CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

020903Orig1s013

Trade Name: REBETOL

Generic or Proper Name: ribavirin

Sponsor: Schering Corporation

Approval Date: 12/28/2001

Indication: REBETOL (ribavirin, USP) Capsules is indicated in combination with INTRON A (interferon alpha-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.

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APPLICATION NUMBER:

NDA 020903/S-013

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APPLICATION NUMBER:

NDA 020903/S-013

APPROVAL LETTER

NDA 20-903/S-013

Schering Corporation
Attention: Joseph F. Lamendola
Senior Director, Marketed Products, Support and Training
2000 Galloping Hill Road
Kenilworth, NJ 07033

Dear Dr. Lamendola,

Please refer to your supplemental new drug application dated February 28, 2001, received March 1, 2001, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for REBETOL® (ribavirin) capsules for use in combination with the approved biologic product Intron®A (interferon alfa 2b) (Rebetron Combination Therapy™).

We also acknowledge receipt of your submissions dated July, 9, 2001, July 13, 2001, July 17, 2001, November 1, 2001, November 8, 2001, November 19, 2001 and December 21, 2001.

This supplemental new drug application provides for the inclusion of new pediatric pharmacokinetic information in a table format, as found in the **CLINICAL PHARMACOLOGY**, **Pharmacokinetics,** ***Special Populations, Pediatric Patients*** section of the **Rebetron Combination Therapy**™ label, as follows:

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

TABLE 2. Mean (% CV) Pharmacokinetic Parameters for REBETOL When Administered to Pediatric Patients with Chronic Hepatitis C

Parameter	12 mg/kg/day as 2 divided doses (n=19)	15 mg/kg/day as 2 divided doses (n=19)
T_{max} (hr)	1.4 (60)	1.9 (81)
C_{max} (ng/mL)	2705 (17)	3243 (24)
AUC_{12} (ng*hr/mL)	25049 (16)	29620 (25)
Apparent Clearance (L/hr/kg)	0.25 (16)	0.27 (25)

This supplemental new drug application also provides for the inclusion of updated information in the **PRECAUTIONS, Pediatric use** section of the **Rebetron Combination Therapy**™ label, as follows:

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

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

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

This supplemental new drug application also provides for the inclusion of new dosing recommendations for REBETOL capsules with respect to administration with food, and for pediatric patients with chronic hepatitis C virus (HCV) infection, as found in the **DOSAGE AND ADMINISTRATION** section of the **Rebetron Combination Therapy**™ label, as follows:

DOSAGE AND ADMINISTRATION

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

Pediatrics

Efficacy of REBETOL and INTRON A for pediatric patients has not been established. Based on pharmacokinetic data, the following doses of REBETOL and INTRON A provide similar exposures in pediatric patients as observed in adult patients treated with the approved doses of REBETOL and INTRON A (see **TABLE 8).**

Table 8. Pediatric Dosing

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

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

Finally, this supplemental new drug application also provides for the inclusion of an amended version of the Rebetron Combination Therapy™ Medguide, in the "**How should I take REBETRON Combination Therapy?"** section, to include the following wording, as amended by the Division of Antiviral Drug Products (DAVDP) on December 28, 2001. This revision to the Medguide was implemented to provide consistency with information contained in the current package insert for Rebetron Combination Therapy™:

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

We have completed the review of this supplemental application, 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 and with the minor editorial revisions listed above and detailed in the label appended to this letter. Accordingly, the supplemental application is approved effective on the date of this letter.

The final printed labeling (FPL) must be identical, and include the minor editorial revisions indicated, to the submitted draft labeling (package insert submitted December 21, 2001, patient package insert submitted December 21, 2001, Medguide submitted December 21, 2001). These revisions are terms of the approval of this application.

Please submit the copies of final printed labeling (FPL) electronically 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, this submission should be designated "FPL for approved supplement NDA 20-903/S-013." Approval of this submission by FDA is not required before the labeling is used.

Be advised that, as of April 1, 1999, all applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred (63 *FR* 66632 and 21CFR 314.55). Based on the information submitted in the application to your NDA, dated February 28, 2001, we are deferring submission of additional pediatric studies until August 1, 2002, pending the review of final study reports for studies P00018 and P00321 in pediatric patients infected with HCV. If we determine that additional pediatric studies are necessary, we will specify a date by which you must submit the required assessments.

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

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}

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

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Jeffrey Murray

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 020903/S-013

LABELING

PRODUCT INFORMATION

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

CONTRAINDICATIONS AND WARNINGS

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

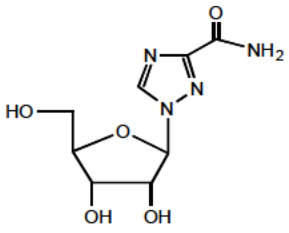
REBETOL monotherapy is not effective for the treatment of chronic hepatitis C and should not be used for this indication. See WARNINGS.

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

DESCRIPTION

REBETOL®

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



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

REBETOL Capsules consist of a white powder in a white, opaque, gelatin capsule. Each capsule contains 200 mg ribavirin and the inactive ingredients microcrystalline cellulose, lactose

monohydrate, croscarmellose sodium, and magnesium stearate. The capsule shell consists of gelatin, 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 Multiple-dose pharmacokinetic properties for ribavirin in pediatric patients with chronic hepatitis C between 5 and 16 years of age are summarized in **TABLE 2**.

TABLE 2. Mean (% CV) Pharmacokinetic Parameters for REBETOL When Administered to Pediatric Patients with Chronic Hepatitis C

Parameter	12 mg/kg/day as 2 divided doses (n=19)	15 mg/kg/day as 2 divided doses (n=19)
T_{max} (hr)	1.4 (60)	1.9 (81)
C_{max} (ng/mL)	2705 (17)	3243 (24)
AUC_{12} (ng*hr/mL)	25049 (16)	29620 (25)
Apparent Clearance (L/hr/kg)	0.25 (16)	0.27 (25)

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

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

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

INDICATIONS AND USAGE

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

Description of Clinical Studies

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

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

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

	US Study				International Study		
	24 weeks of treatment		48 weeks of treatment		24 weeks of treatment	48 weeks of treatment	
	INTRON A plus 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 4**.

TABLE 4. Virologic and Histologic Responses: Relapse Patients*

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

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

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

CONTRAINDICATIONS

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

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

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

WARNINGS

Pregnancy

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

Anemia

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

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

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

Psychiatric

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

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

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

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

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

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

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

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

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

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

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 females treated with human leukocyte interferon. In addition, ribavirin demonstrated significant embryocidal and/or teratogenic effects at doses well below the recommended human dose in all animal species in which adequate studies have been conducted.

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

Combination REBETOL/INTRON A therapy should be used with caution in fertile males. In studies in mice to evaluate the time course and reversibility of ribavirin-induced testicular degeneration at doses of 15 to 150 mg/kg/day (estimated human equivalent of 1.25 -

12.5 mg/kg/day, based on body surface area adjustment for a 60 kg adult; 0.1 - 0.8 X the maximum human 24-hour dose of ribavirin) administered for 3 or 6 months, abnormalities in sperm occurred. Upon cessation of treatment, essentially total recovery from ribavirin-induced testicular toxicity was apparent within 1 or 2 spermatogenesis cycles.

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

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

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

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

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

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

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

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

Pediatric Use

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

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

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

ADVERSE REACTIONS

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

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

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

Selected treatment-emergent adverse events that occurred in the US studies with ≥5% incidence are provided in **TABLE 5** by treatment group. In general, the selected treatment-emergent adverse events reported with lower incidence in the international studies as compared

509 to the US studies with the exception of asthenia, influenza-like symptoms, nervousness, and
510 pruritus.
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TABLE 5. Selected Treatment-Emergent Adverse Events: Previously Untreated and Relapse Patients

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

depression	32	25	36	37	23	14
emotional lability	7	6	11	8	12	8
concentration impaired	11	14	14	14	10	12
nervousness	4	2	4	4	5	4
Respiratory System Disorders						
dyspnea	19	9	18	10	17	12
sinusitis	9	7	10	14	12	7
Skin and Appendages Disorders						
alopecia	28	27	32	28	27	26
rash	20	9	28	8	21	5
pruritus	21	9	19	8	13	4
Special Senses, Other Disorders						
taste perversion	7	4	8	4	6	5

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

Laboratory Values

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

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

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

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

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

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.

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

Percentage of Patients

	US Previously Untreated Study				US Relapse Study	
	24 weeks of treatment		48 weeks of treatment		24 weeks of treatment	
	INTRON A plus REBETOL (N=228)	**INTRON A plus Placebo (N=231)**	**INTRON A plus REBETOL (N=228)**	**INTRON A plus Placebo (N=225)**	**INTRON A plus REBETOL (N=77)**	**INTRON A plus Placebo (N=76)**
Hemoglobin (g/dL)						
9.5-10.9	24	1	32	1	21	3
8.0-9.4	5	0	4	0	4	0
6.5-7.9	0	0	0	0.4	0	0
<6.5	0	0	0	0	0	0
Leukocytes ($x10^9$/L)						
2.0-2.9	40	20	38	23	45	26
1.5-1.9	4	1	9	2	5	3
1.0-1.4	0.9	0	2	0	0	0
<1.0	0	0	0	0	0	0
Neutrophils ($x10^9$/L)						
1.0-1.49	30	32	31	44	42	34
0.75-0.99	14	15	14	11	16	18
0.5-0.74	9	9	14	7	8	4
<0.5	11	8	11	5	5	8
Platelets ($x10^9$/L)						
70-99	9	11	11	14	6	12
50-69	2	3	2	3	0	5
30-49	0	0.4	0	0.4	0	0
<30	0.9	0	1	0.9	0	0
Total Bilirubin (mg/dL)						

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

OVERDOSAGE

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

Adults

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

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

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

TABLE 7. Recommended Adult Dosing

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

Pediatrics

Efficacy of REBETOL and INTRON A for pediatric patients has not been established. Based on pharmacokinetic data, the following doses of REBETOL and INTRON A provide similar exposures in pediatric patients as observed in adult patients treated with the approved doses of REBETOL and INTRON A (see **TABLE 8).**

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

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

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

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

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

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

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

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

TABLE 9. Guidelines for Dose Modifications

	Dose Reduction*	Permanent Discontinuation of Treatment
	REBETOL – Adults 600 mg daily Pediatrics: half the dose INTRON A – Adults 1.5 million IU TIW Pediatrics: 1.5 million IU/m^2 TIW	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	Adults: <50 x 10^9/L (INTRON A) Pediatrics: <80 x 10^9/L (INTRON A)	Adults: <25 x 10^9/L Pediatrics: <50 x 10^9/L

*Study medication to be dose reduced is shown in parenthesis

Administration of INTRON A Injection

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

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

	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)

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

12/21/01

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MEDICATION GUIDE
REBETRON

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

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

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

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

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

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

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

- **REBETRON Combination Therapy** can cause a dangerous drop in the number of cells that help fight infections and stop bleeding, which might cause you to have an infection or abnormal bleeding.

