214. 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.

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- 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

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- 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.

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### **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.

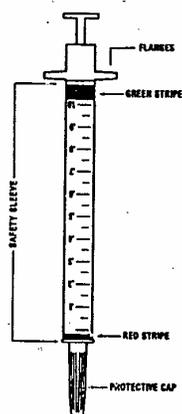


Figure A

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).**

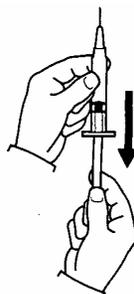
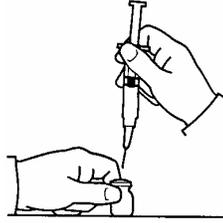


Figure B

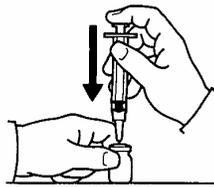
6. Hold the INTRON A vial upright without touching the cleaned top of the vial with your hands **(Figure C).**

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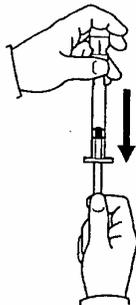
**Figure C**

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



**Figure D**

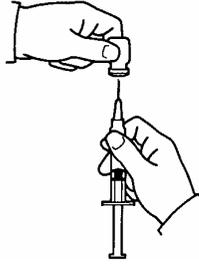
8. Turn vial and syringe upside down in one hand. Be sure tip of needle is in the INTRON A solution. Your other hand will be free to move the plunger. Pull back on plunger slowly to draw the correct dose into syringe (**Figure E**).



**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.

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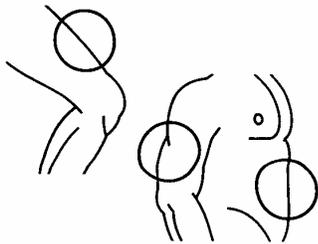
**Figure F**

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.

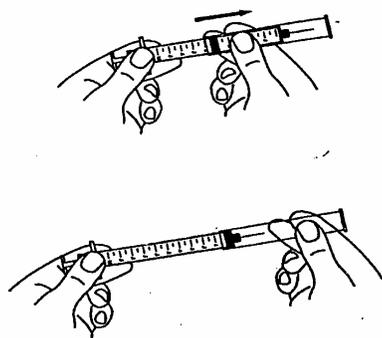
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3. With a quick dart-like motion, push the needle about 1/4 inch into the pinched skin at an angle of 45° to 90°.



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.

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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 REBETOL Combination Therapy, ask your health care provider. Your health care provider or pharmacist can give you information about REBETOL 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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## 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 you or a female sexual partner becomes pregnant, you should tell your healthcare provider. There is a Ribavirin Pregnancy Registry that collects information about pregnancy outcomes in female patients and female partners of male patients exposed to ribavirin. You or your healthcare provider are encouraged to contact the Registry at 1-800-593-2214.

- **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.

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- **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, including some children, 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.**

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- 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.
- **Under no circumstances should REBETOL capsules be opened, crushed or broken.**

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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

Ask your health care provider about the right amount of INTRON A Injection and REBETOL Capsules needed to treat a child with hepatitis C. This amount will depend on a child's weight.

- 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 RebetrON 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 1-800-593-2214. 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.

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- 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**

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- **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*

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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. To avoid possible transmission of disease, **DO NOT** share your multidose pen with anyone; it is for you and you alone
- **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.

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### INTRON A Pen

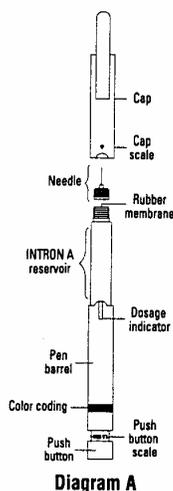


Diagram A

### 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**.

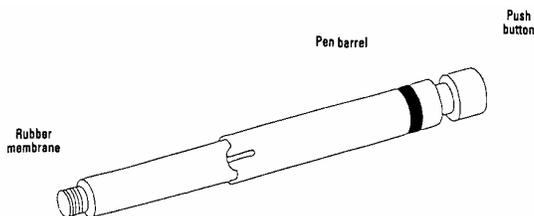


Diagram C

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).

