20-903/S-006
20-903/S-007

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 20-903/S-006
NDA 20-903/S-007

The Schering Corporation
Attention: Joseph F. Lamendola, Ph.D.
Vice President, U.S. Regulatory Affairs
2000 Galloping Hill Road
Kenilworth, NJ 07033

Dear Dr. Lamendola:

Please refer to your supplemental new drug applications dated May 26, 2000 (S-006) and September 15, 2000 (S-007), received May 27, 2000 and September 18, 2000, respectively, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for REBETRON COMBINATION THERAPY [SCH 30500 - Intron® A (Interferon alfa-2b, recombinant) for Injection/ SCH 18908 - Ribavirin].

We acknowledge receipt of your submissions dated May 26, 2000, September 15, 2000, December 1, 2000, January 29, 2001, and March 1, 2001.

The supplemental new drug application **S-006** provides for revisions to the WARNINGS section of the REBETRON COMBINATION THERAPY™ label, to include a bone marrow toxicity section, as follows:

> **Bone marrow toxicity:**
> INTRON A therapy suppresses bone marrow function and may result in severe cytopenias including very rare events of aplastic anemia. It is advised that complete blood counts (CBC) be obtained pre-treatment and monitored routinely during therapy (see **PRECAUTIONS: Laboratory Tests**). INTRON A therapy should be discontinued in patients who develop severe decreases in neutrophil ($<0.5 \times 10^9$/L) or platelet counts ($<25 \times 10^9$/L) (see **DOSAGE AND ADMINISTRATION: Guidelines for Dose Modifications**).

This supplemental new drug application also provides for revisions to the ADVERSE REACTIONS section, to include vertigo and hearing disorders (b), as follows:

> In addition hearing disorders (tinnitus and hearing loss) and vertigo have occurred in patients treated with combination REBETOL/INTRON A therapy.

The supplemental new drug application **S-007** provides for the inclusion of a Geriatric Use section, pursuant to the requirements of CFR 201.57 (f) (10), as follows:

> **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 Modifications**). REBETOL (ribavirin) should be used in elderly patients with creatinine clearance <50 mL/min only if the potential benefit outweighs the risk, and should not be administered to patients with creatinine clearance <30 mL/min (see **WARNINGS**).

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

We have completed the review of these supplemental applications, as amended, and have concluded that adequate information has been presented to demonstrate that the drug product is safe and effective for use as recommended in the agreed upon labeling text. Accordingly, these supplemental applications are approved effective on the date of this letter.

The final printed labeling (FPL) must be identical to the submitted draft labeling (package insert submitted March 1, 2001, patient package insert submitted March 1, 2001).

Please submit the copies of final printed labeling (FPL) electronically to each application according to the guidance for industry titled *Providing Regulatory Submissions in Electronic Format - NDA* (January 1999). Alternatively, you may submit 20 paper copies of the FPL as soon as it is available but no more than 30 days after it is printed. Please individually mount ten of the copies on heavy-weight paper or similar material. For administrative purposes, these submissions should be designated "FPL for approved supplement NDA 20-903/S-006, S-007." Approval of these submissions by FDA is not required before the labeling is used.

In addition, please submit three copies of the introductory promotional materials that you propose to use for this product. All proposed materials should be submitted in draft or mock-up form, not final print. Please submit one copy to this Division and two copies of both the promotional materials and the package insert directly to:

Division of Drug Marketing, Advertising, and Communications, HFD-42
Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857

If a letter communicating important information about this drug product (i.e., a "Dear Health Care Professional" letter) is issued to physicians and others responsible for patient care, we request that you submit a copy of the letter to this NDA and a copy to the following address:

MEDWATCH, HF-2
FDA
5600 Fishers Lane
Rockville, MD 20857

Please submit one market package of the drug product when it is available.

We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 314.80 and 314.81.

If you have any questions, call Destry M. Sillivan, M.S., Regulatory Project Manager, at (301) 827-2335.

Sincerely,

{See appended electronic signature page}

Debra Birnkrant, M.D.
Acting Director
Division of Antiviral Drug Products
Office of Drug Evaluation IV
Center for Drug Evaluation and Research

F-

PRODUCT INFORMATION

REBETRON™

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

CONTRAINDICATIONS AND WARNINGS

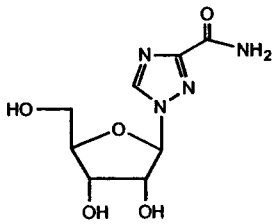
Combination REBETOL/INTRON A therapy is contraindicated in women who are pregnant and in the male partners of women who are pregnant. Extreme care must be taken to avoid pregnancy during therapy and for 6 months after completion of treatment in female patients, and in female partners of male patients who are taking combination REBETOL/INTRON A therapy. Women of childbearing potential and men 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.

DESCRIPTION

REBETOL®

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



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

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

INTRON® A

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

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

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

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

Mechanism of Action

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

CLINICAL PHARMACOLOGY

Pharmacokinetics

Interferon alfa-2b, recombinant Single- and multiple-dose pharmacokinetic properties of INTRON A (interferon alfa-2b, recombinant) are summarized in **TABLE 1**. Following a single 3 million IU (MIU) subcutaneous dose in 12 patients with chronic hepatitis C, mean (% CV*) serum concentrations peaked at 7 (44%) hours. Following 4 weeks of subcutaneous dosing with 3 MIU three times a week (TIW), interferon serum concentrations were undetectable predose. However, a twofold increase in bioavailability was noted upon multiple dosing of interferon; the reason for this is unknown. Mean half-life values following single- and multiple-dose administrations were 6.8 (24%) hours and 6.5 (29%)

hours, respectively.

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

Upon multiple oral dosing, based on $AUC12_{hr}$, a sixfold accumulation of ribavirin was observed in plasma. Following oral dosing with 600 mg BID, steady-state was reached by approximately 4 weeks, with mean steady-state plasma concentrations of 2200 (37%) ng/mL. Upon discontinuation of dosing, the mean half-life was 298 (30%) hours, which probably reflects slow elimination from nonplasma compartments.

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

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

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

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

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

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

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

†† N = 6

*** N = 11

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

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

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

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

Special Populations

Renal Dysfunction The pharmacokinetics of ribavirin were assessed after administration of a single oral dose (400 mg) of ribavirin to subjects with varying degrees of renal dysfunction. The mean AUC_{tf} value was threefold greater in subjects with creatinine clearance values between 10 to 30 mL/min when compared to control subjects (creatinine clearance >90 mL/min). This appears to be due to reduction of apparent clearance in these patients. Ribavirin was not removed by hemodialysis. REBETOL is not recommended for patients with severe renal impairment (see **WARNINGS**).

