

20-903 / S-006

20-903 / S-007



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

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

Dear Dr. Lamendola:

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

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

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

**Bone marrow toxicity:**

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

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

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

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

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

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

concomitant disease or other drug therapy.

REBETOL (ribavirin) is known to be substantially excreted by the kidney, and the risk of adverse reactions to ribavirin may be greater in patients with impaired renal function. Because elderly patients often have decreased renal function, care should be taken in dose selection. Renal function should be monitored and dosage adjustments of ribavirin should be made accordingly (see **DOSAGE AND ADMINISTRATION: Guidelines for Dose Modifications**). REBETOL (ribavirin) should be used in elderly patients with creatinine clearance <50 mL/min only if the potential benefit outweighs the risk, and should not be administered to patients with creatinine clearance <30 mL/min (see **WARNINGS**).

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

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

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

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

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

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

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

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

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

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

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

Sincerely,

*{See appended electronic signature page}*

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

1 F-

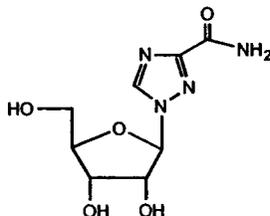
2 **PRODUCT**  
3 **INFORMATION**4 **REBETRON™**5 **Combination Therapy**6 *containing*7 **REBETOL® (ribavirin, USP) Capsules**8 *and*9 **INTRON® A (interferon alfa-2b, recombinant) Injection**10  
11  
12 **CONTRAINDICATIONS AND WARNINGS**

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

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

24  
25  
26 **DESCRIPTION**27 **REBETOL®**

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



32  
33  
34 Ribavirin is a white, crystalline powder. It is freely soluble in water and slightly  
35 soluble in anhydrous alcohol. The empirical formula is C<sub>8</sub>H<sub>12</sub>N<sub>4</sub>O<sub>5</sub> and the molecular weight  
36 is 244.21.

37 REBETOL Capsules consist of a white powder in a white, opaque, gelatin capsule.  
38 Each capsule contains 200 mg ribavirin and the inactive ingredients microcrystalline  
39 cellulose, lactose monohydrate, croscarmellose sodium, and magnesium stearate. The  
40 capsule shell consists of gelatin, sodium lauryl sulfate, silicon dioxide, and titanium dioxide.  
41 The capsule is printed with edible blue pharmaceutical ink which is made of shellac,

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

44

#### 45 **INTRON® A**

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

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

56 INTRON A Injection is a clear, colorless solution. The 3 million IU vial of INTRON  
57 A Injection contains 3 million IU of interferon alfa-2b, recombinant per 0.5 mL. The 18  
58 million IU multidose vial of INTRON A Injection contains a total of 22.8 million IU of  
59 interferon alfa-2b, recombinant per 3.8 mL (3 million IU/0.5 mL) in order to provide the  
60 delivery of six 0.5 mL doses, each containing 3 million IU of INTRON A (for a label strength  
61 of 18 million IU). The 18 million IU INTRON A Injection multidose pen contains a total of  
62 22.5 million IU of interferon alfa-2b, recombinant per 1.5 mL (3 million IU/0.2 mL) in order  
63 to provide the delivery of six 0.2-mL doses, each containing 3 million IU of INTRON A (for  
64 a label strength of 18 million IU). Each mL also contains 7.5 mg sodium chloride, 1.8 mg  
65 sodium phosphate dibasic, 1.3 mg sodium phosphate monobasic, 0.1 mg edetate disodium,  
66 0.1 mg polysorbate 80, and 1.5 mg m-cresol as a preservative.

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

71

#### 72 **Mechanism of Action**

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

76

77

## 77 CLINICAL PHARMACOLOGY

78

#### 78 **Pharmacokinetics**

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

87 hours, respectively.

88

89 *Ribavirin* Single- and multiple-dose pharmacokinetic properties in adults with chronic  
 90 hepatitis C are summarized in **TABLE 1**. Ribavirin was rapidly and extensively absorbed  
 91 following oral administration. However, due to first-pass metabolism, the absolute  
 92 bioavailability averaged 64% (44%). There was a linear relationship between dose and  
 93 AUC<sub>tf</sub> (AUC from time zero to last measurable concentration) following single doses of 200-  
 94 1200 mg ribavirin. The relationship between dose and C<sub>max</sub> was curvilinear, tending to  
 95 asymptote above single doses of 400-600 mg.

96

97 Upon multiple oral dosing, based on AUC<sub>12hr</sub>, a sixfold accumulation of ribavirin  
 98 was observed in plasma. Following oral dosing with 600 mg BID, steady-state was reached  
 99 by approximately 4 weeks, with mean steady-state plasma concentrations of 2200 (37%)  
 100 ng/mL. Upon discontinuation of dosing, the mean half-life was 298 (30%) hours, which  
 101 probably reflects slow elimination from nonplasma compartments.

102

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

109

110 *Effect of Antacid on Absorption of Ribavirin* Coadministration with an antacid containing  
 111 magnesium, aluminum, and simethicone (Mylanta<sup>®</sup>) resulted in a 14% decrease in mean  
 112 ribavirin AUC<sub>tf</sub>. The clinical relevance of results from this single-dose study is unknown.

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

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

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

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

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

116 †† N = 6

117 \*\*\* N = 11

118

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

123

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

131

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

134

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

136

### 137 ***Special Populations***

138 ***Renal Dysfunction*** The pharmacokinetics of ribavirin were assessed after administration of a

139 single oral dose (400 mg) of ribavirin to subjects with varying degrees of renal dysfunction.

140 The mean AUC<sub>0-t</sub> value was threefold greater in subjects with creatinine clearance values

141 between 10 to 30 mL/min when compared to control subjects (creatinine clearance >90

142 mL/min). This appears to be due to reduction of apparent clearance in these patients.

143 Ribavirin was not removed by hemodialysis. REBETOL is not recommended for patients

144 with severe renal impairment (see **WARNINGS**).

145

146 ***Hepatic Dysfunction*** The effect of hepatic dysfunction was assessed after a single oral dose

147 of ribavirin (600 mg). The mean AUC<sub>0-t</sub> values were not significantly different in subjects

148 with mild, moderate, or severe hepatic dysfunction (Child-Pugh Classification A, B, or C),

149 when compared to control subjects. However, the mean C<sub>max</sub> values increased with severity

150 of hepatic dysfunction and was twofold greater in subjects with severe hepatic dysfunction

151 when compared to control subjects.

152

153 ***Pediatric Patients*** Pharmacokinetic evaluations for pediatric subjects have not been

154 performed.

155

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

157

158 ***Gender*** There were no clinically significant pharmacokinetic differences noted in a single-

159 dose study of eighteen male and eighteen female subjects.

160

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

162

**INDICATIONS AND USAGE**

163  
164 REBETOL (ribavirin, USP) Capsules is indicated in combination with INTRON A  
165 (interferon alfa-2b, recombinant) Injection for the treatment of chronic hepatitis C in patients  
166 with compensated liver disease previously untreated with alpha interferon or who have  
167 relapsed following alpha interferon therapy.