- **Serious mental problems: REBETRON Combination Therapy may cause or worsen mood or behavioral problems.** These can include irritability (getting easily upset) and depression (feeling low, feeling bad about yourself). **Some patients, including some children, think about hurting or killing themselves or other people, and some have killed themselves (suicide) or hurt themselves or others.** If you experience any of these thoughts or symptoms you should tell your health care provider right away. **See "What are the possible side effects of REBETRON Combination Therapy?" for important information on signs of mental problems.**

- **You should not take REBETOL Capsules alone to treat your hepatitis C virus infection**. REBETOL Capsules should be used only in combination with interferon alfa-2b (INTRON A) for the treatment of chronic hepatitis C infection; the combination is called REBETRON Combination Therapy.

What is REBETRON Combination Therapy?

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

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

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

Who should not take REBETRON Combination Therapy?

Do not use these medicines if:

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

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

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

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

How should I take REBETRON Combination Therapy?

- Your health care provider has determined the correct doses of REBETOL and INTRON A. Your doses of REBETOL and INTRON A may be lowered if you have side effects.
- **Under no circumstances should REBETOL capsules be opened, crushed or broken.**

The recommended adult dose of INTRON A Injection and REBETOL Capsules are shown in the

table below.

If your weight is:	**Take this many REBETOL Capsules each day:**	**Inject this amount of INTRON A under your skin (subcutaneously)**
165 pounds or less	2 capsules in the AM 3 capsules in the PM	3 million international units 3times a week
More than 165 pounds	3 capsules in the AM 3 capsules in the PM	3 million international units 3times a week

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

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

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

What should I avoid while taking REBETRON Combination Therapy?

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

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

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

What are the possible side effects of REBETRON Combination Therapy?

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

- Anemia**. REBETRON Combination Therapy causes anemia (a reduction in the number of red blood cells you have) which can be dangerous, especially if you have heart, or breathing problems. Tell your health care provider right away if you feel tired, have chest pain or shortness of breath. These may be signs of low red blood counts.**
- **Infections.** INTRON A therapy may lower your white blood cell count, making it easier for you to get serious infections. You must have your blood tested regularly during treatment to check for this problem.
- **Mental Problems**. Tell your health care provider if you have ever had any mental illness, including depression, suicidal behavior, or psychosis (loss of contact with reality such as hearing voices or seeing things that are not there). Also, tell your health care provider if you are taking any medications for these problems. **Tell your health care provider right away if you have the following:**

  - Start to feel unusually sad or have crying spells
  - **Lose interest in your usual activities**
  - **Have changes in your normal sleep patterns**
  - **Become more irritable than usual**
  - **Lose your appetite**
  - **Become unusually tired**
  - **Have trouble concentrating**
  - **Withdraw from family and friends**
  - **Have thoughts about hurting yourself or others.**

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

- **trouble breathing, hives or swelling**
- **chest pain**
- **severe stomach or lower back pain**
- **bloody diarrhea or bloody stools (bowel movements). These may appear to be black**

and tarry.

- **high fever**
- **bruising**
- **bleeding**
- **decreased vision**

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

- **"Flu-like" symptoms.** These include headache, feeling very tired (fatigue), muscle aches, and fever. These get better as treatment continues. You can reduce some of these flu-like symptoms by injecting your INTRON A about 2 hours before bedtime. Some health care providers suggest taking non-prescription pain and fever reducers, such as acetaminophen or ibuprofen before taking INTRON A. This may be helpful to prevent or relieve the fever and headache.
- **Feeling tired**
- **Hair thinning**
- **Rash and itching**
- **Nausea and appetite loss**
- **Abdominal pain with nausea and vomiting**
- **Trouble breathing**
- **Trouble with your vision**
- **Trouble sleeping at night**

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

What should I know about the hepatitis C virus?

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

How do I Inject INTRON A?

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

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

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

- The INTRON A multidose pen should **ONLY** be used with the enclosed **Novofine*** needles. The use of other needles may result in the pen not working properly and/or the wrong dose of INTRON A solution delivered.

- **ALWAYS** discard needles and used pens carefully; **NEVER** discard the pen with a needle attached.

- Use the INTRON A multidose pen **ONLY** in accordance with these instructions. **DO NOT** allow the INTRON A multidose pen to be handled roughly or otherwise misused.

- **KEEP** out of reach of children.
- When not in use you should **STORE** the INTRON A multidose pen in the **REFRIGERATOR at 36°-46°F (2° to 8°C)** (not too near the freezer compartment).

- **ALWAYS** check that INTRON A **IS CLEAR** in appearance prior to use. If it DOES NOT have a clear uniform appearance **DO NOT USE**. Please consult your health care provider or pharmacist.

- ***ALWAYS*** *check the expiration date;* ***NEVER*** *use after the expiration date.*

Description of your INTRON A multidose pen

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

- The **push button scale** tells you what dose has been set.

- The **color coding** strip and the **push button** are at the bottom of the pen as it is held cap up. (The six doses of 3 MIU multidose pen have a brown coding strip)

- The INTRON A multidose pen can only be fully capped when the **triangle** on the **cap scale** is aligned with the **dosage indicator** on the barrel.

INTRON A Pen

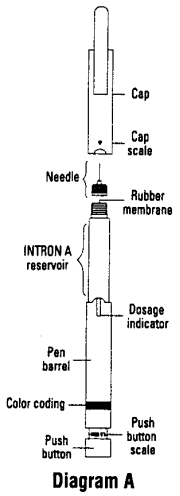


Diagram A

Novofine* Needle Assembly

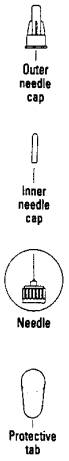


Diagram B

HOW TO USE YOUR INTRON A Multidose Pen

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

1. **First check that you have the correct INTRON A multidose pen as prescribed by your health care provider**, (i.e. the six doses of 3 MIU INTRON A multidose pen which have a **brown** push button and a **brown** color coding strip).

2. **Pull off the cap of the pen and disinfect the rubber membrane** (see Diagram C) **with one alcohol wipe**.

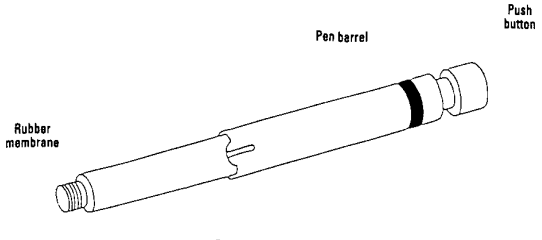


Diagram C

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

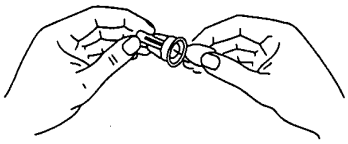


Diagram D

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

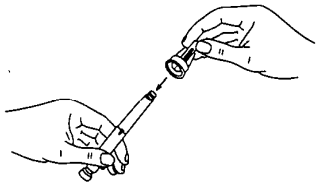


Diagram E

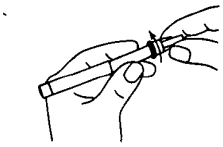


Diagram F

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

outer needle cap for later use.

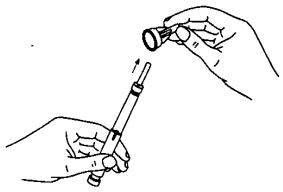


Diagram G

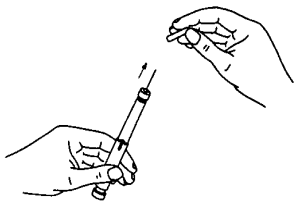


Diagram H

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

6. **Hold the INTRON A multidose pen with the needle point upwards**.

7. **Tap the reservoir with your finger so that any air bubbles rise to the top of the reservoir, just below the needle** (Diagram I).

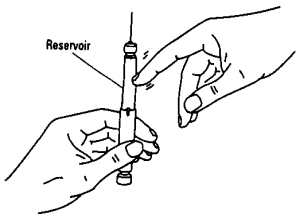


Diagram I

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

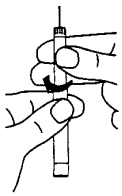


Diagram J

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

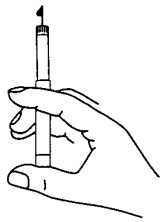


Diagram K

10. **If no drop appears then repeat Steps 7, 8, and 9 until a drop appears at the needle tip.** Note: Some air may still remain in the pen, but this is not important as you have removed the air from the needle and the dose will be accurate.

11. **Replace the INTRON A multidose pen cap with the 'triangle' opposite the dosage indicator as seen in Diagram L.**

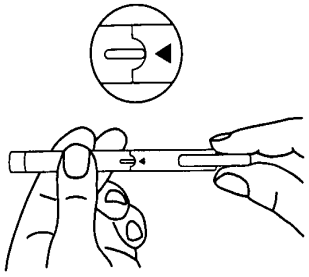


Diagram L

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

12. **To set the required dose, hold the pen horizontally by the barrel with one hand. With the other hand, turn the cap in a clockwise direction indicated by the arrow in Diagram M.** You will observe the push button rising, indicating the dose set. To set a 3

MIU dose, turn the cap 2 full turns (10 clicks) = 3.0 MIU.