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

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

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

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

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

INDICATIONS AND USAGE

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

Description of Clinical Studies

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

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

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

	US Study				International Study		
	24 weeks of treatment		48 weeks of treatment		24 weeks of treatment	48 weeks of treatment	
	INTRON A plus REBETOL (N=228)	**INTRON A plus Placebo (N=231)**	**INTRON A plus REBETOL (N=228)**	**INTRON A plus Placebo (N=225)**	**INTRON A plus REBETOL (N=265)**	**INTRON A plus REBETOL (N=268)**	**INTRON A plus Placebo (N=266)**
Virologic Response							
-Responder[1]	65(29)	13(6)	85(37)	27(12)	86(32)	113(42)	46(17)
-Nonresponder	147(64)	194(84)	110(48)	168(75)	158(60)	120(45)	196(74)
-Missing Data	16(7)	24(10)	33(14)	30(13)	21(8)	35(13)	24(9)
Histologic Response							
-Improvement[2]	102(45)	77(33)	96(42)	65(29)	103(39)	102(38)	69(26)
-No improvement	77(34)	99(43)	61(27)	93(41)	85(32)	58(22)	111(41)
-Missing Data	49(21)	55(24)	71(31)	67(30)	77(29)	108(40)	86(32)

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

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

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

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

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

TABLE 3. Virologic and Histologic Responses: Relapse Patients*

	US Study		International Study	
	INTRON A plus REBETOL N=77	**INTRON A plus Placebo N=76**	**INTRON A plus REBETOL N=96**	**INTRON A plus Placebo N=96**
Virologic Response				
-Responder[1]	33(43)	3(4)	46(48)	5(5)
-Nonresponder	36(47)	66(87)	45(47)	91(95)
-Missing Data	8(10)	7(9)	5(5)	0(0)
Histologic Response				
-Improvement[2]	38(49)	27(36)	49(51)	30(31)
-No improvement	23(30)	37(49)	29(30)	44(46)
-Missing Data	16(21)	12(16)	18(19)	22(23)

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

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

CONTRAINDICATIONS

Combination REBETOL/INTRON A therapy must not be used by 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 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. Women of childbearing potential and men must use two forms of effective contraception during treatment and during the 6 months after treatment has been concluded. Significant teratogenic and/or embryocidal effects have been demonstrated for ribavirin in all animal species in which adequate studies have been conducted. These effects occurred at doses as low as one twentieth of the recommended human dose of REBETOL Capsules. If pregnancy occurs in a patient or partner of a patient during treatment or during the 6 months after treatment stops, physicians are encouraged to report such cases by calling (800) 727-7064. **See boxed CONTRAINDICATIONS AND WARNINGS. See WARNINGS.**

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

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

WARNINGS

Pregnancy

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

Anemia

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

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

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

Psychiatric

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

Bone marrow toxicity:

INTRON A therapy suppresses bone marrow function and may result in severe cytopenias including very rare events of aplastic anemia. It is advised that complete blood counts (CBC) be obtained pre-treatment and monitored routinely during therapy (see **PRECAUTIONS: Laboratory Tests**). INTRON A therapy should be discontinued in patients who develop severe decreases in neutrophil ($<0.5 \times 10^9$/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, including fatality, have been reported during therapy with REBETOL/INTRON A. 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 be used with caution in patients with creatinine clearance <50 mL/min.
- Diabetes mellitus and hyperglycemia have been observed in patients treated with INTRON A.
- Ophthalmologic disorders have been reported with treatment with alpha interferons (including INTRON A therapy). Investigators using alpha interferons have reported the occurrence of retinal hemorrhages, cotton wool spots, and retinal artery or vein obstruction in rare instances. Any patient complaining of loss of visual acuity or visual field should have an eye examination. Because these ocular events may occur in conjunction with other disease states, a visual exam prior to initiation of combination REBETOL/INTRON A therapy is recommended in patients with diabetes mellitus or hypertension.

•Acute serious hypersensitivity reactions (eg, urticaria, angioedema, bronchoconstriction, anaphylaxis) have been observed in INTRON A-treated patients; if such an acute reaction develops, combination REBETOL/INTRON A therapy should be discontinued immediately and appropriate medical therapy instituted. •Combination REBETOL/INTRON A therapy should be discontinued for patients developing thyroid abnormalities during treatment whose thyroid function cannot be controlled by medication.

PRECAUTIONS

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

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

The safety and efficacy of REBETOL/INTRON A therapy has not been established in liver or other organ transplant patients, decompensated hepatitis C patients, patients who are

nonresponders to interferon therapy, or patients coinfected with HBV or HIV.

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

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

Information for Patients Combination REBETOL/INTRON A therapy 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 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. 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 combination REBETOL/INTRON A therapy and for 6 months posttherapy. Patients (male and female) should be advised to notify the physician immediately in the event of a pregnancy. (See **CONTRAINDICATIONS.**)

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

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

If home use is prescribed, a puncture-resistant container for the disposal of used syringes and needles should be supplied to the patient. Patients should be thoroughly instructed in the importance of proper disposal and cautioned against any reuse of needles and syringes. The full container should be disposed of according to the directions provided by the physician (see **MEDICATION GUIDE**).

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 women 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.

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

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

Impairment of Fertility No reproductive toxicology studies have been performed using interferon alfa-2b, recombinant in combination with ribavirin. However, evidence provided below for interferon alfa-2b, recombinant and ribavirin when administered alone indicate that both agents have adverse effects on reproduction. It should be assumed that the effects produced by either agent alone will also be caused by the combination of the two agents. Interferons may impair human fertility. In studies of interferon alfa-2b recombinant administration in nonhuman primates, menstrual cycle abnormalities have been observed. Decreases in serum estradiol and progesterone concentrations have been reported in women 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 women and partners of fertile women 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 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) 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 women.

Ribavirin produced significant embryocidal and/or teratogenic effects in all animal species in which adequate studies have been conducted. Malformations of the skull, palate, eye, jaw, limbs, skeleton, and gastrointestinal tract were noted. The incidence and severity of teratogenic effects increased with escalation of the drug dose. Survival of fetuses and offspring was reduced. In conventional embryotoxicity/teratogenicity studies in rats and rabbits, observed no effect dose levels were well below those for proposed clinical use (0.3 mg/kg/day for both the rat and rabbit; approximately 0.06 X the recommended human 24-hour dose of ribavirin). No maternal toxicity or effects on offspring were observed in a peri/postnatal toxicity study in rats dosed orally at up to 1 mg/kg/day (estimated human equivalent dose of 0.17 mg/kg based on body surface area adjustment for a 60 kg adult; approximately 0.01 X the maximum recommended human 24-hour dose of ribavirin).
Treatment and Posttreatment: Potential Risk to the Fetus Ribavirin is known to accumulate in intracellular components from where it is cleared very slowly. It is not known whether ribavirin contained in sperm will exert a potential teratogenic effect upon fertilization of the ova. In a study in rats, it was concluded that dominant lethality was not induced by ribavirin at doses up to 200 mg/kg for 5 days (estimated human equivalent doses of 7.14 - 28.6 mg/kg, based on body surface area adjustment for a 60 kg adult; up to 1.7 X the maximum recommended human dose of ribavirin). However, because of the potential human teratogenic effects of ribavirin, male patients should be advised to take every precaution to avoid risk of pregnancy for their female partners.

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

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

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

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

Pediatric Use Safety and effectiveness in pediatric patients below the age of 18 years have not been established.

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 Modifications**). REBETOL (ribavirin) should be used in elderly patients with creatinine clearance <50 mL/min only if the potential benefit outweighs the risk, and should not be administered to patients with creatinine clearance <30 mL/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 hearing disorders (tinnitus and hearing loss) and vertigo have occurred in patients treated with combination REBETOL/INTRON A therapy.

Selected treatment-emergent adverse events that occurred in the US studies with ≥5% incidence are provided in **TABLE 4** by treatment group. In general, the selected treatment-emergent adverse events reported with lower incidence in the international studies as compared to the US studies with the exception of asthenia, influenza-like symptoms, nervousness, and pruritus.