168

**Description of Clinical Studies**

169  
170 **Previously Untreated Patients** Adults with compensated chronic hepatitis C and  
171 detectable HCV RNA (assessed by a central laboratory using a research-based RT-PCR  
172 assay) who were previously untreated with alpha interferon therapy were enrolled into  
173 two multicenter, double-blind trials (US and International) and randomized to receive  
174 REBETOL Capsules 1200 mg/day (1000 mg/day for patients weighing  $\leq 75$  kg) plus  
175 INTRON A Injection 3 MIU TIW or INTRON A Injection plus placebo for 24 or 48  
176 weeks followed by 24 weeks of off-therapy follow-up. The International study did not  
177 contain a 24-week INTRON A plus placebo treatment arm. The US study enrolled 912  
178 patients who, at baseline, were 67% male, 89% caucasian with a mean Knodell HAI  
179 score (I+II+III) of 7.5, and 72% genotype 1. The International study, conducted in  
180 Europe, Israel, Canada, and Australia, enrolled 799 patients (65% male, 95% caucasian,  
181 mean Knodell score 6.8, and 58% genotype 1).

182

183

Study results are summarized in TABLE 2.

184

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

185

\* Number (%) of Patients.

186

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

187

<sup>2</sup> Defined as posttreatment (end of follow-up) minus pretreatment liver biopsy Knodell HAI score (I+II+III) improvement of  $\geq 2$  points.

188

189

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.

192

193

194

195

196

197

198

199

200

201

202

203

204

205

206

207

208

209

210

211

212

Study results are summarized in TABLE 3.

213

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

\* Number (%) of Patients.

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

<sup>2</sup> Defined as posttreatment (end of follow-up) minus pretreatment liver biopsy Knodell HAI score (I+II+III) improvement of  $\geq 2$  points.

214

215

216

217

218

219

220

221

222

223

224

225

226

227

228

229

230

231

232

233

234

235

236

237

238

239

240

241

242

243

244

245

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

### CONTRAINDICATIONS

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

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

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

### WARNINGS

#### Pregnancy

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

248

249 **Anemia**

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

259

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

268

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

271

272 **Psychiatric**

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

284

285 **Bone marrow toxicity:**

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

291 **AND ADMINISTRATION: Guidelines for Dose Modifications).**

292

293 **Pulmonary**

294 Pulmonary symptoms, including dyspnea, pulmonary infiltrates, pneumonitis and pneumonia,  
295 including fatality, have been reported during therapy with REBETOL/INTRON A. If there is  
296 evidence of pulmonary infiltrates or pulmonary function impairment, the patient should be  
297 closely monitored, and, if appropriate, combination REBETOL/INTRON A treatment should  
298 be discontinued.

299

300 **Other**

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

325

326

**PRECAUTIONS**

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

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

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

336 nonresponders to interferon therapy, or patients coinfecting with HBV or HIV.

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

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

342

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

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

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

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

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

379 Patients should be advised that laboratory evaluations are required prior to starting  
380 therapy and periodically thereafter (see **Laboratory Tests**). It is advised that patients be well

381 hydrated, especially during the initial stages of treatment.

382

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

386 •Standard hematologic tests - including hemoglobin (pretreatment, week 2 and week  
387 4 of therapy, and as clinically appropriate [see WARNINGS]), complete and  
388 differential white blood cell counts, and platelet count.

389 •Blood chemistries - liver function tests and TSH.

390 •Pregnancy - including monthly monitoring for women of childbearing potential.

391

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

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

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

409

410 **Impairment of Fertility** No reproductive toxicology studies have been performed using  
411 interferon alfa-2b, recombinant in combination with ribavirin. However, evidence provided  
412 below for interferon alfa-2b, recombinant and ribavirin when administered alone indicate that  
413 both agents have adverse effects on reproduction. It should be assumed that the effects  
414 produced by either agent alone will also be caused by the combination of the two agents.  
415 Interferons may impair human fertility. In studies of interferon alfa-2b recombinant  
416 administration in nonhuman primates, menstrual cycle abnormalities have been observed.  
417 Decreases in serum estradiol and progesterone concentrations have been reported in women  
418 treated with human leukocyte interferon. In addition, ribavirin demonstrated significant  
419 embryocidal and/or teratogenic effects at doses well below the recommended human dose in  
420 all animal species in which adequate studies have been conducted.

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

426           Combination REBETOL/INTRON A therapy should be used with caution in fertile  
427 men. In studies in mice to evaluate the time course and reversibility of ribavirin-induced  
428 testicular degeneration at doses of 15 to 150 mg/kg/day (estimated human equivalent of 1.25  
429 - 12.5 mg/kg/day, based on body surface area adjustment for a 60 kg adult; 0.1 - 0.8 X the  
430 maximum human 24-hour dose of ribavirin) administered for 3 or 6 months, abnormalities in  
431 sperm occurred. Upon cessation of treatment, essentially total recovery from ribavirin-  
432 induced testicular toxicity was apparent within 1 or 2 spermatogenesis cycles.

433  
434 **Animal Toxicology** Long-term studies in the mouse and rat (18 - 24 months; doses of 20 -  
435 75 and 10 - 40 mg/kg/day, respectively [estimated human equivalent doses of 1.67 - 6.25 and  
436 1.43 - 5.71 mg/kg/day, respectively, based on body surface area adjustment for a 60 kg adult;  
437 approximately 0.1 - 0.4 X the maximum human 24-hour dose of ribavirin]) have  
438 demonstrated a relationship between chronic ribavirin exposure and increased incidences of  
439 vascular lesions (microscopic hemorrhages) in mice. In rats, retinal degeneration occurred in  
440 controls, but the incidence was increased in ribavirin-treated rats.

441  
442 **Pregnancy Category X** (see **CONTRAINDICATIONS**) Interferon alfa-2b, recombinant  
443 has been shown to have abortifacient effects in *Macaca mulatta* (rhesus monkeys) at 15 and  
444 30 million IU/kg (estimated human equivalent of 5 and 10 million IU/kg, based on body  
445 surface area adjustment for a 60 kg adult). There are no adequate and well-controlled studies  
446 in pregnant women.

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

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

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

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

474 If pregnancy occurs in a patient or partner of a patient during treatment or during the 6  
475 months after treatment cessation, physicians are encouraged to report such cases by calling  
476 (800) 727-7064.

477 **Nursing Mothers** It is not known whether REBETOL and INTRON A are excreted in human  
478 milk. However, studies in mice have shown that mouse interferons are excreted into the milk.

479 Because of the potential for serious adverse reactions from the drugs in nursing infants, a  
480 decision should be made whether to discontinue nursing or to discontinue combination  
481 REBETOL/INTRON A therapy, taking into account the importance of the therapy to the  
482 mother.

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

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

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

493 REBETOL (ribavirin) is known to be substantially excreted by the kidney, and the  
494 risk of adverse reactions to ribavirin may be greater in patients with impaired renal function.  
495 Because elderly patients often have decreased renal function, care should be taken in dose  
496 selection. Renal function should be monitored and dosage adjustments of ribavirin should be  
497 made accordingly (see **DOSAGE AND ADMINISTRATION: Guidelines for Dose**  
498 **Modifications**). REBETOL (ribavirin) should be used in elderly patients with creatinine  
499 clearance <50 mL/min only if the potential benefit outweighs the risk, and should not be  
500 administered to patients with creatinine clearance <30 mL/min (see **WARNINGS**).