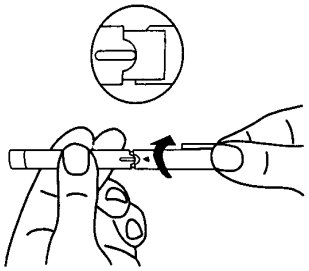


Diagram M

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

1 full turn (5 clicks) = 1.5 MIU
3 full turns (15 clicks) = 4.5 MIU
4 full turns (20 clicks) = 6.0 MIU

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

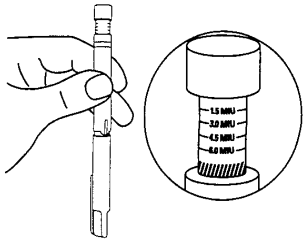


Diagram N

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

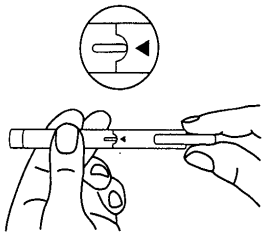


Diagram O

14. **To give the injection, remove the pen cap from the needle. With one hand, pinch a 2-inch fold of loose skin.**

15. **With your other hand, pick up the pen and hold it as you would a pencil. Insert the needle into the pinched skin at an angle of approximately 45°** (see Diagram P) **then press the push button down fully.**

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

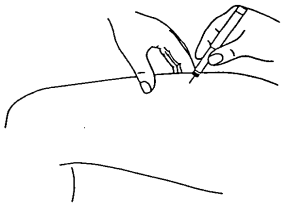


Diagram P

16. **Leave the needle in place for a few seconds, while holding down the push button, to allow the INTRON A Solution to distribute under the skin.**

17. **Slowly release the push button, then remove the needle.**

18. **Carefully replace the *outer* needle cap using a scooping motion** (See Diagram Q).

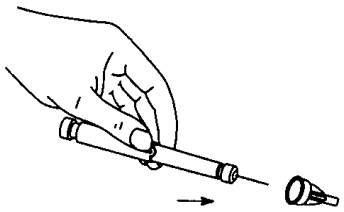


Diagram Q

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

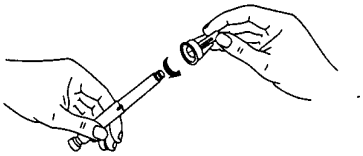


Diagram R

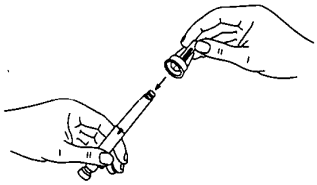


Diagram S

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

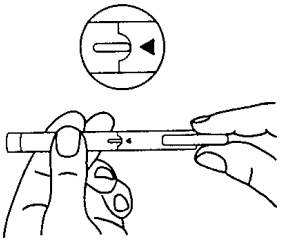


Diagram T

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

How do I store my medications?
STORAGE OF REBETOL CAPSULES
REBETOL capsules should be stored in the refrigerator between 36° and 46°F (2° and 8°C) or at room temperature 77°F (25°C).

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

* Novofine is a registered trademark of Novo Nordisk.

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

Ingredients:
REBETOL capsules contain ribavirin and the inactive ingredients microcrystalline cellulose, lactose monohydrate, croscarmellose sodium, and magnesium stearate. The capsule shell consists of gelatin and titanium dioxide. The capsule is printed with edible blue pharmaceutical ink which is made of shellac, anhydrous ethyl alcohol, isopropyl alcohol, n-butyl alcohol, propylene glycol, ammonium hydroxide, and FD&C Blue #2 aluminum lake.
INTRON A contains interferon alfa-2b recombinant, sodium chloride, dibasic sodium phosphate, monobasic sodium phosphate, edetate disodium, polysorbate 80, m-cresol (as a preservative).

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

Manufactured by:

Schering Corporation
Kenilworth, NJ 07033 USA

Rev. X/01 B-

F-XXXXXXXX

MEDICATION GUIDE
REBETRON

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

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

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

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

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

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

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

- **REBETRON Combination Therapy** can cause a dangerous drop in the number of cells that help fight infections and stop bleeding, which might cause you to have an infection or abnormal bleeding.

- **Serious mental problems: REBETRON Combination Therapy may cause or worsen mood or behavioral problems.** These can include irritability (getting easily upset) and depression (feeling low, feeling bad about yourself). **Some patients, including some children, think about hurting or killing themselves or other people, and some have killed themselves (suicide) or hurt themselves or others.** If you experience any of these thoughts or symptoms you should tell your health care provider right away. **See "What are the possible side effects of REBETRON Combination Therapy?" for important information on signs of mental problems.**

- **You should not take REBETOL Capsules alone to treat your hepatitis C virus infection**. REBETOL Capsules should be used only in combination with interferon alfa-2b (INTRON A) for the treatment of chronic hepatitis C infection; the combination is called REBETRON Combination Therapy.

What is REBETRON Combination Therapy?

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

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

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

Who should not take REBETRON Combination Therapy?

Do not use these medicines if:

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

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

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

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

How should I take REBETRON Combination Therapy?

- Your health care provider has determined the correct doses of REBETOL and INTRON A. Your doses of REBETOL and INTRON A may be lowered if you have side effects.
- **Under no circumstances should REBETOL capsules be opened, crushed or broken.**

The recommended adult dose of INTRON A Injection and REBETOL Capsules are shown in the

table below.

If your weight is:	Take this many REBETOL Capsules each day:	Inject this amount of INTRON A under your skin (subcutaneously)
165 pounds or less	2 capsules in the AM 3 capsules in the PM	3 million international units 3times a week
More than 165 pounds	3 capsules in the AM 3 capsules in the PM	3 million international units 3times a week

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

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

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

What should I avoid while taking REBETRON Combination Therapy?

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

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

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

What are the possible side effects of REBETRON Combination Therapy?

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

- Anemia**. REBETRON Combination Therapy causes anemia (a reduction in the number of red blood cells you have) which can be dangerous, especially if you have heart, or breathing problems. Tell your health care provider right away if you feel tired, have chest pain or shortness of breath. These may be signs of low red blood counts.**
- **Infections.** INTRON A therapy may lower your white blood cell count, making it easier for you to get serious infections. You must have your blood tested regularly during treatment to check for this problem.
- **Mental Problems**. Tell your health care provider if you have ever had any mental illness, including depression, suicidal behavior, or psychosis (loss of contact with reality such as hearing voices or seeing things that are not there). Also, tell your health care provider if you are taking any medications for these problems. **Tell your health care provider right away if you have the following:**

  - Start to feel unusually sad or have crying spells
  - **Lose interest in your usual activities**
  - **Have changes in your normal sleep patterns**
  - **Become more irritable than usual**
  - **Lose your appetite**
  - **Become unusually tired**
  - **Have trouble concentrating**
  - **Withdraw from family and friends**
  - **Have thoughts about hurting yourself or others.**

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

- **trouble breathing, hives or swelling**
- **chest pain**
- **severe stomach or lower back pain**
- **bloody diarrhea or bloody stools (bowel movements). These may appear to be black**

and tarry.

- **high fever**
- **bruising**
- **bleeding**
- **decreased vision**

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

- **"Flu-like" symptoms.** These include headache, feeling very tired (fatigue), muscle aches, and fever. These get better as treatment continues. You can reduce some of these flu-like symptoms by injecting your INTRON A about 2 hours before bedtime. Some health care providers suggest taking non-prescription pain and fever reducers, such as acetaminophen or ibuprofen before taking INTRON A. This may be helpful to prevent or relieve the fever and headache.
- **Feeling tired**
- **Hair thinning**
- **Rash and itching**
- **Nausea and appetite loss**
- **Abdominal pain with nausea and vomiting**
- **Trouble breathing**
- **Trouble with your vision**
- **Trouble sleeping at night**

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

What should I know about the hepatitis C virus?

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

How do I Inject INTRON A?

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

Preparing the INTRON A Dose

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

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

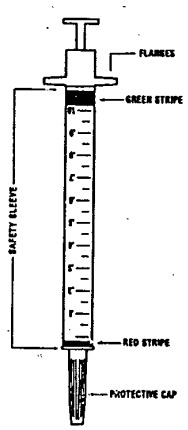


Figure A

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

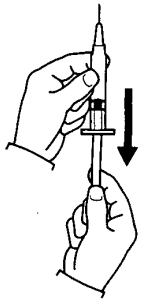


Figure B

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

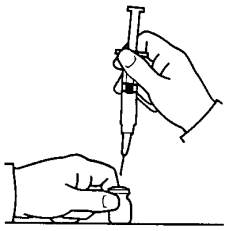


Figure C

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

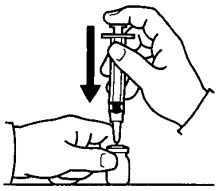


Figure D

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

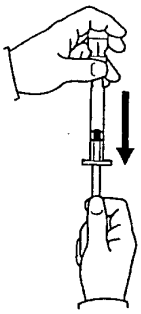


Figure E

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

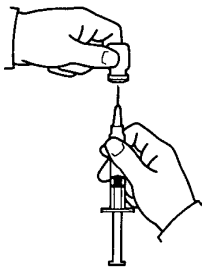


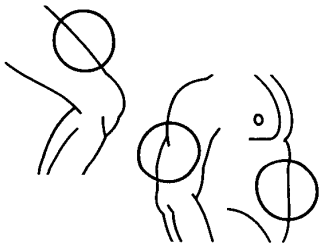
Figure F

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

Subcutaneous (under the skin) Injection

1. Select the site for injection

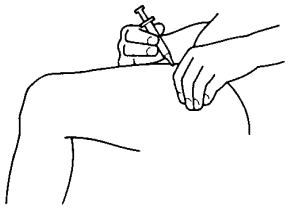
- The best sites for injection are tissues with a layer of fat between skin and muscle, such as the
    - thigh
    - outer surface of the upper arm
    - abdomen (stomach area), except the navel (belly button) or waistline
- If you are very thin, use only the thigh or outer surface of the arm for injection.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



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

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

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

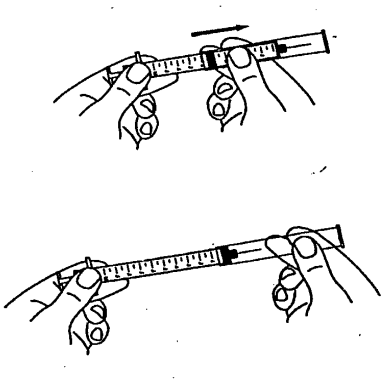


After the needle is in, remove hand used to pinch skin and use it to hold syringe barrel. Pull back the plunger very slightly with one hand. If blood comes into the syringe, the needle has entered a blood vessel. Do not inject. Withdraw and discard needle and syringe as instructed in step 6 below. Prepare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

4. If blood does not appear in the syringe, gently push the plunger all the way down.

5. Hold an alcohol swab near the needle and pull the needle straight out of the skin. Press the alcohol swab over the injection site for several seconds. Do not massage (rub) the injection site. If there is bleeding, cover the area with an adhesive bandage.