529

TABLE 4. Selected Treatment-Emergent Adverse Events: Previously Untreated and Relapse Patients

	Percentage of Patients					
	US Previously Untreated Study				US Relapse Study	
	24 weeks of treatment		48 weeks of treatment		24 weeks of treatment	
Patients Reporting Adverse Events*	**INTRON A plus REBETOL (N=228)**	**INTRON A plus Placebo (N=231)**	**INTRON A plus REBETOL (N=228)**	**INTRON A plus Placebo (N=225)**	**INTRON A plus REBETOL (N=77)**	**INTRON A plus Placebo (N=76)**
Application Site Disorders						
injection site inflammation	13	10	12	14	6	8
injection site reaction	7	9	8	9	5	3
Body as a Whole - General Disorders						
headache	63	63	66	67	66	68
fatigue	68	62	70	72	60	53
rigors	40	32	42	39	43	37
fever	37	35	41	40	32	36
influenza-like symptoms	14	18	18	20	13	13
asthenia	9	4	9	9	10	4
chest pain	5	4	9	8	6	7
Central & Peripheral Nervous System Disorders						
dizziness	17	15	23	19	26	21
Gastrointestinal System Disorders						
nausea	38	35	46	33	47	33
anorexia	27	16	25	19	21	14
dyspepsia	14	6	16	9	16	9
vomiting	11	10	9	13	12	8
Musculoskeletal System Disorders						
myalgia	61	57	64	63	61	58
arthralgia	30	27	33	36	29	29
musculoskeletal pain	20	26	28	32	22	28
Psychiatric Disorders						
insomnia	39	27	39	30	26	25
irritability	23	19	32	27	25	20
depression	32	25	36	37	23	14
emotional lability	7	6	11	8	12	8
concentration impaired	11	14	14	14	10	12
nervousness	4	2	4	4	5	4
Respiratory System Disorders						
dyspnea	19	9	18	10	17	12
sinusitis	9	7	10	14	12	7
Skin and Appendages Disorders						
alopecia	28	27	32	28	27	26
rash	20	9	28	8	21	5
pruritus	21	9	19	8	13	4
Special Senses, Other Disorders						

taste perversion	7	4	8	4	6	5

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

Laboratory Values

Changes in selected hematologic values (hemoglobin, white blood cells, neutrophils, and platelets) during combination REBETOL/INTRON A treatment are described below (see **TABLE 5**).

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 1.3×10^9/L and in the International study was 1.5×10^9/L. In relapse patients the mean maximum decrease in neutrophil count in the US study was 1.3×10^9/L and in the International study was 1.6×10^9/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 5. Selected Hematologic Values During Treatment with REBETOL plus INTRON A: Previously Untreated and Relapse Patients

	Percentage of Patients					
	US Previously Untreated Study				US Relapse Study	
	24 weeks of treatment		48 weeks of treatment		24 weeks of treatment	
	INTRON A plus REBETOL (N=228)	**INTRON A plus Placebo (N=231)**	**INTRON A plus REBETOL (N=228)**	**INTRON A plus Placebo (N=225)**	**INTRON A plus REBETOL (N=77)**	**INTRON A plus Placebo (N=76)**
Hemoglobin (g/dL)						
9.5-10.9	24	1	32	1	21	3
8 0-9.4	5	0	4	0	4	0
6.5-7.9	0	0	0	0.4	0	0
<6 5	0	0	0	0	0	0
Leukocytes (x10^9/L)						
2.0-2.9	40	20	38	23	45	26
1.5-1.9	4	1	9	2	5	3
1.0-1.4	0.9	0	2	0	0	0
<1 0	0	0	0	0	0	0
Neutrophils (x10^9/L)						
1.0-1.49	30	32	31	44	42	34
0.75-0.99	14	15	14	11	16	18
0.5-0.74	9	9	14	7	8	4
<0.5	11	8	11	5	5	8
Platelets (x10^9/L)						
70-99	9	11	11	14	6	12
50-69	2	3	2	3	0	5
30-49	0	0.4	0	0.4	0	0
<30	0.9	0	1	0.9	0	0
Total Bilirubin (mg/dL)						
1.5 -3.0	27	13	32	13	21	7
3.1-6.0	0.9	0.4	2	0	3	0
6.1-12.0	0	0	0.4	0	0	0
>12.0	0	0	0	0	0	0

OVERDOSAGE

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

DOSAGE AND ADMINISTRATION

INTRON A Injection should be administered subcutaneously and REBETOL Capsules should be administered orally (see **TABLE 6**).

The recommended dose of REBETOL Capsules depends on the patient's body weight. The recommended doses of REBETOL and INTRON A are given in **TABLE 6.**

The recommended duration of treatment for patients previously untreated with

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

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

TABLE 6. Recommended Dosing		
Body weight	REBETOL Capsules	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.

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

Dose Modifications (TABLE 7)

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

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

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

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

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

TABLE 7. Guidelines for Dose Modifications

	Dose Reduction*	Permanent Discontinuation of Treatment
	REBETOL - 600 mg daily INTRON A - 1.5 million IU TIW	REBETOL and INTRON A

Hemoglobin	<10 g/dL (REBETOL) **Cardiac History Patients only. ≥2 g/dL decrease during any 4-week period during treatment (REBETOL/INTRON A)**	<8.5 g/dL **Cardiac History Patients only. <12 g/dL after 4 weeks of dose reduction**
White blood count	<1.5 x 10^9/L (INTRON A)	<1.0 x 10^9/L
Neutrophil count	<0.75 x 10^9/L (INTRON A)	<0.5 x 10^9/L
Platelet count	<50 x 10^9/L (INTRON A)	<25 x 10^9/L

*Study medication to be dose reduced is shown in parenthesis

627
628 *Administration of INTRON A Injection*
629 At the discretion of the physician, the patient may self-administer the INTRON A. (See illustrated
630 **MEDICATION GUIDE** for instructions.)
631 The Intron A Injection is supplied as a clear and colorless solution. The appropriate
632 INTRON A dose should be withdrawn from the vial or set on the multidose pen and injected
633 subcutaneously. After administration of INTRON A Injection, it is essential to follow the
634 procedure for proper disposal of syringes and needles. (See **MEDICATION GUIDE** for
635 detailed instructions.)
636

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

637 †This is a multidose vial which contains a total of 22.8 million IU of interferon alfa-2b,
638 recombinant per 3.8 mL in order to provide the delivery of six 0.5-mL doses, each containing
639 3 million IU of interferon alfa-2b, recombinant (for a label strength of 18 million IU).
640 †† This is a multidose pen which contains a total of 22.5 million IU of interferon alfa-2b,
641 recombinant per 1.5 mL in order to provide the delivery of six 0.2-mL doses, each containing
642 3 million IU of interferon alfa-2b, recombinant (for a label strength of 18 million IU).
643
644 Parenteral drug products should be inspected visually for particulate matter and discoloration
645 prior to administration, whenever solution and container permit. INTRON A Injection may be
646 administered using either sterilized glass or plastic disposable syringes.
647 *Stability* INTRON A Injection provided in vials is stable at 35°C (95°F) for up to 7 days and
648 at 30°C (86°F) for up to 14 days. INTRON A Injection provided in a multidose pen is stable
649 at 30°C (86°F) for up to 2 days. The solution is clear and colorless.
650
651 HOW SUPPLIED
652 REBETOL 200-mg Capsules are white, opaque capsules with REBETOL, 200 mg, and the
653 Schering Corporation logo imprinted on the capsule shell; the capsules are packaged in a
654 bottle.
655 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:

660

	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)
	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)

661

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).