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

## 503 504 505 **ADVERSE REACTIONS**

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

514 **The primary toxicity of ribavirin is hemolytic anemia. Reductions in**  
515 **hemoglobin levels occurred within the first 1-2 weeks of therapy (see WARNINGS).**

516 **Cardiac and pulmonary events associated with anemia occurred in approximately 10%**  
517 **of patients treated with REBETOL/INTRON A therapy. (See WARNINGS.)**

518       The most common psychiatric events occurring in US studies of previously untreated  
519 and relapse patients treated with REBETOL/INTRON A therapy, respectively, were insomnia  
520 (39%, 26%), depression (34%, 23%), and irritability (27%, 25%). Suicidal behavior  
521 (ideation, attempts, and suicides) occurred in 1% of patients. (See WARNINGS.). In  
522 addition hearing disorders (tinnitus and hearing loss) and vertigo have occurred in patients  
523 treated with combination REBETOL/INTRON A therapy.

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

529

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

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

taste perversion

7

4

8

4

6

5

530  
531

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

532

**533 Laboratory Values**

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

537

538 *Hemoglobin* Hemoglobin decreases among patients on combination therapy began at Week  
539 1, with stabilization by Week 4. In previously untreated patients treated for 48 weeks the  
540 mean maximum decrease from baseline was 3.1 g/dL in the US study and 2.9 g/dL in the  
541 International study. In relapse patients the mean maximum decrease from baseline was 2.8  
542 g/dL in the US study and 2.6 g/dL in the International study. Hemoglobin values returned to  
543 pretreatment levels within 4 - 8 weeks of cessation of therapy in most patients.

544

545 *Neutrophils* There were decreases in neutrophil counts in both the combination  
546 REBETOL/INTRON A and INTRON A plus placebo dose groups. In previously untreated  
547 patients treated for 48 weeks the mean maximum decrease in neutrophil count in the US  
548 study was  $1.3 \times 10^9$ /L and in the International study was  $1.5 \times 10^9$ /L. In relapse patients the  
549 mean maximum decrease in neutrophil count in the US study was  $1.3 \times 10^9$ /L and in the  
550 International study was  $1.6 \times 10^9$ /L. Neutrophil counts returned to pretreatment levels within  
551 4 weeks of cessation of therapy in most patients.

552

553 *Platelets* In both previously untreated and relapse patients mean platelet counts generally  
554 remained in the normal range in all treatment groups, however, mean platelet counts were  
555 10% to 15% lower in the INTRON A plus placebo group than the REBETOL/INTRON A  
556 group. Mean platelet counts returned to baseline levels within 4 weeks after treatment  
557 discontinuation.

558

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

563

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

569

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

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

570

571

### OVERDOSAGE

572

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.

573

574

575

576

577

578

### DOSAGE AND ADMINISTRATION

579

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

580

581

582

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

583

584

The recommended duration of treatment for patients previously untreated with

585 interferon is 24 to 48 weeks. The duration of treatment should be individualized to the  
586 patient depending on baseline disease characteristics, response to therapy, and tolerability of  
587 the regimen (see **Description of Clinical Studies** and **ADVERSE REACTIONS**). After 24  
588 weeks of treatment virologic response should be assessed. Treatment discontinuation should  
589 be considered in any patient who has not achieved an HCV-RNA below the limit of detection  
590 of the assay by 24 weeks. There are no safety and efficacy data on treatment for longer than  
591 48 weeks in the previously untreated patient population.

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

595

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.

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

598

599 *Dose Modifications (TABLE 7)*

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

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

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

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

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

624

625

626

---

**TABLE 7. Guidelines for Dose Modifications**

---

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

---

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

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

627

628 Administration of INTRON A Injection

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

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

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

637 †This is a multidose vial which contains a total of 22.8 million IU of interferon alfa-2b,  
638 recombinant per 3.8 mL in order to provide the delivery of six 0.5-mL doses, each containing  
639 3 million IU of interferon alfa-2b, recombinant (for a label strength of 18 million IU).

640 †† This is a multidose pen which contains a total of 22.5 million IU of interferon alfa-2b,  
641 recombinant per 1.5 mL in order to provide the delivery of six 0.2-mL doses, each containing  
642 3 million IU of interferon alfa-2b, recombinant (for a label strength of 18 million IU).  
643

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

647 **Stability** INTRON A Injection provided in vials is stable at 35°C (95°F) for up to 7 days and  
648 at 30°C (86°F) for up to 14 days. INTRON A Injection provided in a multidose pen is stable  
649 at 30°C (86°F) for up to 2 days. The solution is clear and colorless.  
650

651 **HOW SUPPLIED**

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

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

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

660

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

661

662

**STORAGE CONDITIONS**

663

**Store the REBETOL Capsules plus INTRON A Injection combination package**

664

**refrigerated between 2°C and 8°C (36° and 46° F).**

665

**When separated, the individual bottle of REBETOL Capsules should be stored**

666

**refrigerated between 2° and 8°C (36° and 46°F) or at 25°C (77°F); excursions are**

667

**permitted between 15° and 30°C (59° and 86°F).**

668

**When separated, the individual vials of INTRON A Injection and the INTRON**

669

**A Multidose Pen should be stored refrigerated between 2° and 8°C (36° and 46°F).**

670



671

**Schering Corporation**

672

**Kenilworth, NJ 07033 USA**

673

674

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

675

**Copyright © 1998, Schering Corporation. All rights reserved.**

676

677

**B-**

678 F-

679

680

681

682 **Combination Therapy**683 *containing*684 **REBETOL<sup>®</sup> (ribavirin, USP) Capsules**685 *and*686 **INTRON<sup>®</sup> A (interferon alfa-2b, recombinant) Injection**

687

688

689

**CONTRAINDICATIONS AND WARNINGS**

690

691

692

693

694

695

696

697

698

699

700

701

702

703

**DESCRIPTION**

704

**REBETOL<sup>®</sup>**

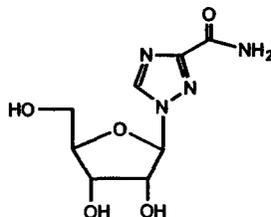
705

706

707

708

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



709

710

711

712

713

Ribavirin is a white, crystalline powder. It is freely soluble in water and slightly soluble in anhydrous alcohol. The empirical formula is C<sub>8</sub>H<sub>12</sub>N<sub>4</sub>O<sub>5</sub> and the molecular weight is 244.21.