6. After use, firmly grasp the safety sleeve and pull over the exposed needle until you hear a click, and the green stripe on the safety sleeve covers the red stripe on the needle.



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

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

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

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

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

How do I store my medications?
STORAGE OF REBETOL CAPSULES
REBETOL capsules should be stored in the refrigerator between 36° and 46°F (2° and 8°C) or at room temperature 77°F (25°C).

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

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

Ingredients:
REBETOL capsules contain ribavirin and the inactive ingredients microcrystalline cellulose, lactose monohydrate, croscarmellose sodium, and magnesium stearate. The capsule shell consists of gelatin and titanium dioxide. The capsule is printed with edible blue pharmaceutical ink which is made of shellac, anhydrous ethyl alcohol, isopropyl alcohol, n-butyl alcohol, propylene glycol, ammonium hydroxide, and FD&C Blue #2 aluminum lake.
INTRON A contains interferon alfa-2b recombinant, sodium chloride, dibasic sodium phosphate, monobasic sodium phosphate, edetate disodium, polysorbate 80, m-cresol (as a preservative).

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

Manufactured by:

Schering Corporation
Kenilworth, NJ 07033 USA

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Jeffrey Murray
12/28/01 04:38:40 PM

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 020903/S-013

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW

BRAND NAME	(b) (4)
GENERIC NAME	:Ribavirin
DOSAGE FORM and STRENGTH	:oral 200 mg capsules
INDICATION	:Chronic hepatitis C (in combination with INTRON A)
NDA	:20-903
TYPE	:Pediatric Supplement (SE8-013)
APPLICANT NAME	:Schering-Plough
SUBMISSION DATE	:February 28, 2001 :November 1, 2001
OCPB DIVISION	:DPEIII
ORM DIVISION	:DAVDP
OCPB REVIEWER	:Jooran S. Kim, Pharm.D.
TEAM LEADER	:Kellie S. Reynolds, Pharm.D.

I. Executive Summary

The applicant submitted NDA 20-903 to seek approval for ribavirin (in combination with INTRON A) for the treatment of chronic hepatitis C in children. The proposed regimen is ribavirin (b) (4) mg/kg/day (divided in 2 daily doses) with INTRON A 3 MIU/m^2 tiw.

A. Recommendations

The pediatric supplement information submitted by the applicant for NDA 20-903 (SE8-013) is generally acceptable from a Clinical Pharmacology and Biopharmaceutics perspective.

The applicant conducted their pediatric trials with formulations that are not currently marketed. The only available strength and formulation are oral 200 mg capsules. Because of this limitation, ribavirin (12-15 mg/kg/day) will only be labeled for children $\geq$ 25 kg who are able to swallow capsules. Pharmacokinetic information will be included in the label.

The applicant should submit the NDA for the syrup formulation of ribavirin as soon as possible so that an appropriate formulation of ribavirin will be available to the pediatric population.

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III. Summary of Clinical Pharmacology and Biopharmaceutics Findings

Ribavirin is a purine analog that is approved (in combination with INTRON A and PEG-INTRON) for the treatment of chronic hepatitis C (CHC) in adults. The mechanism for antiviral activity against HCV-RNA (nor the mechanism for synergistic activity observed with INTRON A) is unknown. At this time, there is no available therapy for CHC in the pediatric population.

The only approved formulation of ribavirin is 200 mg oral capsules. The applicant conducted two studies using 50 mg capsules and 40 mg/mL syrup. Both the 50 mg capsule and syrup formulation are currently unavailable. (b) (4)

The sponsor conducted two main studies evaluating ribavirin plus INTRON A in pediatric patients. P00018 was a clinical trial to determine the pharmacokinetics and dose of ribavirin and the safety and efficacy of ribavirin and INTRON A in pediatric patients (age range: 5-16 years) with CHC. P00321 evaluated the safety and efficacy of ribavirin 15 mg/kg (dose determined in P00018) and INTRON A 3 MIU/m^2 in pediatric patients (age range: 3-16 years) with CHC. P00018 was divided into two cohorts. Cohort 1 was a dose-ranging study to select a ribavirin dose based on pharmacokinetics and pharmacodynamics for further evaluation of its safety and efficacy in pediatric patients in Cohort 2 of P00018 and in P00321. The dose of INTRON A was fixed at 3 MIU/m^2. Dose selection of ribavirin (15 mg/kg/day) was based on similar pharmacokinetics of ribavirin in pediatric patients compared to adult ribavirin pharmacokinetics at the approved dose, serum HCV-RNA at weeks 4 and 12, and safety through week 4. INTRON A is labeled for use in pediatric patients down to 3 years of age (indication: chronic hepatitis B), therefore the dose of INTRON A was fixed at 3 MIU/m^2 tiw. This review mainly addresses the use of ribavirin in pediatric patients.

In Study P00018, the pharmacokinetics, safety and efficacy of ribavirin 8, 12 and 15 mg/kg/day (divided in two daily doses) were initially evaluated at week 4. At week 4, ribavirin 8, 12 and 15 mg/kg/day yielded mean (%CV) C_{max} and AUC values that appeared generally dose proportional:

Dose (mg/kg/day)	n	C_{max} (ng/mL)	AUC (ng*h/mL)
8	20	2211 (43)	18309 (28)
12	19	2705 (17)	25049 (16)
15	19	3243 (24)	29620 (25)

These PK parameters in pediatric patients were comparable to adult PK values observed with adult ribavirin doses of 800, 1000 and 1200 mg/day (divided in two daily doses). Age (range: 5-16 years) was evenly distributed in each dosing group. Mean ribavirin clearance in children ranged between 0.23-0.27 L/h/kg (16-26%) for all dose groups.

In terms of efficacy, change in HCV RNA at week 4 was similar in all three dose groups. There was, however, a larger decrease in hemoglobin values with ribavirin 15 mg/kg/day compared to other dose groups. Because this decline in hemoglobin was within

acceptable limits for adults, ribavirin 15 mg/kg/day was the dose selected for evaluation in Cohort 2 of P00018 and in P00321.

Data support the 15 mg/kg/day dose of ribavirin. Due to the availability of one capsule strength (200 mg) of ribavirin, pediatric patients 25 to 61 kg will be dosed between 12-15 mg/kg. Based on comparison of the range of exposure in pediatric patients receiving 12-15 mg/kg versus adults at the approved ribavirin dose of 1000-1200 mg/day, the proposed dosing chart is acceptable:

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

Note: Ribavirin will only be labeled for children $\geq$ 25 kg that are able to swallow capsules.

The Clinical Pharmacology and Biopharmaceutics briefing was held on Dec. 13th, 2001.

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IV. Question-Based Review

A. General Attributes

What are the highlights of the chemistry and physical-chemical properties of the drug substance, and the formulation of the drug product?

Please refer to Dr. Rajagopalan's review of ribavirin in May 1998.

What is the proposed mechanism of drug action and therapeutic indication? What is the proposed dosage and route of administration?

Ribavirin (in combination with interferon alfa-2b) was approved in 1998 for the treatment of chronic hepatitis C (CHC) in patients ≥ 18 years of age. There has been in vitro evidence since the 1970s of antiviral activity against some DNA and RNA viruses; the mechanism of action, however, has not yet been determined. The proposed dosage regimen of ribavirin for pediatric patients is (b) (4) mg/kg + interferon alfa-2b 3 MIU/m^2 tiw. The only available formulation of ribavirin is oral 200 mg capsules.

What efficacy and safety information contribute to the assessment of clinical pharmacology and biopharmaceutics study data?

P00018:
Age range: 5-16 years
Study duration: 48 weeks
Cohort 1 (n=61): Dose-ranging trial of ribavirin (8-15 mg/kg/day) and INTRON A in pediatric patients with CHC: PK, safety and efficacy (50 mg capsules)
Cohort 2 (n=35): Safety, efficacy and tolerability evaluation of ribavirin 15 mg/kg/day + INTRON A (50 mg capsules)

P00321 (n=70):
Age range: 3-16 years
Study Duration: 48 weeks
Phase III: Safety, efficacy and tolerability evaluation of ribavirin 15 mg/kg/day + INTRON A (ribavirin 200 mg capsules, 40 mg/mL syrup)

B. General Clinical Pharmacology (pediatric versus adult population)

What is the basis for selecting the response endpoints, i.e., clinical or surrogate endpoints, or biomarkers (also called pharmacodynamics, PD) and how are they measured in clinical pharmacology and clinical studies?

In adults, HCV-RNA viral load measured in log 10 copies/mL is the primary surrogate endpoint for efficacy, with antiviral activity measured at 48 weeks of treatment and over 24 weeks of follow-up. Hematological changes usually represent adverse events associated with CHC therapy, particularly a decrease in hemoglobin. Although, it is unknown if the disease course of chronic hepatitis C in pediatric patients is similar to that

of adults, the primary safety and efficacy parameters measured in adults are also measured in pediatric patients to evaluate the clinical course of CHC.

What are the characteristics of the exposure-response relationships (dose-response, concentration-response) for efficacy and safety?

The exposure-response relationships for efficacy and safety of ribavirin in adults have not been well characterized. At this time, the highest ribavirin dose that has been evaluated is 1200 mg/day in adults.

Study P00018 investigated 3 different mg/kg doses of ribavirin (8, 12 and 15 mg/kg/day divided as two daily doses) for safety and efficacy in children. These doses were comparable to approved adult doses of ribavirin on a per kg basis. Among the three dose groups, decreases in hemoglobin were mainly observed at the highest ribavirin dose. Three out of 20 children (15%) who received ribavirin 15 mg/kg required a dose reduction due to anemia. Dose reductions were not required in the other dose groups. Generally, these hematological changes are comparable to those observed with adults (Protocol C96-114) with ribavirin doses between 400-1200 mg/day.

In C96-114, a dose-response relationship was observed with changes in HCV-RNA at doses between 400 and 1200 mg/day in adults. Largest decrease in HCV RNA was observed at ribavirin 1000-1200 mg/day. In pediatric patients, HCV-RNA decreases were similar across all dose groups (Table 1) . This is most likely due to the smaller number of evaluable patients in the pediatric study (n=20-21 per dose arm) than in the adult study (n=40-45 per dose arm). HCV-RNA and hemoglobin changes were similar after week 4.