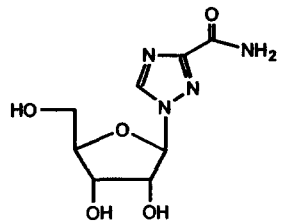
When separated, the individual vials of INTRON A Injection and the INTRON A Multidose Pen should be stored refrigerated between 2° and 8°C (36° and 46°F).

 Schering Corporation
Kenilworth, NJ 07033 USA

U.S. Patents 4,530,901 & 4,211,771

B-

678 F-
679 **PRODUCT**
680 **INFORMATION**
681 REBETRON™
682 **Combination Therapy**
683 ***containing***
684 **REBETOL® (ribavirin, USP) Capsules**
685 ***and***
686 **INTRON® A (interferon alfa-2b, recombinant) Injection**
687
688
689 **CONTRAINDICATIONS AND WARNINGS**
690 **Combination REBETOL/INTRON A therapy is contraindicated in women who are**
691 **pregnant and in the male partners of women who are pregnant. Extreme care must be**
692 **taken to avoid pregnancy during therapy and for 6 months after completion of**
693 **treatment in female patients, and in female partners of male patients who are taking**
694 **combination REBETOL/INTRON A therapy. Women of childbearing potential and**
695 **men must use two reliable forms of effective contraception during treatment and during**
696 **the 6-month posttreatment follow-up period. Significant teratogenic and/or**
697 **embryocidal effects have been demonstrated for ribavirin in all animal species studied.**
698 **See CONTRAINDICATIONS and WARNINGS.**
699 **REBETOL monotherapy is not effective for the treatment of chronic hepatitis C and**
700 **should not be used for this indication. See WARNINGS.**
701
702
703 ## DESCRIPTION
704 ***REBETOL®***
705 REBETOL is Schering Corporation's brand name for ribavirin, a nucleoside analog with
706 antiviral activity. The chemical name of ribavirin is 1-ß-D-ribofuranosyl-1*H*-1,2,4-triazole-3-
707 carboxamide and has the following structural formula:
708



709
710
711 Ribavirin is a white, crystalline powder. It is freely soluble in water and slightly
712 soluble in anhydrous alcohol. The empirical formula is $C_8H_{12}N_4O_5$ and the molecular weight
713 is 244.21.
714 REBETOL Capsules consist of a white powder in a white, opaque, gelatin capsule.
715 Each capsule contains 200 mg ribavirin and the inactive ingredients microcrystalline
716 cellulose, lactose monohydrate, croscarmellose sodium, and magnesium stearate. The
717 capsule shell consists of gelatin, sodium lauryl sulfate, silicon dioxide, and titanium dioxide.
718 The capsule is printed with edible blue pharmaceutical ink which is made of shellac,

anhydrous ethyl alcohol, isopropyl alcohol, n-butyl alcohol, propylene glycol, ammonium hydroxide, and FD&C Blue #2 aluminum lake.

INTRON® A

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

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

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

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

Mechanism of Action

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

CLINICAL PHARMACOLOGY

Pharmacokinetics

Interferon alfa-2b, recombinant Single- and multiple-dose pharmacokinetic properties of INTRON A (interferon alfa-2b, recombinant) are summarized in **TABLE 1**. Following a single 3 million IU (MIU) subcutaneous dose in 12 patients with chronic hepatitis C, mean (% CV*) serum concentrations peaked at 7 (44%) hours. Following 4 weeks of subcutaneous dosing with 3 MIU three times a week (TIW), interferon serum concentrations were undetectable predose. However, a twofold increase in bioavailability was noted upon multiple dosing of interferon; the reason for this is unknown. Mean half-life values following single- and multiple-dose administrations were 6.8 (24%) hours and 6.5 (29%)

hours, respectively.

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

Upon multiple oral dosing, based on $AUC12_{hr}$, a sixfold accumulation of ribavirin was observed in plasma. Following oral dosing with 600 mg BID, steady-state was reached by approximately 4 weeks, with mean steady-state plasma concentrations of 2200 (37%) ng/mL. Upon discontinuation of dosing, the mean half-life was 298 (30%) hours, which probably reflects slow elimination from nonplasma compartments.

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

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

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

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

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

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

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

†† N = 6

*** N = 11

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

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

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

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

Special Populations

Renal Dysfunction The pharmacokinetics of ribavirin were assessed after administration of a single oral dose (400 mg) of ribavirin to subjects with varying degrees of renal dysfunction. The mean AUC_{tf} value was threefold greater in subjects with creatinine clearance values between 10 to 30 mL/min when compared to control subjects (creatinine clearance >90 mL/min). This appears to be due to reduction of apparent clearance in these patients. Ribavirin was not removed by hemodialysis. REBETOL is not recommended for patients with severe renal impairment (see **WARNINGS**).

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

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

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

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

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

INDICATIONS AND USAGE

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

Description of Clinical Studies

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

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

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

	US Study				International Study		
	24 weeks of treatment		48 weeks of treatment		24 weeks of treatment	48 weeks of treatment	
	INTRON A plus REBETOL (N=228)	**INTRON A plus Placebo (N=231)**	**INTRON A plus REBETOL (N=228)**	**INTRON A plus Placebo (N=225)**	**INTRON A plus REBETOL (N=265)**	**INTRON A plus REBETOL (N=268)**	**INTRON A plus Placebo (N=266)**
Virologic Response							
-Responder[1]	65(29)	13(6)	85(37)	27(12)	86(32)	113(42)	46(17)
-Nonresponder	147(64)	194(84)	110(48)	168(75)	158(60)	120(45)	196(74)
-Missing Data	16(7)	24(10)	33(14)	30(13)	21(8)	35(13)	24(9)
Histologic Response							
-Improvement[2]	102(45)	77(33)	96(42)	65(29)	103(39)	102(38)	69(26)
-No improvement	77(34)	99(43)	61(27)	93(41)	85(32)	58(22)	111(41)
-Missing Data	49(21)	55(24)	71(31)	67(30)	77(29)	108(40)	86(32)

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

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

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

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

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

TABLE 3. Virologic and Histologic Responses: Relapse Patients*

	US Study		International Study	
	INTRON A plus REBETOL N=77	**INTRON A plus Placebo N=76**	**INTRON A plus REBETOL N=96**	**INTRON A plus Placebo N=96**
Virologic Response				
-Responder[1]	33(43)	3(4)	46(48)	5(5)
-Nonresponder	36(47)	66(87)	45(47)	91(95)
-Missing Data	8(10)	7(9)	5(5)	0(0)
Histologic Response				
-Improvement[2]	38(49)	27(36)	49(51)	30(31)
-No improvement	23(30)	37(49)	29(30)	44(46)
-Missing Data	16(21)	12(16)	18(19)	22(23)

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

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

CONTRAINDICATIONS

Combination REBETOL/INTRON A therapy must not be used by 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 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. Women of childbearing potential and men must use two forms of effective contraception during treatment and during the 6 months after treatment has been concluded. Significant teratogenic and/or embryocidal effects have been demonstrated for ribavirin in all animal species in which adequate studies have been conducted. These effects occurred at doses as low as one twentieth of the recommended human dose of REBETOL Capsules. If pregnancy occurs in a patient or partner of a patient during treatment or during the 6 months after treatment stops, physicians are encouraged to report such cases by calling (800) 727-7064. **See boxed CONTRAINDICATIONS AND WARNINGS. See WARNINGS.**