714

715

716

717

718

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,

**PRODUCT  
INFORMATION**

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

721

### 722 **INTRON® A**

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

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

733 INTRON A Injection is a clear, colorless solution. The 3 million IU vial of INTRON  
734 A Injection contains 3 million IU of interferon alfa-2b, recombinant per 0.5 mL. The 18  
735 million IU multidose vial of INTRON A Injection contains a total of 22.8 million IU of  
736 interferon alfa-2b, recombinant per 3.8 mL (3 million IU/0.5 mL) in order to provide the  
737 delivery of six 0.5 mL doses, each containing 3 million IU of INTRON A (for a label strength  
738 of 18 million IU). The 18 million IU INTRON A Injection multidose pen contains a total of  
739 22.5 million IU of interferon alfa-2b, recombinant per 1.5 mL (3 million IU/0.2 mL) in order  
740 to provide the delivery of six 0.2-mL doses, each containing 3 million IU of INTRON A (for  
741 a label strength of 18 million IU). Each mL also contains 7.5 mg sodium chloride, 1.8 mg  
742 sodium phosphate dibasic, 1.3 mg sodium phosphate monobasic, 0.1 mg edetate disodium,  
743 0.1 mg polysorbate 80, and 1.5 mg m-cresol as a preservative.

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

748

### 749 **Mechanism of Action**

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

753

754

## CLINICAL PHARMACOLOGY

755

### 755 **Pharmacokinetics**

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

764 hours, respectively.

765

766 *Ribavirin* Single- and multiple-dose pharmacokinetic properties in adults with chronic  
 767 hepatitis C are summarized in TABLE 1. Ribavirin was rapidly and extensively absorbed  
 768 following oral administration. However, due to first-pass metabolism, the absolute  
 769 bioavailability averaged 64% (44%). There was a linear relationship between dose and  
 770 AUC<sub>tf</sub> (AUC from time zero to last measurable concentration) following single doses of 200-  
 771 1200 mg ribavirin. The relationship between dose and C<sub>max</sub> was curvilinear, tending to  
 772 asymptote above single doses of 400-600 mg.

773 Upon multiple oral dosing, based on AUC<sub>12hr</sub>, a sixfold accumulation of ribavirin  
 774 was observed in plasma. Following oral dosing with 600 mg BID, steady-state was reached  
 775 by approximately 4 weeks, with mean steady-state plasma concentrations of 2200 (37%)  
 776 ng/mL. Upon discontinuation of dosing, the mean half-life was 298 (30%) hours, which  
 777 probably reflects slow elimination from nonplasma compartments.

778

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

785

786 *Effect of Antacid on Absorption of Ribavirin* Coadministration with an antacid containing  
 787 magnesium, aluminum, and simethicone (Mylanta<sup>®</sup>) resulted in a 14% decrease in mean  
 788 ribavirin AUC<sub>tf</sub>. The clinical relevance of results from this single-dose study is unknown.

789

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

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

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

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

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

793 †† N = 6

794 \*\*\* N = 11

795

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

800

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

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

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

813

#### 814 ***Special Populations***

815 ***Renal Dysfunction*** The pharmacokinetics of ribavirin were assessed after administration of a  
816 single oral dose (400 mg) of ribavirin to subjects with varying degrees of renal dysfunction.  
817 The mean AUC<sub>0-t</sub> value was threefold greater in subjects with creatinine clearance values  
818 between 10 to 30 mL/min when compared to control subjects (creatinine clearance >90  
819 mL/min). This appears to be due to reduction of apparent clearance in these patients.  
820 Ribavirin was not removed by hemodialysis. REBETOL is not recommended for patients  
821 with severe renal impairment (see **WARNINGS**).

822

823 ***Hepatic Dysfunction*** The effect of hepatic dysfunction was assessed after a single oral dose  
824 of ribavirin (600 mg). The mean AUC<sub>0-t</sub> values were not significantly different in subjects  
825 with mild, moderate, or severe hepatic dysfunction (Child-Pugh Classification A, B, or C),  
826 when compared to control subjects. However, the mean C<sub>max</sub> values increased with severity  
827 of hepatic dysfunction and was twofold greater in subjects with severe hepatic dysfunction  
828 when compared to control subjects.

829

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

832

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

834

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

837

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

839

840

**INDICATIONS AND USAGE**

841

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.

843

844

845

846

**Description of Clinical Studies**

847

848

849

850

851

852

853

854

855

856

857

858

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  $\leq 75$  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).

859

860

Study results are summarized in TABLE 2.

861

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

862

\* Number (%) of Patients.

863

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

864

<sup>2</sup> Defined as posttreatment (end of follow-up) minus pretreatment liver biopsy Knodell HAI score (I+II+III) improvement of  $\geq 2$  points.

865

866

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.

869

870

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.

876

877

878

879

880

881

882

883

884

885

886

887

888

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

889

Study results are summarized in TABLE 3.

890

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

891

\* Number (%) of Patients.

892

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

893

<sup>2</sup> Defined as posttreatment (end of follow-up) minus pretreatment liver biopsy Knodell HAI score (I+II+III) improvement of  $\geq 2$  points.

894

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

897

898

### CONTRAINDICATIONS

899

900

901

902

903

904

905

906

907

908

909

910

911

912

913

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

914

915

916

917

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.

918

919

920

921

922

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

### WARNINGS

#### Pregnancy

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

925

926 **Anemia**

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

936

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

945

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

948

949 **Psychiatric**

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

961

962 **Bone marrow toxicity:**

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

**968 AND ADMINISTRATION: Guidelines for Dose Modifications).**

969

**970 Pulmonary**

971 Pulmonary symptoms, including dyspnea, pulmonary infiltrates, pneumonitis and pneumonia,  
972 including fatality, have been reported during therapy with REBETOL/INTRON A. If there is  
973 evidence of pulmonary infiltrates or pulmonary function impairment, the patient should be  
974 closely monitored, and, if appropriate, combination REBETOL/INTRON A treatment should  
975 be discontinued.

976

**977 Other**

- 978 • REBETOL Capsule monotherapy is not effective for the treatment of chronic hepatitis C  
979 and should not be used for this indication.
- 980 • Fatal and nonfatal pancreatitis has been observed in patients treated with  
981 REBETOL/INTRON A therapy. REBETOL/INTRON A therapy should be suspended in  
982 patients with signs and symptoms of pancreatitis and discontinued in patients with  
983 confirmed pancreatitis.
- 984 • Combination REBETOL/INTRON A therapy should be used with caution in patients with  
985 creatinine clearance <50 mL/min.
- 986 • Diabetes mellitus and hyperglycemia have been observed in patients treated with  
987 INTRON A.
- 988 • Ophthalmologic disorders have been reported with treatment with alpha interferons  
989 (including INTRON A therapy). Investigators using alpha interferons have reported the  
990 occurrence of retinal hemorrhages, cotton wool spots, and retinal artery or vein  
991 obstruction in rare instances. Any patient complaining of loss of visual acuity or visual  
992 field should have an eye examination. Because these ocular events may occur in  
993 conjunction with other disease states, a visual exam prior to initiation of combination  
994 REBETOL/INTRON A therapy is recommended in patients with diabetes mellitus or  
995 hypertension.
- 996 • Acute serious hypersensitivity reactions (eg, urticaria, angioedema, bronchoconstriction,  
997 anaphylaxis) have been observed in INTRON A-treated patients; if such an acute reaction  
998 develops, combination REBETOL/INTRON A therapy should be discontinued immediately  
999 and appropriate medical therapy instituted. • Combination REBETOL/INTRON A therapy  
1000 should be discontinued for patients developing thyroid abnormalities during treatment whose  
1001 thyroid function cannot be controlled by medication.