Table 1. Mean changes in hemoglobin after 4 weeks of treatment with Intron A and ribavirin 8, 12, and 15 mg/kg in pediatric patients

	Ribavirin dose			
Pediatric dose (P00018)		**8 mg/kg**	**12 mg/kg**	**15 mg/kg**
Change in Hgb (g/dL)		-1.1	-1.1	-1.5
Change in HCV-RNA (log 10 copies/mL)		-1.83	-1.77	-1.92
Adult dose (C96-114)	**400 mg/day**	**600 mg/day**	**800 mg/day**	**1000-1200 mg/day**
Change in Hgb (g/dL)	-1.17	-1.37	-1.7	-2.23
Change in HCV-RNA (log 10 copies/mL)	-1.62	-1.76	-2.09	-2.22

Are the pharmacokinetics of ribavirin dose-proportional in children?

Mean concentration-time profiles illustrate dose proportionality over 8, 12, and 15 mg/kg in pediatric patients (Figure 1). Individual data suggest that the 12 mg/kg and 15 mg/kg doses provide a comparable range of exposures (Figure 2).

Figure 1. Mean concentration-time curves for ribavirin 8, 12 and 15 mg/kg in pediatric patients

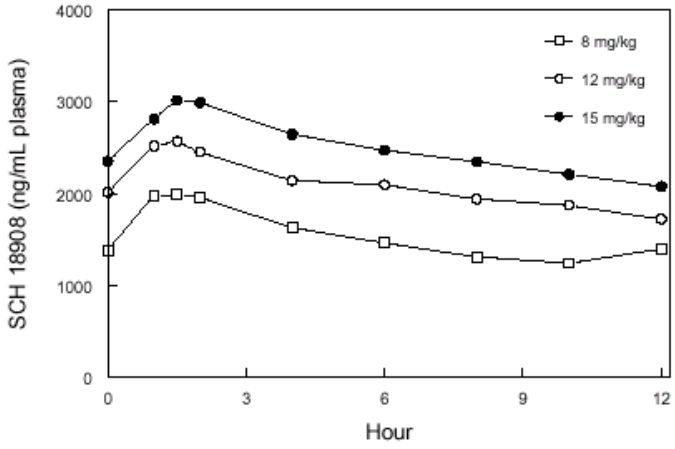
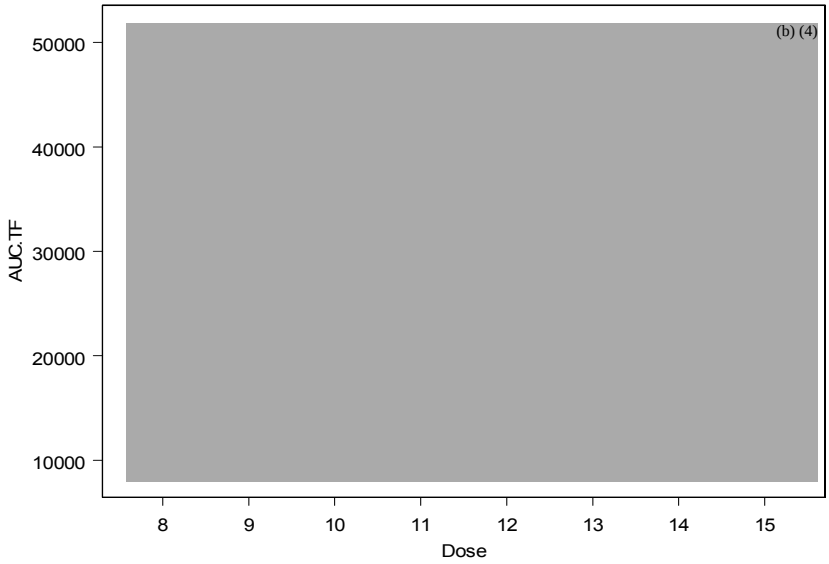


Figure 2. Ribavirin AUC values for individual patients receiving ribavirin 8, 12 and 15 mg/kg



What are the basic pharmacokinetics of ribavirin in adults?

Generally, the pharmacokinetics of ribavirin are variable. In a mass balance study following oral administration of 14C-ribavirin 600 mg, 61% and 12% of radioactivity was recovered in urine and feces within 336 hours of dosing. Approximately 17% of the dose was eliminated as unchanged ribavirin. The percentage of unchanged drug eliminated in the urine decreased as the dose increased. In subjects that received ribavirin 600 mg in the morning and 400 mg in the evening for 4 weeks, C_{max} and AUC_{12} values were 3230

(1680-6760) ng/mL and 27800 (16500-45900) ng*h/mL, respectively. For those that received ribavirin 600 mg bid, C_{max} was approximately 3480 (2020-7200) ng/mL and AUC_{12} was 30300 (16300-59350) ng*h/mL. T_{max} of ribavirin was around 1.5 hours. Following single doses of ribavirin (400, 800 and 1200 mg), AUC was dose proportional, whereas C_{max} was less than dose proportional. These findings suggest that there may be saturable urinary elimination and saturable absorption of ribavirin in the GI tract. In regards to ribavirin metabolism, in vitro studies indicate that ribavirin is not metabolized by cytochrome P450 enzymes. It is, however, postulated that ribavirin may undergo deribosylation followed by amide hydrolysis. The apparent terminal half-life of ribavirin is approximately 274 hours after multiple dose administration. The long half-life may be due to sequestration of ribavirin into red blood cells. To date, the highest ribavirin dose the Agency has reviewed is 1200 mg/day.

How does the PK of ribavirin in pediatric patients compare to that in adults?

The sponsor conducted a regression analysis to compare the pharmacokinetics of pediatric doses to adult doses (from 3 studies). In their analysis, the AUC and Cmax of pediatric doses 8, 12 and 15 mg/kg appear to be superimposable over the AUC and Cmax values obtained with 800, 1000 and 1200 mg/day of ribavirin in adults (Figures 3 and 4). The approved ribavirin dose in adults with INTRON A is 1000 mg/day (600 mg in am, 400 mg in pm) for individuals < 75 kg and 1200 mg/day (600 mg bid) for those > 75 kg. Because ribavirin exposure from the15 mg/kg dose in children did not exceed that of ribavirin 1200 mg/day, ribavirin 15 mg/kg was chosen as the dose to be studied in the second cohort of this study.

Figure 3. Ribavirin mean AUC of adults compared to pediatric patients

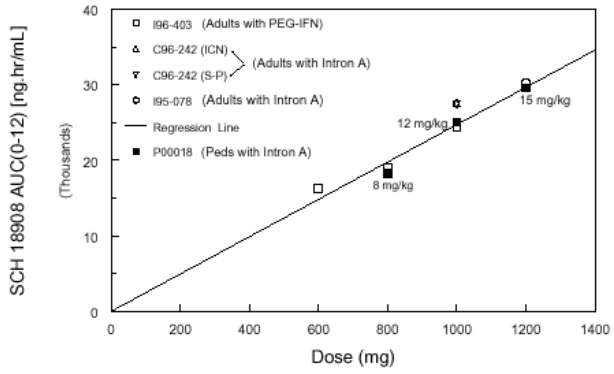
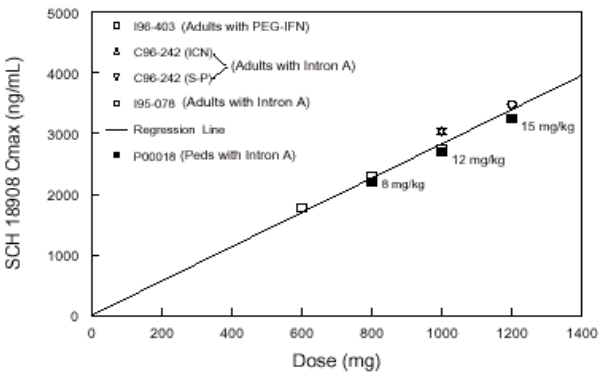


Figure 4. Ribavirin mean Cmax of adults compared to pediatric patients



However, when taking into consideration the variability observed with adult and pediatric ribavirin pharmacokinetics, the mean Cmax and AUC values of ribavirin 12 and 15 mg/kg/day in children fell within observed values for 1000 mg/day as well as 1200 mg/day in the adults (Table 2).

Table 2. Mean Cmax and AUC values of ribavirin 12 mg/kg and 15 mg/kg in pediatric patients and ribavirin 1000 mg/day and 1200 mg/day in adults

Dose	Cmax, ng/mL	AUC, ng*h/mL
	Pediatric (%CV)	
12 mg/kg	2705 (17)	25049 (16)
15 mg/kg	3243 (24)	29620 (25)
	Adults (range)	
1000 mg/day	3230 (1680-6760)	27800 (16500-45900)
1200 mg/day	3480 (2020-7200)	30300 (16300-59350)

What dose was selected for pediatric patients and how was this dose selected?

Based on ribavirin pharmacokinetics in Cohort 1 in P00018, ribavirin 15 mg/kg was chosen as the dose for evaluation in the second cohort of P00018 and Study P00321, which evaluated the safety, efficacy and tolerability of ribavirin 15 mg/kg with INTRON A. Based on these safety and efficacy data, ribavirin 15 mg/kg/day was selected as the dose in pediatric patients with CHC.

Intermittent ribavirin trough concentrations were measured throughout the remainder of both studies and were consistent with trough concentrations achieved in the first cohort of P00018.

P00321 used a syrup formulation of ribavirin (40 mg/mL) that is currently not available. Ribavirin trough concentrations in children receiving ribavirin 15 mg/kg of the syrup formulation were comparable to trough concentrations measured in children who received capsules.

Due to capsule strength, recommended doses range from 12 mg/kg/day to 15 mg/kg/day. This dosage range is acceptable based on comparison of the range of exposure in pediatric patients at 12-15 mg/kg/day versus adults at 1000-1200 mg/day.

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

C. Intrinsic Factors

What intrinsic factors (age, gender, race, weight, height, disease, genetic polymorphism, pregnancy, and organ dysfunction) influence exposure and/or

response and what is the impact of any differences in exposure on the pharmacodynamics?

There is a suggestion that CL/F in children varies according to age as shown in Figures 5-7, however, the relationship is not consistent across the three dose groups. Ribavirin clearance in children is also similar to adult values (adults: CL/F~0. 28 L/h/kg).