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

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

WARNINGS

Pregnancy

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

Anemia

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

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

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

Psychiatric

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

Bone marrow toxicity:

INTRON A therapy suppresses bone marrow function and may result in severe cytopenias including very rare events of aplastic anemia. It is advised that complete blood counts (CBC) be obtained pre-treatment and monitored routinely during therapy (see **PRECAUTIONS: Laboratory Tests**). INTRON A therapy should be discontinued in patients who develop severe decreases in neutrophil ($<0.5 \times 10^9$/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, including fatality, have been reported during therapy with REBETOL/INTRON A. 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 be used with caution in patients with creatinine clearance <50 mL/min.
- Diabetes mellitus and hyperglycemia have been observed in patients treated with INTRON A.
- Ophthalmologic disorders have been reported with treatment with alpha interferons (including INTRON A therapy). Investigators using alpha interferons have reported the occurrence of retinal hemorrhages, cotton wool spots, and retinal artery or vein obstruction in rare instances. Any patient complaining of loss of visual acuity or visual field should have an eye examination. Because these ocular events may occur in conjunction with other disease states, a visual exam prior to initiation of combination REBETOL/INTRON A therapy is recommended in patients with diabetes mellitus or hypertension.

•Acute serious hypersensitivity reactions (eg, urticaria, angioedema, bronchoconstriction, anaphylaxis) have been observed in INTRON A-treated patients; if such an acute reaction develops, combination REBETOL/INTRON A therapy should be discontinued immediately and appropriate medical therapy instituted. •Combination REBETOL/INTRON A therapy should be discontinued for patients developing thyroid abnormalities during treatment whose thyroid function cannot be controlled by medication.

PRECAUTIONS

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

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

The safety and efficacy of REBETOL/INTRON A therapy has not been established in liver or other organ transplant patients, decompensated hepatitis C patients, patients who are

nonresponders to interferon therapy, or patients coinfected with HBV or HIV.

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

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

Information for Patients Combination REBETOL/INTRON A therapy 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 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. 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 combination REBETOL/INTRON A therapy and for 6 months posttherapy. Patients (male and female) should be advised to notify the physician immediately in the event of a pregnancy. (See **CONTRAINDICATIONS.**)

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

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

If home use is prescribed, a puncture-resistant container for the disposal of used syringes and needles should be supplied to the patient. Patients should be thoroughly instructed in the importance of proper disposal and cautioned against any reuse of needles and syringes. The full container should be disposed of according to the directions provided by the physician (see **MEDICATION GUIDE**).

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 women 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.

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

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

Impairment of Fertility No reproductive toxicology studies have been performed using interferon alfa-2b, recombinant in combination with ribavirin. However, evidence provided below for interferon alfa-2b, recombinant and ribavirin when administered alone indicate that both agents have adverse effects on reproduction. It should be assumed that the effects produced by either agent alone will also be caused by the combination of the two agents. Interferons may impair human fertility. In studies of interferon alfa-2b recombinant administration in nonhuman primates, menstrual cycle abnormalities have been observed. Decreases in serum estradiol and progesterone concentrations have been reported in women 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 women and partners of fertile women 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 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) 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 women.

Ribavirin produced significant embryocidal and/or teratogenic effects in all animal species in which adequate studies have been conducted. Malformations of the skull, palate, eye, jaw, limbs, skeleton, and gastrointestinal tract were noted. The incidence and severity of teratogenic effects increased with escalation of the drug dose. Survival of fetuses and offspring was reduced. In conventional embryotoxicity/teratogenicity studies in rats and rabbits, observed no effect dose levels were well below those for proposed clinical use (0.3 mg/kg/day for both the rat and rabbit; approximately 0.06 X the recommended human 24-hour dose of ribavirin). No maternal toxicity or effects on offspring were observed in a peri/postnatal toxicity study in rats dosed orally at up to 1 mg/kg/day (estimated human equivalent dose of 0.17 mg/kg based on body surface area adjustment for a 60 kg adult; approximately 0.01 X the maximum recommended human 24-hour dose of ribavirin).
Treatment and Posttreatment: Potential Risk to the Fetus Ribavirin is known to accumulate in intracellular components from where it is cleared very slowly. It is not known whether ribavirin contained in sperm will exert a potential teratogenic effect upon fertilization of the ova. In a study in rats, it was concluded that dominant lethality was not induced by ribavirin at doses up to 200 mg/kg for 5 days (estimated human equivalent doses of 7.14 - 28.6 mg/kg, based on body surface area adjustment for a 60 kg adult; up to 1.7 X the maximum recommended human dose of ribavirin). However, because of the potential human teratogenic effects of ribavirin, male patients should be advised to take every precaution to avoid risk of pregnancy for their female partners.

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

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

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

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

Pediatric Use Safety and effectiveness in pediatric patients below the age of 18 years have not been established.

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 Modifications**). REBETOL (ribavirin) should be used in elderly patients with creatinine clearance <50 mL/min only if the potential benefit outweighs the risk, and should not be administered to patients with creatinine clearance <30 mL/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 hearing disorders (tinnitus and hearing loss) and vertigo have occurred in patients treated with combination REBETOL/INTRON A therapy. Selected treatment-emergent adverse events that occurred in the US studies with ≥5% incidence are provided in **TABLE 4** by treatment group. In general, the selected treatment-emergent adverse events reported with lower incidence in the international studies as compared to the US studies with the exception of asthenia, influenza-like symptoms, nervousness, and pruritus.

1205

TABLE 4. Selected Treatment-Emergent Adverse Events: Previously Untreated and Relapse Patients

	Percentage of Patients					
	US Previously Untreated Study				US Relapse Study	
	24 weeks of treatment		48 weeks of treatment		24 weeks of treatment	
Patients Reporting Adverse Events*	**INTRON A plus REBETOL (N=228)**	**INTRON A plus Placebo (N=231)**	**INTRON A plus REBETOL (N=228)**	**INTRON A plus Placebo (N=225)**	**INTRON A plus REBETOL (N=77)**	**INTRON A plus Placebo (N=76)**
Application Site Disorders						
injection site inflammation	13	10	12	14	6	8
injection site reaction	7	9	8	9	5	3
Body as a Whole - General Disorders						
headache	63	63	66	67	66	68
fatigue	68	62	70	72	60	53
rigors	40	32	42	39	43	37
fever	37	35	41	40	32	36
influenza-like symptoms	14	18	18	20	13	13
asthenia	9	4	9	9	10	4
chest pain	5	4	9	8	6	7
Central & Peripheral Nervous System Disorders						
dizziness	17	15	23	19	26	21
Gastrointestinal System Disorders						
nausea	38	35	46	33	47	33
anorexia	27	16	25	19	21	14
dyspepsia	14	6	16	9	16	9
vomiting	11	10	9	13	12	8
Musculoskeletal System Disorders						
myalgia	61	57	64	63	61	58
arthralgia	30	27	33	36	29	29
musculoskeletal pain	20	26	28	32	22	28
Psychiatric Disorders						
insomnia	39	27	39	30	26	25
irritability	23	19	32	27	25	20
depression	32	25	36	37	23	14
emotional lability	7	6	11	8	12	8
concentration impaired	11	14	14	14	10	12
nervousness	4	2	4	4	5	4
Respiratory System Disorders						
dyspnea	19	9	18	10	17	12
sinusitis	9	7	10	14	12	7
Skin and Appendages Disorders						
alopecia	28	27	32	28	27	26
rash	20	9	28	8	21	5
pruritus	21	9	19	8	13	4
Special Senses, Other Disorders						

taste perversion	7	4	8	4	6	5

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

Laboratory Values

Changes in selected hematologic values (hemoglobin, white blood cells, neutrophils, and platelets) during combination REBETOL/INTRON A treatment are described below (see **TABLE 5**).