1002

1003

**PRECAUTIONS**

1004 Exacerbation of autoimmune disease has been reported in patients receiving alpha interferon  
1005 therapy (including INTRON A therapy). REBETOL/INTRON A therapy should be used with  
1006 caution in patients with other autoimmune disorders.

1007 There have been reports of interferon, including INTRON A (interferon alfa-2b,  
1008 recombinant) exacerbating pre-existing psoriasis; therefore, combination  
1009 REBETOL/INTRON A therapy should be used in these patients only if the potential benefit  
1010 justifies the potential risk.

1011 The safety and efficacy of REBETOL/INTRON A therapy has not been established in  
1012 liver or other organ transplant patients, decompensated hepatitis C patients, patients who are

1013 nonresponders to interferon therapy, or patients coinfecting with HBV or HIV.

1014 The safety and efficacy of REBETOL Capsule monotherapy for the treatment of HIV  
1015 infection, adenovirus, early RSV infection, parainfluenza, or influenza have not been  
1016 established and REBETOL Capsules should not be used for these indications.

1017 There is no information regarding the use of REBETOL Capsules with other  
1018 interferons.

1019

1020 **Information for Patients** Combination REBETOL/INTRON A therapy must not be used by  
1021 women who are pregnant or by men whose female partners are pregnant. Extreme care must  
1022 be taken to avoid pregnancy in female patients and in female partners of male patients taking  
1023 combination REBETOL/INTRON A therapy. Combination REBETOL/INTRON A therapy  
1024 should not be initiated until a report of a negative pregnancy test has been obtained  
1025 immediately prior to initiation of therapy. Patients must perform a pregnancy test monthly  
1026 during therapy and for 6 months posttherapy. Women of childbearing potential must be  
1027 counseled about use of effective contraception (two reliable forms) prior to initiating therapy.  
1028 Patients (male and female) must be advised of the teratogenic/embryocidal risks and must be  
1029 instructed to practice effective contraception during combination REBETOL/INTRON A  
1030 therapy and for 6 months posttherapy. Patients (male and female) should be advised to notify  
1031 the physician immediately in the event of a pregnancy. (See **CONTRAINDICATIONS**.)

1032 If pregnancy does occur during treatment or during 6 months posttherapy, the patient  
1033 must be advised of the significant teratogenic risk of REBETOL therapy to the fetus. Patients,  
1034 or partners of patients, should immediately report any pregnancy that occurs during treatment  
1035 or within 6 months after treatment cessation to their physician. Physicians are encouraged to  
1036 report such cases by calling (800) 727-7064.

1037 Patients receiving combination REBETOL/INTRON A treatment should be directed  
1038 in its appropriate use, informed of the benefits and risks associated with treatment, and  
1039 referred to the patient **MEDICATION GUIDE**. There are no data evaluating whether  
1040 REBETOL/INTRON A therapy will prevent transmission of infection to others. Also, it is  
1041 not known if treatment with REBETOL/INTRON A therapy will cure hepatitis C or prevent  
1042 cirrhosis, liver failure, or liver cancer that may be the result of infection with the hepatitis C  
1043 virus.

1044 If home use is prescribed, a puncture-resistant container for the disposal of used  
1045 syringes and needles should be supplied to the patient. Patients should be thoroughly  
1046 instructed in the importance of proper disposal and cautioned against any reuse of needles  
1047 and syringes. The full container should be disposed of according to the directions provided by  
1048 the physician (see **MEDICATION GUIDE**).

1049 The most common adverse experiences occurring with combination REBETOL/INTRON  
1050 A therapy are "flu-like" symptoms, such as headache, fatigue, myalgia, and fever (see  
1051 **ADVERSE REACTIONS**) and appear to decrease in severity as treatment continues. Some  
1052 of these "flu-like" symptoms may be minimized by bedtime administration of INTRON A  
1053 therapy. Antipyretics should be considered to prevent or partially alleviate the fever and  
1054 headache. Another common adverse experience associated with INTRON A therapy is  
1055 thinning of the hair.

1056 Patients should be advised that laboratory evaluations are required prior to starting  
1057 therapy and periodically thereafter (see **Laboratory Tests**). It is advised that patients be well

1058 hydrated, especially during the initial stages of treatment.

1059

1060 **Laboratory Tests** The following laboratory tests are recommended for all patients on  
1061 combination REBETOL/INTRON A therapy, prior to beginning treatment and then  
1062 periodically thereafter.

1063 •Standard hematologic tests - including hemoglobin (pretreatment, week 2 and week  
1064 4 of therapy, and as clinically appropriate [see **WARNINGS**]), complete and  
1065 differential white blood cell counts, and platelet count.

1066 •Blood chemistries - liver function tests and TSH.

1067 •Pregnancy - including monthly monitoring for women of childbearing potential.

1068

1069 **Carcinogenesis and Mutagenesis** Carcinogenicity studies with interferon alfa-2b,  
1070 recombinant have not been performed because neutralizing activity appears in the serum after  
1071 multiple dosing in all of the animal species tested.

1072 Adequate studies to assess the carcinogenic potential of ribavirin in animals have not  
1073 been conducted. However, ribavirin is a nucleoside analog that has produced positive  
1074 findings in multiple *in vitro* and animal *in vivo* genotoxicity assays, and should be considered  
1075 a potential carcinogen. Further studies to assess the carcinogenic potential of ribavirin in  
1076 animals are ongoing.

1077 Mutagenicity studies have demonstrated that interferon alfa-2b, recombinant is not  
1078 mutagenic. Ribavirin demonstrated increased incidences of mutation and cell transformation  
1079 in multiple genotoxicity assays. Ribavirin was active in the Balb/3T3 *In Vitro* Cell  
1080 Transformation Assay. Mutagenic activity was observed in the mouse lymphoma assay, and  
1081 at doses of 20-200 mg/kg (estimated human equivalent of 1.67 - 16.7 mg/kg, based on body  
1082 surface area adjustment for a 60 kg adult; 0.1 - 1 X the maximum recommended human 24-  
1083 hour dose of ribavirin) in a mouse micronucleus assay. A dominant lethal assay in rats was  
1084 negative, indicating that if mutations occurred in rats they were not transmitted through male  
1085 gametes.

1086

1087 **Impairment of Fertility** No reproductive toxicology studies have been performed using  
1088 interferon alfa-2b, recombinant in combination with ribavirin. However, evidence provided  
1089 below for interferon alfa-2b, recombinant and ribavirin when administered alone indicate that  
1090 both agents have adverse effects on reproduction. It should be assumed that the effects  
1091 produced by either agent alone will also be caused by the combination of the two agents.  
1092 Interferons may impair human fertility. In studies of interferon alfa-2b recombinant  
1093 administration in nonhuman primates, menstrual cycle abnormalities have been observed.  
1094 Decreases in serum estradiol and progesterone concentrations have been reported in women  
1095 treated with human leukocyte interferon. In addition, ribavirin demonstrated significant  
1096 embryocidal and/or teratogenic effects at doses well below the recommended human dose in  
1097 all animal species in which adequate studies have been conducted.