Figure 5. Clearance (CL/F) versus age (yrs) for ribavirin 8 mg/kg/day

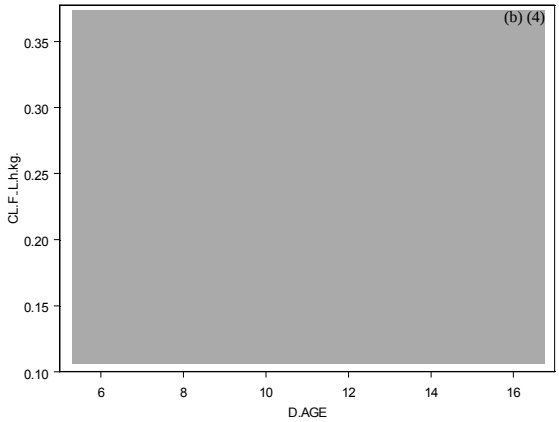


Figure 6. Clearance (CL/F) versus age (yrs) for ribavirin 12 mg/kg/day

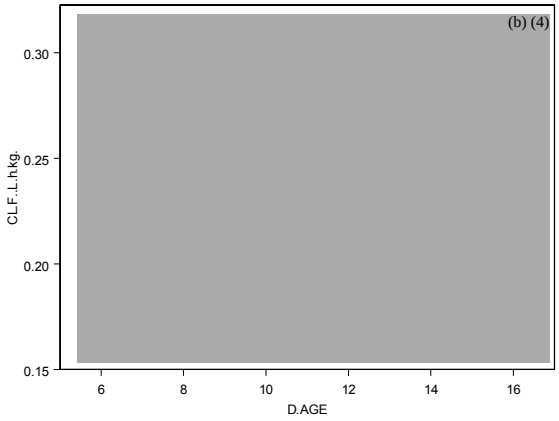
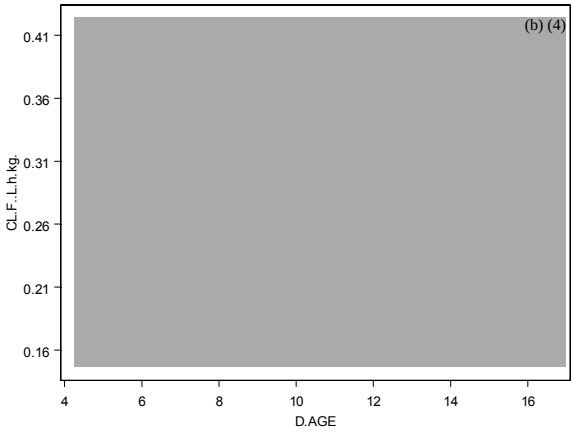


Figure 7. Clearance (CL/F) versus and age (yrs) for ribavirin 15 mg/kg/day



D. Extrinsic Factors

Drug interactions

In adults, a significant drug interaction was not observed with concomitant administration of ribavirin and INTRON A.

Extrinsic factors in pediatric patients have not been evaluated in this submission.

E. General Biopharmaceutics

In adults, the bioavailability of ribavirin increased significantly (70%) with food. Because subjects took ribavirin without regard to food in previous clinical trials, the pediatric studies were conducted the same way, but patients were instructed to take ribavirin consistently with respect to food.

F. Analytical Section

Assay methods are acceptable.

V. Detailed labeling recommendations

APPEARS THIS WAY ON ORIGINAL

CLINICAL PHARMACOLOGY

Special populations

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

TABLE 2. Mean (% CV) Pharmacokinetic Parameters for REBETOL When Administered to Pediatric Patients with Chronic Hepatitis C		
Parameter	12 mg/kg/day (n=19)	15 mg/kg/day (n=19)
T_{max} (hr)	1.4 (60)	1.9 (81)
C_{max} (ng/mL) AUC_{12} (ng*h/mL)	2705 (17) 25049 (16)	3243 (24) 29620 (25)
Apparent Clearance (L/hr/kg)	0.25 (16)	0.27 (25)

DOSAGE AND ADMINISTRATION

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

Adults

The recommended dose of REBETOL Capsules depends on the patient's body weight. The recommended doses of REBETOL and INTRON A for adults are given in **TABLE 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 Adult Dosing		
Body weight	REBETOL Capsules	INTRON A Injection
≤ 75 kg	2 x 200 mg capsules AM, 3 x 200 mg capsules PM daily p.o.	3 million IU 3 times weekly s.c.
> 75 kg	3 x 200 mg capsules AM, 3 x 200 mg capsules PM daily p.o.	3 million IU 3 times weekly s.c.

Pediatrics

The recommended doses of REBETOL and INTRON A for pediatric patients are given in **TABLE 7.**

Table 7. Recommended Pediatric Dosing		
Body weight	REBETOL Capsules	INTRON A Injection
25-36 kg	1 x 200 mg capsule AM 1 x 200 mg capsule PM daily p.o.	3 million IU/m^2 3 times weekly s.c.
37-49 kg	1 x 200 mg capsule AM 2 x 200 mg capsules PM daily p.o.	3 million IU/m^2 3 times weekly s.c.
50-61 kg	2 x 200 mg capsules AM 2 x 200 mg capsules PM daily p.o.	3 million IU/m^2 3 times weekly s.c.
>61 kg	Refer to adult dosing table	Refer to adult dosing table

REBETOL Capsules should be swallowed whole. Do not open or break.

Appendices

A. Clinical Pharmacology and Biopharmaceutics Individual Study Review

Study P00018

B. Cover Sheet and OCPB Filing/Review Form

Investigator and study location: 17 study sites (15 U.S., 2 outside U.S.)

TITLE: Assessment of the safety, tolerability, pharmacokinetics and pharmacodynamics of the combination of INTRON A plus ribavirin (I/R) in pediatric patients with chronic hepatitis C (CHC): Protocol P00018

BACKGROUND:
This study was divided into two parts. Cohort 1 was a dose-ranging study to select a ribavirin dose based on pharmacokinetics and pharmacodynamics for further evaluation of its safety and efficacy in pediatric patients. The ribavirin dose selected in Cohort 1 was used in Cohort 2 of this study (P00018) and P00321. Dose selection of ribavirin (15 mg/kg/day) was based on the pharmacokinetics of ribavirin, serum HCV-RNA at weeks 4 and 12 and safety through week 4. INTRON A is labeled for use in pediatric patients down to 3 years of age (indication: chronic hepatitis B), therefore the dose of INTRON A was fixed at 3 MIU/m^2 three times per week (tiw).

OBJECTIVES:

Cohort 1: To assess the safety, tolerability, multiple-dose pharmacokinetics and antiviral activity of the combination of interferon A and ribavirin in pediatric subjects with CHC.

Cohort 2: To assess the safety and efficacy of the optimal dose in pediatric subjects with CHC.

SUBJECTS: Pediatric patients (5-16 years of age) with CHC who were interferon-treatment naïve or relapsed with prior interferon treatment were enrolled.
Cohort 1: Sixty-one subjects received treatment. Fifty-eight subjects provided pharmacokinetic samples.
Cohort 2: Thirty-five subjects received treatment.

DESIGN: This was a multiple-dose, open-label, uncontrolled study.

Cohort 1: Subjects were randomized to receive the following treatments in parallel (1:1:1):

Treatment A: INTRON A 3 MIU/m^2 SC tiw plus ribavirin 8 mg/kg/day po administered in 2 divided doses
Treatment B: INTRON A 3 MIU/m^2 SC tiw plus ribavirin 12 mg/kg/day po administered in 2 divided doses
Treatment C: INTRON A 3 MIU/m^2 SC tiw plus ribavirin 15 mg/kg/day po administered in 2 divided doses

Treatment duration was 48 weeks and subjects were followed for 24 weeks following treatment.

Cohort 2: All subjects were treated with ribavirin (dose determined in Cohort 1) plus INTRON A:

INTRON A 3 MIU/m^2 SC tiw plus ribavirin 15 mg/kg/day po divided in 2 daily doses

*Note: There were no food restrictions, but subjects fasted for PK days. Regular meals were resumed following PK sampling. The study report does not indicate if meals were consumed in a consistent manner with regard to food.

FORMULATIONS: Ribavirin was supplied as 50 mg capsules by Schering-Plough and was administered orally.

PHARMACOKINETIC SAMPLE COLLECTION: Blood samples were obtained at predose, 2, 4, 6, 8, 12 and 24 hours following interferon-alfa 2b and at predose, 1, 1.5, 2, 4, 6, 8, 10 and 12 hours following ribavirin at week 4 for Cohort 1. Additional trough samples for interferon-alfa 2b and ribavirin were obtained at weeks 12, 24, 36 and 48 for both cohorts.

ANALYTICAL METHODS: Validated high performance liquid chromatographic mass spectrometric (LC/MS/MS) methods were performed by (b) (4) for determining ribavirin concentrations. LOQ < 50.1 ng/mL (as previous assay methods in original NDA). Calibration range: 50.1-5012 ng/mL. These methods are acceptable.

PHARMACOKINETIC ANALYSIS:

Cohort 1 PK results

Mean Cmax, AUC and Tmax values of ribavirin 8 (n=20), 12 (n=19), and 15 mg/kg/day (n=19) are summarized in Table 1 and ribavirin Cmin values for weeks 4 to 48 are summarized in Table 2.

Table 1. Mean Cmax, AUC and Tmax for ribavirin 8, 12, and 15 mg/kg/day

Protocol No. P00018

		REBETOL		
		Cmax	AUC(0-12)	Tmax
		(ng/mL)	(ng.hr/mL)	(hr)
8 mg/kg/day	Mean	2211	18309	2.93
	%CV	43	28	134
12 mg/kg/day	Mean	2705	25049	1.39
	%CV	17	16	60
15 mg/kg/day	Mean	3243	29620	1.89
	%CV	24	25	81
		INTRON A		
		Cmax	AUC(0-24)	Tmax
		(IU/mL)	(IU.hr/mL)	(hr)
3 MIU/m^2 TIW	Mean	50.0	621	5.97
	%CV	47	47	36

Table 2. Mean Cmin values of ribavirin 8, 12 and 15 mg/kg/day at 4, 12, 24, 36 and 48 weeks.