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

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

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

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

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

TABLE 5. Selected Hematologic Values During Treatment with REBETOL plus INTRON A: Previously Untreated and Relapse Patients

	Percentage of Patients					
	US Previously Untreated Study				US Relapse Study	
	24 weeks of treatment		48 weeks of treatment		24 weeks of treatment	
	INTRON A plus REBETOL (N=228)	**INTRON A plus Placebo (N=231)**	**INTRON A plus REBETOL (N=228)**	**INTRON A plus Placebo (N=225)**	**INTRON A plus REBETOL (N=77)**	**INTRON A plus Placebo (N=76)**
Hemoglobin (g/dL)						
9.5-10.9	24	1	32	1	21	3
8.0-9.4	5	0	4	0	4	0
6.5-7.9	0	0	0	0.4	0	0
<6.5	0	0	0	0	0	0
Leukocytes ($x10^9$/L)						
2.0-2.9	40	20	38	23	45	26
1.5-1.9	4	1	9	2	5	3
1.0-1.4	0 9	0	2	0	0	0
<1 0	0	0	0	0	0	0
Neutrophils ($x10^9$/L)						
1.0-1 49	30	32	31	44	42	34
0.75-0.99	14	15	14	11	16	18
0.5-0.74	9	9	14	7	8	4
<0.5	11	8	11	5	5	8
Platelets ($x10^9$/L)						
70-99	9	11	11	14	6	12
50-69	2	3	2	3	0	5
30-49	0	0.4	0	0.4	0	0
<30	0.9	0	1	0.9	0	0
Total Bilirubin (mg/dL)						
1.5 -3.0	27	13	32	13	21	7
3.1-6.0	0.9	0.4	2	0	3	0
6.1-12.0	0	0	0.4	0	0	0
>12.0	0	0	0	0	0	0

OVERDOSAGE

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

DOSAGE AND ADMINISTRATION

INTRON A Injection should be administered subcutaneously and REBETOL Capsules should be administered orally (see **TABLE 6**).

The recommended dose of REBETOL Capsules depends on the patient's body weight. The recommended doses of REBETOL and INTRON A are given in **TABLE 6.**

The recommended duration of treatment for patients previously untreated with

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

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

TABLE 6. Recommended Dosing		
Body weight	REBETOL Capsules	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.

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

Dose Modifications (TABLE 7)

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

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

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

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

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

TABLE 7. Guidelines for Dose Modifications		
	Dose Reduction*	Permanent Discontinuation of Treatment
	REBETOL - 600 mg daily INTRON A - 1.5 million IU TIW	REBETOL and INTRON A

Hemoglobin	<10 g/dL (REBETOL)	<8.5 g/dL
	Cardiac History Patients only. ≥2 g/dL decrease during any 4-week period during treatment (REBETOL/INTRON A)	**Cardiac History Patients only. <12 g/dL after 4 weeks of dose reduction**
White blood count	<1.5 x 10^9/L (INTRON A)	<1.0 x 10^9/L
Neutrophil count	<0.75 x 10^9/L (INTRON A)	<0.5 x 10^9/L
Platelet count	<50 x 10^9/L (INTRON A)	<25 x 10^9/L

*Study medication to be dose reduced is shown in parenthesis

Administration of INTRON A Injection

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

The Intron A Injection is supplied as a clear and colorless solution. The appropriate INTRON A dose should be withdrawn from the vial or set on the multidose pen and injected subcutaneously. 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

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

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

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

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

HOW SUPPLIED

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

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

vials, and a multidose pen.
INTRON A Injection and REBETOL Capsules are available in the following combination package
presentations:

1336

	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)
	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)

1337

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

U.S. Patents 4,530,901 & 4,211,771

B-

Labeling History-Revisions from RIC21617679 to Proposed Labeling

1. Addition of Bone Marrow Toxicity Warning in WARNINGS section (following Psychiatric Warning) as submitted on January 29, 2001 for S-006(original communication received via fax dated November 8, 2000). Line 282-288.
2. REVISION of "Dose Modification" to "Dose Modifications" (addition of "s" at end of "Modification") in the bone marrow toxicity warning for consistency to title of Table 7. Line 288.
3. Bolding "Guidelines for Dose Modifications" of bone marrow toxicity warning consistent with geriatric use formatting and other section references in approved labeling. Line 288.
4. Addition of Geriatric Use information in PRECAUTIONS section as submitted on January 29, 2001 for S-007. Line 481-498
5. REVISION of "DOSAGE ADJUSTMENT" (submitted on January 29, 2001) to "DOSE MODIFICATIONS" in Geriatric Use section on lines 493-494 for consistency to title of Table 7 of approved package insert and proposed bone marrow toxicity warning.
6. Revision of hearing disorder adverse event language in ADVERSE EVENTS section to specify tinnitus and hearing loss as submitted on January 29, 2001 for S-006 (original communication received via fax dated November 8, 2000). Line 518-524.

/s/

Debra Birnkrant
3/13/01 04:05:37 PM
NDA 20-903/S-006, S-007

DEPARTMENT OF HEALTH AND HUMAN SERVICES Public Health Service
Food and Drug Administration
Rockville, MD 20857

DATE: **February 2, 2001**

TO: **NDA 20-903/SLR-006**

FROM: **Russell Fleischer, PA-C, MPH**
Senior Clinical Analyst, DAVDP

TROUGH: **Therese Cvetkovich, MD**
Medical Team Leader, DAVDP

RE: **Medical Review of Rebetron™ Combination Therapy Labeling Supplement**

This submission contains proposed Changes Being Effected to include information about aplastic anemia to the WARNINGS section, and vertigo and hearing disorder to the ADVERSE REACTIONS section of the Rebetron™ Combination Therapy (Intron A/Rebetol [ribavirin]) label. To support revisions to the label, the sponsor submitted15 Drug Safety and Surveillance reports of aplastic anemia and 79 reports of hearing disorders/vertigo.

- **Aplastic Anemia**

The applicant's proposed wording for describing aplastic anemia in the Rebetron label is:

Of the 15 cases of aplastic anemia, 11 occurred in patients treated with Intron® A alone and four were in patients treated with Rebetron™ Combination Therapy. Based on a review of these cases, a causal relationship between the reported events and treatment with Rebetron™ Combination Therapy cannot be excluded. Of note, one of the patients in the database experienced aplastic anemia shortly after initiation of Rebetron™ Combination Therapy; treatment was stopped. The patients had recurrence of aplastic anemia following re-initiation of Rebetron™ Combination Therapy. The patient died due to sepsis.