1098 Fertile women and partners of fertile women should not receive combination  
1099 REBETOL/INTRON A therapy unless the patient and his/her partner are using effective  
1100 contraception (two reliable forms). Based on a multiple dose half-life ( $t_{1/2}$ ) of ribavirin of 12  
1101 days, effective contraception must be utilized for 6 months posttherapy (eg, 15 half-lives of  
1102 clearance for ribavirin).

1103           Combination REBETOL/INTRON A therapy should be used with caution in fertile  
1104 men. In studies in mice to evaluate the time course and reversibility of ribavirin-induced  
1105 testicular degeneration at doses of 15 to 150 mg/kg/day (estimated human equivalent of 1.25  
1106 - 12.5 mg/kg/day, based on body surface area adjustment for a 60 kg adult; 0.1 - 0.8 X the  
1107 maximum human 24-hour dose of ribavirin) administered for 3 or 6 months, abnormalities in  
1108 sperm occurred. Upon cessation of treatment, essentially total recovery from ribavirin-  
1109 induced testicular toxicity was apparent within 1 or 2 spermatogenesis cycles.

1110  
1111 **Animal Toxicology** Long-term studies in the mouse and rat (18 - 24 months; doses of 20 -  
1112 75 and 10 - 40 mg/kg/day, respectively [estimated human equivalent doses of 1.67 - 6.25 and  
1113 1.43 - 5.71 mg/kg/day, respectively, based on body surface area adjustment for a 60 kg adult;  
1114 approximately 0.1 - 0.4 X the maximum human 24-hour dose of ribavirin]) have  
1115 demonstrated a relationship between chronic ribavirin exposure and increased incidences of  
1116 vascular lesions (microscopic hemorrhages) in mice. In rats, retinal degeneration occurred in  
1117 controls, but the incidence was increased in ribavirin-treated rats.

1118  
1119 **Pregnancy Category X** (see **CONTRAINDICATIONS**) Interferon alfa-2b, recombinant  
1120 has been shown to have abortifacient effects in *Macaca mulatta* (rhesus monkeys) at 15 and  
1121 30 million IU/kg (estimated human equivalent of 5 and 10 million IU/kg, based on body  
1122 surface area adjustment for a 60 kg adult). There are no adequate and well-controlled studies  
1123 in pregnant women.

1124           Ribavirin produced significant embryocidal and/or teratogenic effects in all animal  
1125 species in which adequate studies have been conducted. Malformations of the skull, palate,  
1126 eye, jaw, limbs, skeleton, and gastrointestinal tract were noted. The incidence and severity of  
1127 teratogenic effects increased with escalation of the drug dose. Survival of fetuses and  
1128 offspring was reduced. In conventional embryotoxicity/teratogenicity studies in rats and  
1129 rabbits, observed no effect dose levels were well below those for proposed clinical use (0.3  
1130 mg/kg/day for both the rat and rabbit; approximately 0.06 X the recommended human 24-  
1131 hour dose of ribavirin). No maternal toxicity or effects on offspring were observed in a  
1132 peri/postnatal toxicity study in rats dosed orally at up to 1 mg/kg/day (estimated human  
1133 equivalent dose of 0.17 mg/kg based on body surface area adjustment for a 60 kg adult;  
1134 approximately 0.01 X the maximum recommended human 24-hour dose of ribavirin).

1135 **Treatment and Posttreatment: Potential Risk to the Fetus** Ribavirin is known to accumulate  
1136 in intracellular components from where it is cleared very slowly. It is not known whether  
1137 ribavirin contained in sperm will exert a potential teratogenic effect upon fertilization of the  
1138 ova. In a study in rats, it was concluded that dominant lethality was not induced by ribavirin  
1139 at doses up to 200 mg/kg for 5 days (estimated human equivalent doses of 7.14 - 28.6 mg/kg,  
1140 based on body surface area adjustment for a 60 kg adult; up to 1.7 X the maximum  
1141 recommended human dose of ribavirin). However, because of the potential human  
1142 teratogenic effects of ribavirin, male patients should be advised to take every precaution to  
1143 avoid risk of pregnancy for their female partners.

1144           Women of childbearing potential should not receive combination  
1145 REBETOL/INTRON A therapy unless they are using effective contraception (two reliable  
1146 forms) during the therapy period. In addition, effective contraception should be utilized for 6  
1147 months posttherapy based on a multiple dose half-life ( $t_{1/2}$ ) of ribavirin of 12 days.

1148 Male patients and their female partners must practice effective contraception (two  
1149 reliable forms) during treatment with combination REBETOL/INTRON A therapy and for  
1150 the 6-month posttherapy period (eg, 15 half-lives for ribavirin clearance from the body).

1151 If pregnancy occurs in a patient or partner of a patient during treatment or during the 6  
1152 months after treatment cessation, physicians are encouraged to report such cases by calling  
1153 (800) 727-7064.

1154 **Nursing Mothers** It is not known whether REBETOL and INTRON A are excreted in human  
1155 milk. However, studies in mice have shown that mouse interferons are excreted into the milk.

1156 Because of the potential for serious adverse reactions from the drugs in nursing infants, a  
1157 decision should be made whether to discontinue nursing or to discontinue combination  
1158 REBETOL/INTRON A therapy, taking into account the importance of the therapy to the  
1159 mother.

1160 **Pediatric Use** Safety and effectiveness in pediatric patients below the age of 18 years have  
1161 not been established.

1162 **Geriatric Use** Clinical studies of REBETOL Combination Therapy did not include  
1163 sufficient numbers of subjects aged 65 and over to determine if they respond differently from  
1164 younger subjects. In clinical trials, elderly subjects had a higher frequency of anemia (67%)  
1165 than did younger patients (28%) (see **WARNINGS**).

1166 In general, REBETOL (ribavirin) should be administered to elderly patients  
1167 cautiously, starting at the lower end of the dosing range, reflecting the greater frequency of  
1168 decreased renal, hepatic and/or cardiac function, and of concomitant disease or other drug  
1169 therapy.

1170 REBETOL (ribavirin) is known to be substantially excreted by the kidney, and the  
1171 risk of adverse reactions to ribavirin may be greater in patients with impaired renal function.  
1172 Because elderly patients often have decreased renal function, care should be taken in dose  
1173 selection. Renal function should be monitored and dosage adjustments of ribavirin should be  
1174 made accordingly (see **DOSAGE AND ADMINISTRATION: Guidelines for Dose**  
1175 **Modifications**). REBETOL (ribavirin) should be used in elderly patients with creatinine  
1176 clearance <50 mL/min only if the potential benefit outweighs the risk, and should not be  
1177 administered to patients with creatinine clearance <30 mL/min (see **WARNINGS**).

1178 REBETOL Combination Therapy should be used very cautiously in elderly patients  
1179 with a history of psychiatric disorders (see **WARNINGS**).