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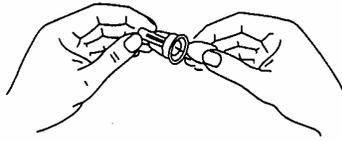


Diagram D

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).

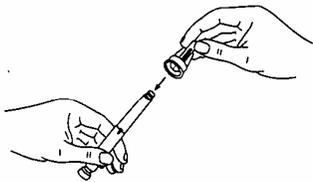


Diagram E

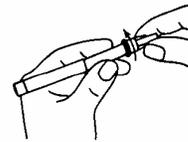


Diagram F

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.

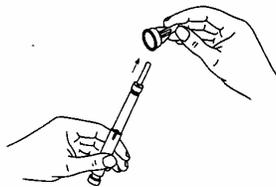


Diagram G



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.**

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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).

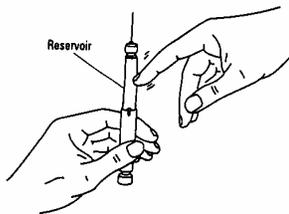


Diagram I

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.

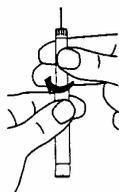


Diagram J

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).

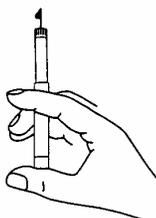
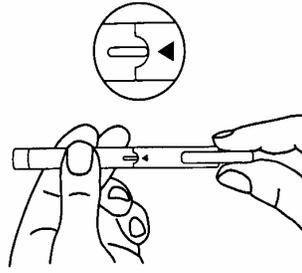


Diagram K

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.

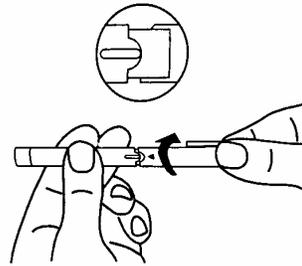
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**Diagram L**

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.

- 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.

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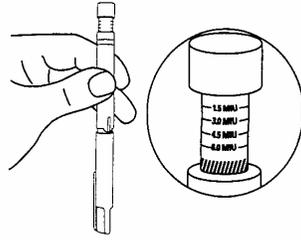


Diagram N

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.

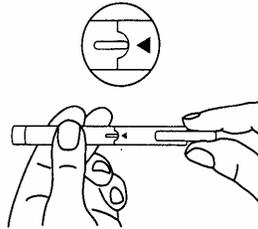


Diagram O

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.**

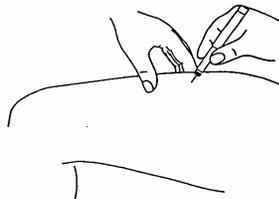


Diagram P

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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).

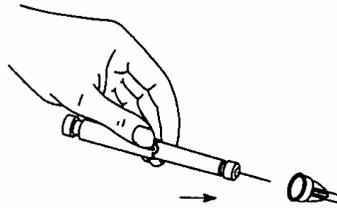


Diagram Q

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).

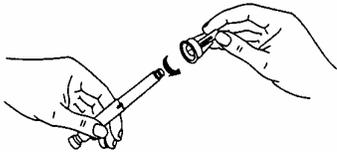


Diagram R



Diagram S

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

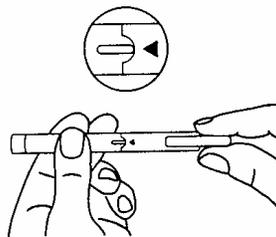


Diagram T

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

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**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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