Ribavirin Dose	n	Week	SampleTime (hr)	Cmin (%CV) ng/mL
8 mg/kg/day	20	4	0	1378 (32)
	20	4	12	1398 (46)
	20	12	0	1606 (36)
	19	24	0	1612 (26)
	10	36	0	1753 (35)
	15	48	0	1332 (60)
12 mg/kg/day	19	4	0	2015 (21)
	19	4	12	1724 (20)
	19	12	0	1967 (26)
	17	24	0	2106 (34)
	11	36	0	1901 (32)
	12	48	0	1601 (51)
15 mg/kg/day	19	4	0	2350 (28)
	19	4	12	2078 (31)
	19	12	0	2382 (31)
	18	24	0	2069 (47)
	14	36	0	2345 (38)
	13	48	0	1956 (55)

Trough concentrations of ribavirin did not differ at Week 48 versus Week 4 for each dose group, suggesting no long term change in C_{min}. Variability increased by Week 48 but this may be reflective of the smaller number of subjects available for analysis compared to Week 4.

Age and weight demographics

The sponsor enrolled pediatric patients between the ages of 5-16 years in this study. Table 3 summarizes mean (SD) age and weight for the 8, 12 and 15 mg/kg/day dose groups. Refer to Figures 5b, 6b and 7b for age distribution in all three dose groups.

Table 3. Mean (SD) age and weight demographics for each ribavirin dose group of Cohort 1 in Study P00018

Parameter	8 mg/kg	12 mg/kg	15 mg/kg
Age	11 (3)	11 (3)	11 (3)
Weight	46 (20)	46 (21)	42 (21)

Ribavirin pharmacokinetics in adult versus pediatric patients

The sponsor conducted a regression analysis to compare the pharmacokinetics of pediatric doses to adult doses (from 3 studies). In their analysis, the AUC and Cmax of pediatric doses 8, 12 and 15 mg/kg appear to be superimposable over the AUC and Cmax values obtained with 800, 1000 and 1200 mg/day of ribavirin in adults (Figures 2 and 3). The approved adult dose of ribavirin is 1000 mg/day for individuals < 75 kg and 1200 mg/day for those $\geq$ 75 kg. Because ribavirin exposure of the 15 mg/kg dose in

children did not exceed those of ribavirin 1200 mg/day, ribavirin 15 mg/kg was chosen as the dose to be studied in the second cohort of this study.

Figure 1. Ribavirin mean AUC of adults compared to pediatric patients

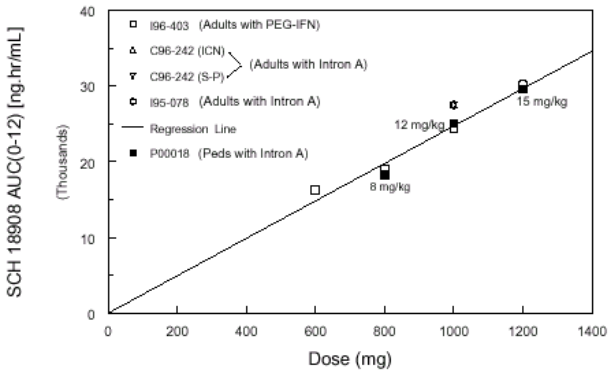
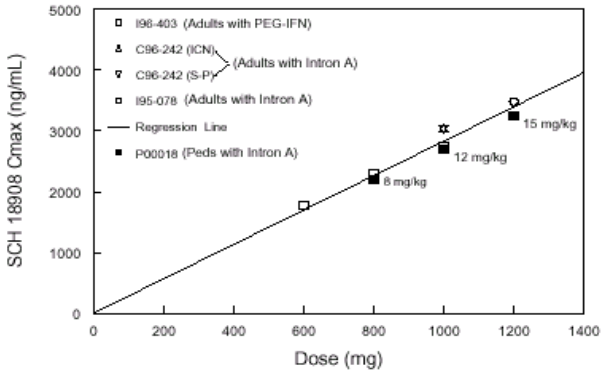


Figure 2. Ribavirin mean Cmax of adults compared to pediatric patients



However, when taking into consideration the variability observed with adult and pediatric ribavirin pharmacokinetics, the PK parameters of ribavirin 12 and 15 mg/kg/day in children fell within observed Cmax and AUC values for 1000 mg/day as well as 1200 mg/day in the adults (Table 4). Also, although mean concentration-time profiles illustrate dose proportionality over 8, 12, and 15 mg/kg in pediatric patients (Figure 3), individual data suggest that the 12 mg/kg/day and 15 mg/kg/day doses were comparable (Figure 4).

Table 4. Mean Cmax and AUC values of ribavirin 12 mg/kg and 15 mg/kg in pediatric patients and ribavirin 1000 mg/day and 1200 mg/day in adults

Dose	Cmax, ng/mL	AUC, ng*h/mL
	Pediatric (%CV)	
12 mg/kg	2705 (17)	25049 (16)
15 mg/kg	3243 (24)	29620 (25)
	Adults (range)	
1000 mg/day	3230 (1680-6760)	27800 (16500-45900)
1200 mg/day	3480 (2020-7200)	30300 (16300-59350)

Figure 3. Mean concentration-time curves for ribavirin 8, 12 and 15 mg/kg in pediatric patients

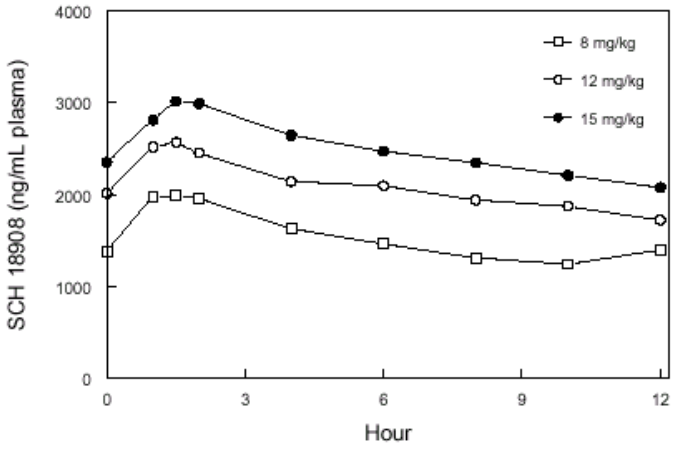
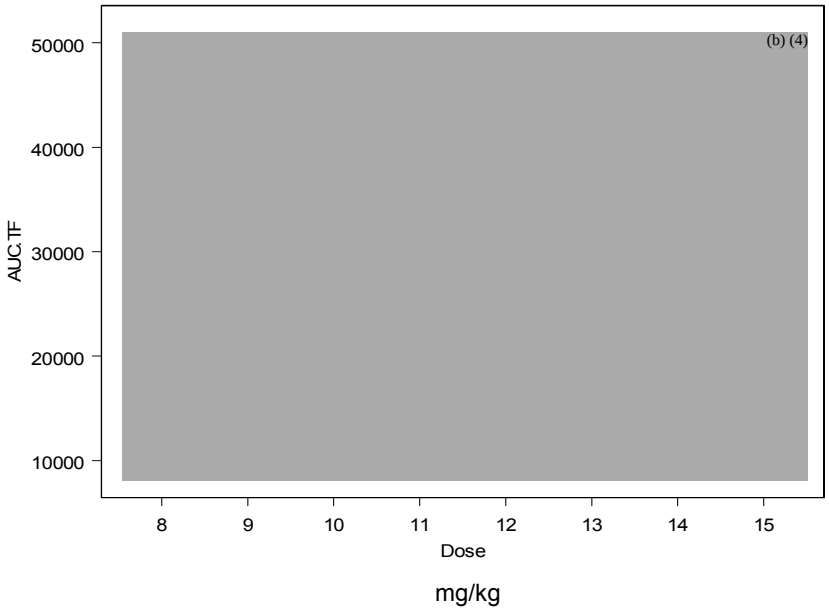


Figure 4. Ribavirin AUC values for individual patients receiving ribavirin 8, 12 and 15 mg/kg



There is a suggestion that CL/F in children varies according to age as shown in Figures 5-7, however, the relationship is not consistent across the three dose groups. Ribavirin clearance in children is also similar to adult values (adults: CL/F~0. 28 L/h/kg. In the absence of data, this value was calculated using ribavirin AUC_T~29,000 ng*h/mL at Week 6 in adults receiving ribavirin 600 mg bid. The mean weight was 73 kg).

Figure 5a and b. Clearance (CL/F) versus baseline weight (kg) and age (yrs) for ribavirin 8 mg/kg/day

Figure 5a.

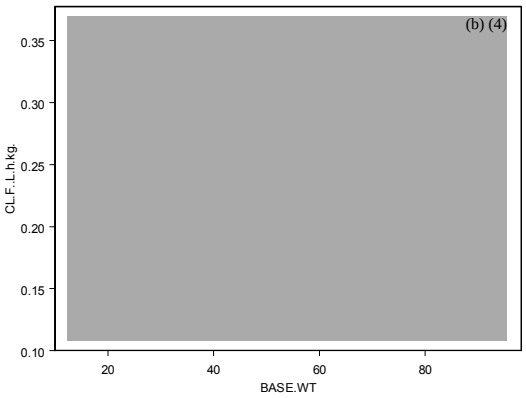


Figure 5b.

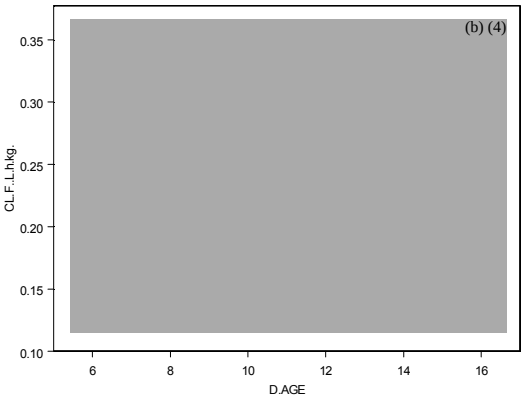


Figure 6a and b. Clearance (CL/F) versus baseline weight (kg) and age (yrs) for ribavirin 12 mg/kg/day

Figure 6a.

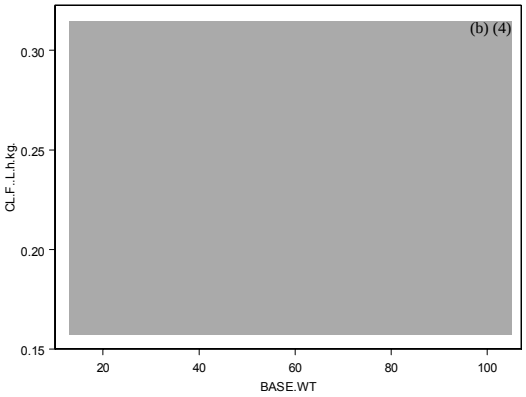


Figure 6b.