- **Hearing Disorders and Vertigo**

The summaries of 40 cases of vertigo and 39 cases of hearing disorders were reviewed. The cases were from both clinical trials and post-marketing reports

Vertigo often occurred with other symptoms that made it difficult to determine causality. There were reports that documented improvement in symptoms following discontinuation of ribavirin and/or Intron A. In addition, there were occasional cases of positive re-challenges. The hearing disorders, were most commonly tinnitus and loss of hearing,

ASSESSMENT

Aplastic anemia has been reported to occur in patients with chronic HCV infection and in patients treated with alpha interferons. Dose reduction and/or discontinuation of interferon for severe cases of pancytopenia have been reported to result in recovery, although persistence and sequelae including death have been reported. Intron A is known to adversely affect white cell production. Rebetol is known to cause dose related anemia due to extravascular hemolysis and dose related suppression of the bone marrow. Aplastic anemia specifically, and bone marrow suppression generally are well-characterized toxicities associated with Intron A and ribavirin therapies. Thus, it is incumbent upon the applicant to adequately inform patients and clinicians of this important risk associated with their use. For this reason, a discussion of bone marrow suppression should appear in the WARNINGS section of the Rebetron™ Combination Therapy label.

The mechanism of action leading to hearing disorders and vertigo is not clear. There does appear to be a relationship between treatment with Rebetron and the occurrence of these adverse events.

LABELING REVIEW

The sponsor proposed to include both vertigo/hearing disorders and aplastic anemia in the general Adverse Events section of the Rebetron label. This proposal was deemed unacceptable because of the significant risk to patients of aplastic anemia. Therefore, it was recommended that information about aplastic anemia be included in the WARNINGS section of the Rebetron Combination Therapy. The following language was agreed upon:

Bone Marrow Toxicity

INTRON A therapy suppresses bone marrow function and may result in severe cytopenias including very rare events of aplastic anemia. It is advised that complete blood counts (CBC) be obtained pre-treatment and monitored routinely during therapy (see PRECAUTIONS: Laboratory Tests). INTRON A therapy should be discontinued in patients who develop severe decreases in neutrophil (<0.5 x 10^9/L) or platelet counts (<25 x 10^9/L) (see DOSAGE AND ADMINISTRATION: Guidelines for Dose Modification).

In addition, it was agreed that the ADVERSE REACTIONS section would be revised to include the following statement relative to hearing disorders and vertigo:

In addition, hearing disorders (tinnitus and hearing loss) and vertigo have occurred in patients treated with combination REBETOL/INTRON A therapy.

RECOMMENDED REGULATORY ACTION

The labeling revisions are acceptable. Therefore, this supplement to include a discussion of bone marrow toxicity in the WARNINGS and hearing disorder and vertigo to the ADVERSE REACTIONS section of the Rebetron® Combination Therapy label should be approved.

/s/

Russell Fleischer
2/2/01 11:10:14 AM
MEDICAL OFFICER
Rebetron Bone Marrow Toxicity Warning

Therese Cvetkovich
2/6/01 11:57:38 AM
MEDICAL OFFICER

DEPARTMENT OF HEALTH AND HUMAN SERVICES Public Health Service
Food and Drug Administration
Rockville, MD 20857

DATE: **February 2, 2001**

TO: **NDA 20-903/Rebetron Combination Therapy**

FROM: **Russell Fleischer, PA-C, MPH**
Senior Clinical Analyst, DAVDP

TROUGH: **Therese Cvetkovich, MD**
Medical Team Leader, DAVDP

RE: **Medical Review of Geriatric Labeling Supplement (SLR-007)**

BACKGROUND

Pursuant to the requirements of 201.57 (f)(10), Schering Corporation (the applicant) submitted a GERIATRIC LABELING SUPPLEMENT to revise the GERIATRIC USE section of the REBETRON Combination Therapy label to read:

[redacted]

To support this revision the applicant submitted the following data:

- Data on geriatric patients included in the REBETRON clinical trials database.
- Postmarketing spontaneous reports from Drug Safety and Surveillance database.
- Results of a literature search.

REBETRON clinical trials database

Of 1,685 patients who received the combination of Intron A plus ribavirin for 6-12 months in the applicant's registration trials, 2% (33 patients) were aged 65 years or older. There were no on-study deaths. The primary adverse event experienced by elderly patients was anemia, which occurred in 67% (22/33). Among these, 15 underwent dose modification and 4 discontinued therapy due to complications of anemia (dyspnea and/or chest pain). Other common treatment-related events reported included neutropenia, elevated bilirubin, rash, and malaise/fatigue.

Post marketing reports

The applicant submitted 265 spontaneous post-marketing reports of elderly patients who experienced a serious adverse event while receiving ribavirin alone or in combination with Intron A or PEG-Intron. The types of events were generally similar to the known adverse events associated with these medications, and included anemia, cardiovascular events, and pulmonary events.

Literature search

The applicant conducted a comprehensive literature search in an attempt to identify publications that reviewed treatment of elderly patients with ribavirin alone or as a component of REBETRON Combination Therapy; no literature references were identified.

ASSESSMENT

The types of adverse events reported in elderly patients were similar to those previously characterized in younger patients and included in the current REBETRON label.

Anemia, alone or associated with pulmonary or cardiovascular events appeared to be the most important and serious adverse events reported in elderly patients. Although anemia is well described in the current REBETRON label, specific mention of anemia in the Geriatric section is warranted.

No efficacy data was submitted so it is not known if elderly patients respond the same as younger patients; this was likely due to the insufficient number of elderly patients included in the clinical trials.

LABELING REVIEW

Based on this review, the applicant's original proposed labeling revision was deemed unacceptable because it minimized the potential for serious problems among the elderly and failed to clarify in which elderly patients REBETRON Combination Therapy should and should not be used and under what conditions. The following revisions were proposed and accepted by the applicant:

"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 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 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 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 Dosage Adjustment**). REBETOL (ribavirin) should be used in elderly patients with creatinine clearance <50 mL/min only if the potential benefit outweighs the risk, and should not be administered to patients with creatinine clearance <30 mL/min (see **WARNINGS**).

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

RECOMMENDED REGULATORY ACTION

The labeling revisions are acceptable. Therefore, this Geriatric-labeling supplement should be approved.

/s/

Russell Fleischer
2/2/01 11:12:33 AM
MEDICAL OFFICER
Rebetron Geriatric Labeling supplement

Therese Cvetkovich
2/6/01 11:59:09 AM
MEDICAL OFFICER

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Division of Antiviral Drug Products
Food and Drug Administration
Rockville MD 20857

MEMORANDUM OF TELEPHONE FACSIMILE CORRESPONDENCE

Date: January 17, 2001

To: Rachel Steiner, Regulatory Affairs Associate
Schering Corporation

Address: Galloping Hill Road
Kenilworth, NJ 07033

From: Destry M. Sillivan, M.S., Regulatory Project Manager, HFD-530

Through: Therese Cvetkovich, M.D., Medical Team Leader, HFD-530
Russell Fleischer, PA-C, M.P.H., Senior Clinical Analyst, HFD-530

NDA NDA 20-903, REBETRON™ COMBINATION THERAPY

Subject: Labeling Supplements, NDA 20-903, S-006 and S-007

Please refer to the May 26, 2000, and September 15, 2000, submission of labeling supplements for NDA 20-903, (S-006 and S-007). Following is our suggested wording for the Bone Marrow Toxicity (S-006) and Geriatric Use (S-007) sections of the REBTRON COMBINATION THERAPY label:

- **Bone Marrow Toxicity**

- **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 Dosage Adjustment**). REBETOL (ribavirin) should be used in elderly patients with creatinine clearance <50 mL/min only if the potential benefit outweighs the risk, and should not be administered to patients with creatinine clearance <30 mL/min (see **WARNINGS**).