1180

1181

1182

### ADVERSE REACTIONS

1183 The safety of combination REBETOL/INTRON A therapy was evaluated in controlled trials  
1184 of 1010 HCV-infected adults who were previously untreated with interferon therapy and were  
1185 subsequently treated for 24 or 48 weeks with combination REBETOL/INTRON A therapy  
1186 and in 173 HCV-infected patients who had relapsed after interferon therapy and were  
1187 subsequently treated for 24 weeks with combination REBETOL/INTRON A therapy. (See  
1188 **Description of Clinical Studies**.) Overall, 19% and 6% of previously untreated and relapse  
1189 patients, respectively, discontinued therapy due to adverse events in the combination arms  
1190 compared to 13% and 3% in the interferon arms.

1191 **The primary toxicity of ribavirin is hemolytic anemia. Reductions in**  
1192 **hemoglobin levels occurred within the first 1-2 weeks of therapy (see WARNINGS).**

1193 **Cardiac and pulmonary events associated with anemia occurred in approximately 10%**  
1194 **of patients treated with REBETOL/INTRON A therapy. (See WARNINGS.)**

1195       The most common psychiatric events occurring in US studies of previously untreated  
1196 and relapse patients treated with REBETOL/INTRON A therapy, respectively, were insomnia  
1197 (39%, 26%), depression (34%, 23%), and irritability (27%, 25%). Suicidal behavior  
1198 (ideation, attempts, and suicides) occurred in 1% of patients. (See WARNINGS.). In  
1199 addition hearing disorders (tinnitus and hearing loss) and vertigo have occurred in patients  
1200 treated with combination REBETOL/INTRON A therapy. Selected treatment-emergent  
1201 adverse events that occurred in the US studies with  $\geq 5\%$  incidence are provided in **TABLE 4**  
1202 by treatment group. In general, the selected treatment-emergent adverse events reported with  
1203 lower incidence in the international studies as compared to the US studies with the exception  
1204 of asthenia, influenza-like symptoms, nervousness, and pruritus.

1205

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

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



1208

1209 **Laboratory Values**

1210 Changes in selected hematologic values (hemoglobin, white blood cells, neutrophils, and  
1211 platelets) during combination REBETOL/INTRON A treatment are described below (see  
1212 TABLE 5).

1213

1214 *Hemoglobin* Hemoglobin decreases among patients on combination therapy began at Week  
1215 1, with stabilization by Week 4. In previously untreated patients treated for 48 weeks the  
1216 mean maximum decrease from baseline was 3.1 g/dL in the US study and 2.9 g/dL in the  
1217 International study. In relapse patients the mean maximum decrease from baseline was 2.8  
1218 g/dL in the US study and 2.6 g/dL in the International study. Hemoglobin values returned to  
1219 pretreatment levels within 4 - 8 weeks of cessation of therapy in most patients.

1220

1221 *Neutrophils* There were decreases in neutrophil counts in both the combination  
1222 REBETOL/INTRON A and INTRON A plus placebo dose groups. In previously untreated  
1223 patients treated for 48 weeks the mean maximum decrease in neutrophil count in the US  
1224 study was  $1.3 \times 10^9$  /L and in the International study was  $1.5 \times 10^9$  /L. In relapse patients the  
1225 mean maximum decrease in neutrophil count in the US study was  $1.3 \times 10^9$  /L and in the  
1226 International study was  $1.6 \times 10^9$  /L. Neutrophil counts returned to pretreatment levels within  
1227 4 weeks of cessation of therapy in most patients.

1228

1229 *Platelets* In both previously untreated and relapse patients mean platelet counts generally  
1230 remained in the normal range in all treatment groups, however, mean platelet counts were  
1231 10% to 15% lower in the INTRON A plus placebo group than the REBETOL/INTRON A  
1232 group. Mean platelet counts returned to baseline levels within 4 weeks after treatment  
1233 discontinuation.

1234

1235 *Thyroid Function* Of patients who entered the previously untreated (24 and 48 week  
1236 treatment) and relapse (24 week treatment) studies without thyroid abnormalities,  
1237 approximately 3% to 6% and 1% to 2%, respectively, developed thyroid abnormalities  
1238 requiring clinical intervention.

1239

1240 *Bilirubin and Uric Acid* Increases in both bilirubin and uric acid, associated with hemolysis,  
1241 were noted in clinical trials. Most were moderate biochemical changes and were reversed  
1242 within 4 weeks after treatment discontinuation. This observation occurs most frequently in  
1243 patients with a previous diagnosis of Gilbert's syndrome. This has not been associated with  
1244 hepatic dysfunction or clinical morbidity.

1245

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

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

1246

1247

**OVERDOSAGE**

1248

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.

1249

1250

1251

1252

1253

**DOSAGE AND ADMINISTRATION**

1254

1255

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

1256

1257

1258

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

1259

1260

The recommended duration of treatment for patients previously untreated with

1261 interferon is 24 to 48 weeks. The duration of treatment should be individualized to the  
1262 patient depending on baseline disease characteristics, response to therapy, and tolerability of  
1263 the regimen (see **Description of Clinical Studies** and **ADVERSE REACTIONS**). After 24  
1264 weeks of treatment virologic response should be assessed. Treatment discontinuation should  
1265 be considered in any patient who has not achieved an HCV-RNA below the limit of detection  
1266 of the assay by 24 weeks. There are no safety and efficacy data on treatment for longer than  
1267 48 weeks in the previously untreated patient population.

1268           In patients who relapse following interferon therapy, the recommended duration of  
1269 treatment is 24 weeks. There are no safety and efficacy data on treatment for longer than 24  
1270 weeks in the relapse patient population.

1271

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.

1272 REBETOL may be administered without regard to food, but should be administered  
1273 in a consistent manner. (See **CLINICAL PHARMACOLOGY**.)

1274

1275 *Dose Modifications (TABLE 7)*

1276 In clinical trials, approximately 26% of patients required modification of their dose of  
1277 REBETOL Capsules, INTRON A Injection, or both agents. If severe adverse reactions or  
1278 laboratory abnormalities develop during combination REBETOL/INTRON A therapy the  
1279 dose should be modified, or discontinued if appropriate, until the adverse reactions abate. If  
1280 intolerance persists after dose adjustment, REBETOL/INTRON A therapy should be  
1281 discontinued.

1282 REBETOL/INTRON A therapy should be administered with caution to patients with  
1283 pre-existing cardiac disease. Patients should be assessed before commencement of therapy  
1284 and should be appropriately monitored during therapy. If there is any deterioration of  
1285 cardiovascular status, therapy should be stopped. (See **WARNINGS**.)

1286 For patients with a history of stable cardiovascular disease, a permanent dose  
1287 reduction is required if the hemoglobin decreases by ≥2 g/dL during any 4-week period. In  
1288 addition, for these cardiac history patients, if the hemoglobin remains <12 g/dL after 4 weeks  
1289 on a reduced dose, the patient should discontinue combination REBETOL/INTRON A  
1290 therapy.

1291 It is recommended that a patient whose hemoglobin level falls below 10 g/dL have  
1292 his/her REBETOL dose reduced to 600 mg daily (1 x 200 mg capsule AM, 2 x 200 mg  
1293 capsules PM). A patient whose hemoglobin level falls below 8.5 g/dL should be permanently  
1294 discontinued from REBETOL/INTRON A therapy. (See **WARNINGS**.)