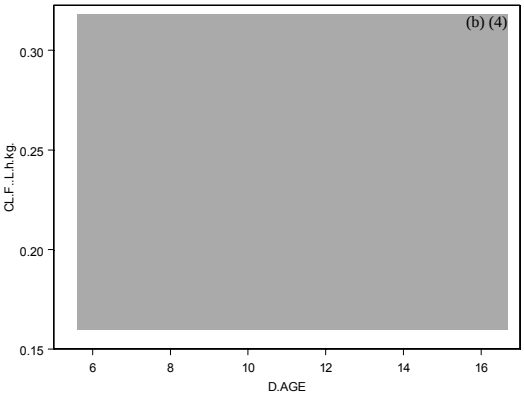


Figure 7a and b. Clearance (CL/F) versus baseline weight (kg) and age (yrs) for ribavirin 15 mg/kg/day

Figure 7a.

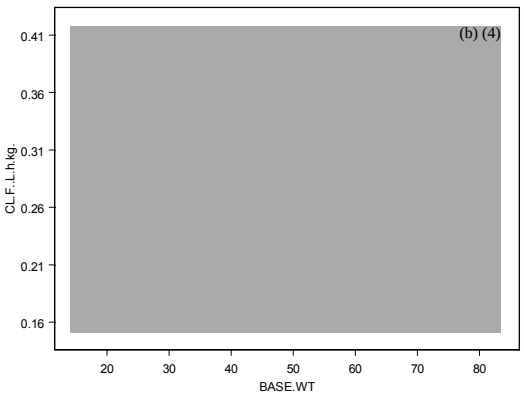
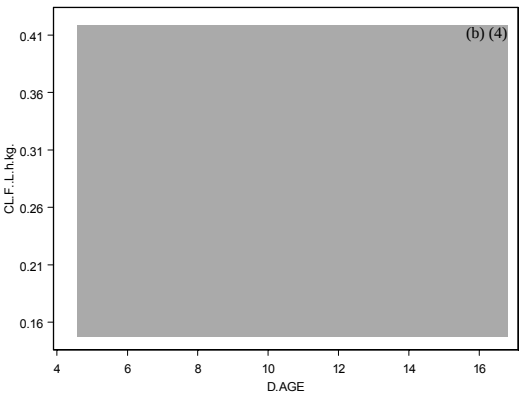


Figure 7b.



Dose-response relationships for safety and efficacy measurements: Hematological and HCV-RNA changes

Decreases in hemoglobin were mainly observed at the highest ribavirin dose. Three out of 20 children (15%) who received ribavirin 15 mg/kg required a dose reduction due to anemia. Dose reductions were not required in the other dose groups. Table 5 compares the decreases in hemoglobin observed in all three dose groups. These hematological changes are comparable to those observed with adults (Protocol C96-114) with varying doses.

In adults, a dose-response relationship was observed with changes in HCV-RNA and doses between 400 and 1200 mg/day whereas HCV-RNA decreases were similar across all dose groups in pediatric patients. This is most likely due to the smaller number of evaluable patients in the pediatric study (n=20-21) than in the adult study (n=40-45).

Table 5. Mean changes in hemoglobin after 4 weeks of treatment with Intron A and ribavirin 8, 12, and 15 mg/kg in pediatric patients

	Ribavirin dose			
Pediatric dose (P00018)		**8 mg/kg**	**12 mg/kg**	**15 mg/kg**
Change in Hgb (g/dL)		-1.1	-1.1	-1.5
Change in HCV-RNA (log 10 copies/mL)		-1.83	-1.77	-1.92
Adult dose (C96-114)	**400 mg/day**	**600 mg/day**	**800 mg/day**	**1000-1200 mg/day**
Change in Hgb (g/dL)	-1.17	-1.37	-1.7	-2.23
Change in HCV-RNA (log 10 copies/mL)	-1.62	-1.76	-2.09	-2.22

Cohort 2 PK results

For this Cohort, all subjects received 15 mg/kg and trough concentrations were measured. Table 6 summarizes mean plasma ribavirin C_{min} values between Cohort 1 and Cohort 2. Ribavirin C_{min} from Cohort 1 were comparable to those achieved in Cohort 2.

Table 6. Mean plasma ribavirin C_{min} for Cohorts 1 and 2 for Study P00018

Week	**Cohort 1**		**Cohort 2**	
	n	**C_{min} (%CV)**	**n**	**C_{min} (%CV)**
12	19	2382 (31)	33	2698 (35)
24	18	2069 (47)	28	2455 (29)
36	14	2345 (38)	20	2286 (28)
48	13	1956 (55)	23	2094 (31)

CONCLUSIONS:

- Ribavirin exposure is comparable to that in adults at the doses studied in pediatric patients (8, 12 and 15 mg/kg/day) versus adult doses of 800 mg to 1200 mg/day.
- Ribavirin 15 mg/kg/day as well as 12 mg/kg/day provided ribavirin exposure that has been determined to be clinically efficacious in adults.
- There is a suggestion that ribavirin clearance in children gradually decreases with age and weight, however, clearance values from all dose groups are comparable to adult values.
- High doses of ribavirin result in decreases in hemoglobin, warranting dose reductions (dose reduced in 15% of pediatric patients dosed with ribavirin 15 mg/kg).

VI. Office of Clinical Pharmacology and Biopharmaceutics

New Drug Application Filing and Review Form

General Information About the Submission

	Information		Information
NDA Number	**20-903**	**Brand Name**	**REBETOL**
OCPB Division (I, II, III)	**III**	**Generic Name**	**Ribavirin**
Medical Division	**Antivirals**	**Drug Class**	**Purine analog**
OCPB Reviewer	**Jooran S. Kim, Pharm.D.**	**Indication(s)**	**Chronic hepatitis C**
OCPB Team Leader	**Kellie S. Reynolds, Pharm.D.**	**Dosage Form**	**200 mg capsules**
		Dosing Regimen	**Adults: 1000 mg/day < 75 kg 1200 mg/day ≥75 kg Proposed Pediatric dose: (b) (4) mg/kg/day**
Date of Submission	**02/28/01, 11/01/01**	**Route of Administration**	**oral**
Estimated Due Date of OCPB Review	**12/13/01**	**Sponsor**	**Schering-Plough**
PDUFA Due Date	**01/01/02**	**Priority Classification**	**1P**
C. Division Due Date	**12/13/01**		

Clin. Pharm. and Biopharm. Information

	"X" if included at filing	**Number of studies submitted**	**Number of studies reviewed**	**Critical Comments If any**
STUDY TYPE				
Table of Contents present and sufficient to locate reports, tables, data, etc.				
Tabular Listing of All Human Studies				
HPK Summary				
Labeling				
Reference Bioanalytical and Analytical Methods				
I. Clinical Pharmacology				
Mass balance:				
Isozyme characterization:				
Blood/plasma ratio:				
Plasma protein binding:				
Pharmacokinetics (e.g., Phase I) -				
Healthy Volunteers-				
single dose:				
multiple dose:				
VII. Patients-				
single dose:				
multiple dose:				
Dose proportionality -				
fasting / non-fasting single dose:				
fasting / non-fasting multiple dose:				
Drug-drug interaction studies -				
In-vivo effects on primary drug:				
In-vivo effects of primary drug:				
In-vitro:				
Subpopulation studies -				
ethnicity:				
gender:				
pediatrics:				
geriatrics:				
renal impairment:				
hepatic impairment:				
PD:				
Phase 2:				
Phase 3:				
PK/PD:				
Phase 1 and/or 2, proof of concept:	X	P00018	P00018	

Phase 3 clinical trial:	X	P00321		
Population Analyses -				
Data rich:				
Data sparse:				
II. Biopharmaceutics				
Absolute bioavailability:				
Relative bioavailability -				
solution as reference:				
alternate formulation as reference:				
Bioequivalence studies -				
traditional design; single / multi dose:				
replicate design; single / multi dose:				
Food-drug interaction studies:				
Dissolution:				
(IVIVC):				
Bio-wavier request based on BCS				
BCS class				
III. Other CPB Studies				
Genotype/phenotype studies:				
Chronopharmacokinetics				
Pediatric development plan				
Literature References				
Total Number of Studies		**2**	**1**	

Filability and QBR comments

D.	**"X" if yes**	**Comments**
E. Application filable ?	**X**	
F. Comments sent to firm ? **G.**		.
QBR questions (key issues to be considered)	**Is the proposed dose appropriate for pediatric patients with chronic hepatitis C?**	
Other comments or information not included above		
Primary reviewer Signature and Date		
Secondary reviewer Signature and Date		

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Jooran Kim
12/21/01 02:46:04 PM
BIOPHARMACEUTICS

Kellie Reynolds
12/30/01 03:15:39 PM
BIOPHARMACEUTICS

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 020903/S-013

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 20-903/S-013 **PRIOR APPROVAL SUPPLEMENT**

Schering Corporation
Attention: Mary Jane Nehring
Senior Director, Marketed Products, Support and Training
2000 Galloping Hill Road
Kenilworth, NJ 07033

Dear Dr. Lamendola,

We have received your supplemental drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for the following:

Name of Drug Product: Rebetron™ Combination Therapy (Interferon alfa-2b, recombinant/ribavirin)

NDA Number: 20-903

Supplement number: S-013

Date of supplement: February 28, 2001

Date of receipt: March 1, 2001

This supplemental application, submitted as a prior approval supplement, provides for the inclusion of safety and efficacy data obtained in studies in pediatric patients in the package insert for Rebetron™ Combination Therapy.

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, this application will be filed under section 505(b) of the Act on April 30, 2001 in accordance with 21 CFR 314.101(a).

All communications concerning this supplement should be addressed as follows:

U.S. Postal Service:
Center for Drug Evaluation and Research
Division of Antiviral Drug Products, HFD-530
Attention: Document Room
5600 Fishers Lane
Rockville, Maryland 20857

Courier/Overnight Mail:
Food and Drug Administration
Center for Drug Evaluation and Research
Division of Antiviral Drug Products, HFD-530
Attention: Document Room # N115
9201 Corporate Boulevard
Rockville, Maryland 20850

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

Sincerely,

Anthony DeCicco, R.Ph.
Chief, Project Management
Division of Antiviral Drug Products, HFD-530
Office of Drug Evaluation IV
Center for Drug

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Tony DeCicco

5/16/01 11:12:18 AM