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

- Please note that these changes should also be incorporated into the labeling proposed in the special labeling supplement (SLR), dated November 7, 2000 (S-008).

We are providing the above information via telephone facsimile for your convenience. **THIS MATERIAL SHOULD BE VIEWED AS UNOFFICIAL CORRESPONDENCE.** Please feel free to contact me if you have any questions regarding the contents of this transmission.

Destry M. Sillivan, M.S.
Regulatory Project Manager
Division of Antiviral Drug Products

/s/

Destry Sillivan
1/19/01 11:29:09 AM
CSO

FAX for Rebetron, SLR 006 and SLR 007 [Bone Marrow warnings and Geriat
ric use, respectively]. You have signed the hard copy.

Therese Cvetkovich
1/19/01 12:47:06 PM
MEDICAL OFFICER

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Division of Antiviral Drug Products
Food and Drug Administration
Rockville MD 20857

MEMORANDUM OF TELEPHONE FACSIMILE CORRESPONDENCE

Date: November 8, 2000

To: Rachel Steiner, Regulatory Affairs Associate
Schering Corporation

Address: Galloping Hill Road
Kenilworth, NJ 07033

From: Destry M. Sillivan, M.S., Regulatory Project Manager, HFD-530

Through: Therese Cvetkovich, M.D., Medical Team Leader, HFD-530
Russell Fleischer, PA-C, M.P.H., Senior Clinical Analyst, HFD-530

IND NDA 20-903, REBETRON™

Subject: Changes Being Effected, NDA 20-903, S-006.

Reference is made to the May 26, 2000 submission of your Special Supplement-Changes Being Effected (CBE), for NDA 20-903, S-006. Please incorporate the following revisions to the REBETRON™ label:

1. New **WARNING (all bold text):**

   BONE MARROW TOXICITY

2. In Adverse Events section:

   In addition, hearing disorders (tinnitus and hearing loss) and vertigo have occurred in patients treated with REBETOL/INTRON A.

We are providing the above information via telephone facsimile for your convenience. **THIS MATERIAL SHOULD BE VIEWED AS UNOFFICIAL CORRESPONDENCE.** Please feel free to contact me if you have any questions regarding the contents of this transmission.

Destry M. Sillivan, M.S.
Regulatory Project Manager
Division of Antiviral Drug Products

/s/

Destry Sillivan
11/9/00 03:20:51 PM
CSO

This is the facsimile for changes to Rebetron's warnings and adverse e vents section

Therese Cvetkovich
11/14/00 12:29:05 PM
MEDICAL OFFICER

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Food and Drug Administration
Rockville MD 20857

Consumer Safety Officer Labeling Review

NDA: 20-903/S-006, S007

Date submitted: May 26, 2000 (S-006), September 15, 2000 (S-007)

Sponsor: The Schering Corporation
2000 Galloping Hill Road
Kenilworth, NJ 07033

Products: REBETRON COMBINATION THERAPY™, SCH 30500 - Intron® A (Interferon alfa-2b, recombinant) for Injection/ SCH 18908 - Ribavirin.

Materials Reviewed: Draft Labeling dated September 15, 2000, January 29, 2001, and March 1, 2001

Background:

The labeling supplement S-006 for NDA 20-903 proposes to revise the WARNINGS section of the REBETRON COMBINATION THERAPY™ label to include information about aplastic anemia, and to revise the ADVERSE REACTIONS section to include vertigo and hearing disorder. This supplement was submitted as Changes Being Effected (CBE) supplement, and has been revised during the course of the review by the Division of Antiviral Drug Products (DAVDP), after the sponsor's initial implementation of the labeling.

The labeling supplement S-007 for NDA 20-903 proposes to include a GERIATRIC USE section of the REBETRON COMBINATION THERAPY™ label, pursuant to the requirements of CFR 201.57 (f) (10).

Label Revisions, S-006:

1. Insertion of a Bone Marrow Toxicity section, as follows:

   Bone marrow toxicity:
   INTRON A therapy suppresses bone marrow function and may result in severe cytopenias including very rare events of aplastic anemia. It is advised that complete blood counts (CBC) be obtained pre-treatment and monitored routinely during therapy (see **PRECAUTIONS: Laboratory Tests).** INTRON A therapy should be discontinued in patients who develop severe decreases in neutrophil ($<0.5 \times 10^9$/L) or platelet counts ($<25 \times 10^9$/L) (see **DOSAGE AND ADMINISTRATION: Guidelines for Dose Modifications).**

2. Inclusion of additional text in the ADVERSE REACTIONS section, as follows:

In addition hearing disorders (tinnitus and hearing loss) and vertigo have occurred in patients treated with combination REBETOL/INTRON A therapy.

3. Deletion of the following text in the ADVERSE REACTIONS section:

Label Revisions, S-007:

1. The inclusion of a Geriatric Use section to the label, as follows:

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 Modifications**). REBETOL (ribavirin) should be used in elderly patients with creatinine clearance <50 mL/min only if the potential benefit outweighs the risk, and should not be administered to patients with creatinine clearance <30 mL/min (see **WARNINGS**).

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

Conclusions/Recommendations:

It should be conveyed to the applicant that the Draft Labeling is acceptable, and an approval letter should be sent.

Destry M. Sillivan, MS

Regulatory Project Manager

Attachment: 1. Clean copy of March 1, 2001Draft Labeling.

2. Annotated (Strike out/delete) copy of the March 1, 2001 Draft Labeling

40 page(s) of revised draft labeling has been redacted from this portion of the review.

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Division of Antiviral Drug Products
Food and Drug Administration
Rockville MD 20857

MEMORANDUM OF TELEPHONE FACSIMILE CORRESPONDENCE

Date: November 15, 2000

To: Rachel Steiner, Regulatory Affairs Associate
Schering Corporation

Address: Galloping Hill Road
Kenilworth, NJ 07033

From: Destry M. Sillivan, M.S., Regulatory Project Manager, HFD-530

Through: Therese Cvetkovich, M.D., Medical Team Leader, HFD-530
Russell Fleischer, PA-C, M.P.H., Senior Clinical Analyst, HFD-530

IND NDA 20-903, REBETRON™

Subject: Geriatric Labeling Supplement, NDA 20-903, S-007.

Reference is made to the September 15, 2000 submission of your Geriatric Labeling Supplement for NDA 20-903, (S-007). Please note the following request, forwarded on behalf of Mr. Russ Fleischer:

- Please conduct analyses on the adverse events listed under Enclosure 3 of the submission. Specifically, you should analyze these events by various age distributions, sex distributions, body system, effect on therapy, and outcomes (e.g., recovered, death, other).

We are providing the above information via telephone facsimile for your convenience. **THIS MATERIAL SHOULD BE VIEWED AS UNOFFICIAL CORRESPONDENCE.** Please feel free to contact me if you have any questions regarding the contents of this transmission.

Destry M. Sillivan, M.S.
Regulatory Project Manager
Division of Antiviral Drug Products

/s/

Destry Sillivan
11/16/00 11:44:23 AM
CSO

Schering Geritatric labeling fax for Rebetron

Therese Cvetkovich
11/20/00 12:24:39 PM
MEDICAL OFFICER