1295 It is recommended that a patient who experiences moderate depression (persistent low  
1296 mood, loss of interest, poor self image, and/or hopelessness) have his/her INTRON A dose  
1297 temporarily reduced and/or be considered for medical therapy. A patient experiencing severe  
1298 depression or suicidal ideation/attempt should be discontinued from REBETOL/INTRON A  
1299 therapy and followed closely with appropriate medical management. (See **WARNINGS**.)

1300

1301

1302

**TABLE 7. Guidelines for Dose Modifications**

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

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

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

1303

1304 Administration of INTRON A Injection

1305 At the discretion of the physician, the patient may self-administer the INTRON A. (See illustrated  
1306 **MEDICATION GUIDE** for instructions.)

1307 The Intron A Injection is supplied as a clear and colorless solution. The appropriate  
1308 INTRON A dose should be withdrawn from the vial or set on the multidose pen and injected  
1309 subcutaneously. After administration of INTRON A Injection, it is essential to follow the  
1310 procedure for proper disposal of syringes and needles. (See **MEDICATION GUIDE** for  
1311 detailed instructions.)  
1312

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

1313 †This is a multidose vial which contains a total of 22.8 million IU of interferon alfa-2b,  
1314 recombinant per 3.8 mL in order to provide the delivery of six 0.5-mL doses, each containing  
1315 3 million IU of interferon alfa-2b, recombinant (for a label strength of 18 million IU).

1316 †† This is a multidose pen which contains a total of 22.5 million IU of interferon alfa-2b,  
1317 recombinant per 1.5 mL in order to provide the delivery of six 0.2-mL doses, each containing  
1318 3 million IU of interferon alfa-2b, recombinant (for a label strength of 18 million IU).  
1319

1320 Parenteral drug products should be inspected visually for particulate matter and discoloration  
1321 prior to administration, whenever solution and container permit. INTRON A Injection may be  
1322 administered using either sterilized glass or plastic disposable syringes.

1323 **Stability** INTRON A Injection provided in vials is stable at 35°C (95°F) for up to 7 days and  
1324 at 30°C (86°F) for up to 14 days. INTRON A Injection provided in a multidose pen is stable  
1325 at 30°C (86°F) for up to 2 days. The solution is clear and colorless.  
1326

1327

**HOW SUPPLIED**

1328 REBETOL 200-mg Capsules are white, opaque capsules with REBETOL, 200 mg, and the  
1329 Schering Corporation logo imprinted on the capsule shell; the capsules are packaged in a  
1330 bottle.

1331 INTRON A Injection is a clear, colorless solution packaged in single dose and multidose

1332 vials, and a multidose pen.  
1333 INTRON A Injection and REBETOL Capsules are available in the following combination  
1334 package  
1335 presentations:

1336

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

1337

1338 STORAGE CONDITIONS

1339 **Store the REBETOL Capsules plus INTRON A Injection combination package**  
1340 **refrigerated between 2°C and 8°C (36° and 46° F).**

1341 **When separated, the individual bottle of REBETOL Capsules should be stored**  
1342 **refrigerated between 2° and 8°C (36° and 46°F) or at 25°C (77°F); excursions are**  
1343 **permitted between 15° and 30°C (59° and 86°F).**

1344 **When separated, the individual vials of INTRON A Injection and the INTRON**  
1345 **A Multidose Pen should be stored refrigerated between 2° and 8°C (36° and 46°F).**  
1346



1347 Schering Corporation  
1348 Kenilworth, NJ 07033 USA

1349  
1350 U.S. Patents 4,530,901 & 4,211,771  
1351 Copyright © 1998, Schering Corporation. All rights reserved.

1352  
1353 B-

1354  
1355 Labeling History-Revisions from RIC21617679 to Proposed Labeling

- 1356 1. Addition of Bone Marrow Toxicity Warning in WARNINGS section (following  
1357 Psychiatric Warning) as submitted on January 29, 2001 for S-006(original  
1358 communication received via fax dated November 8, 2000). Line 282-288.
- 1359 2. REVISION of “Dose Modification” to “Dose Modifications” (addition of “s” at end of  
1360 “Modification”) in the bone marrow toxicity warning for consistency to title of Table 7.  
1361 Line 288.
- 1362 3. Bolding “Guidelines for Dose Modifications” of bone marrow toxicity warning consistent  
1363 with geriatric use formatting and other section references in approved labeling. Line 288.
- 1364 4. Addition of Geriatric Use information in PRECAUTIONS section as submitted on  
1365 January 29, 2001 for S-007. Line 481-498
- 1366 5. REVISION of “DOSAGE ADJUSTMENT” (submitted on January 29, 2001) to “DOSE  
1367 MODIFICATIONS” in Geriatric Use section on lines 493-494 for consistency to title of  
1368 Table 7 of approved package insert and proposed bone marrow toxicity warning.
- 1369 6. Revision of hearing disorder adverse event language in ADVERSE EVENTS section to  
1370 specify tinnitus and hearing loss as submitted on January 29, 2001 for S-006 (original  
1371 communication received via fax dated November 8, 2000). Line 518-524.

1372

1373

1374

/s/

-----  
Debra Birnkrant

3/13/01 04:05:37 PM

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

**DEPARTMENT OF HEALTH AND HUMAN SERVICES**

Public Health Service  
Food and Drug Administration  
Rockville, MD 20857

**DATE:** February 2, 2001

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

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

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

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

This submission contains proposed Changes Being Effected to include information about aplastic anemia to the WARNINGS section, and vertigo and hearing disorder to the ADVERSE REACTIONS section of the Rebetron™ Combination Therapy (Intron A/Rebetol [ribavirin]) label. To support revisions to the label, the sponsor submitted 15 Drug Safety and Surveillance reports of aplastic anemia and 79 reports of hearing disorders/vertigo.

- **Aplastic Anemia**

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

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

- **Hearing Disorders and Vertigo**

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

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

## ASSESSMENT

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

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

## LABELING REVIEW

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

### **Bone Marrow Toxicity**

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

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

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

**RECOMMENDED REGULATORY ACTION**

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

/s/

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

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

**DEPARTMENT OF HEALTH AND HUMAN SERVICES**

Public Health Service  
Food and Drug Administration  
Rockville, MD 20857

**DATE:** February 2, 2001

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

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

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

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

**BACKGROUND**

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

To support this revision the applicant submitted the following data:

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

**REBETRON clinical trials database**

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

## **Post marketing reports**

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

## **Literature search**

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

## **ASSESSMENT**

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

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

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

## **LABELING REVIEW**

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

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

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

REBETOL (ribavirin) is known to be substantially excreted by the kidney, and the risk of        reactions to ribavirin may be greater in patients with impaired renal function. Because elderly patients often have decreased renal function, care should be taken in dose selection. Renal function should be monitored and dosage adjustments of ribavirin should be made accordingly (see **DOSAGE AND ADMINISTRATION: Guidelines for Dosage Adjustment**). REBETOL (ribavirin) should be used in elderly patients with creatinine clearance <50 mL/min only if the potential benefit outweighs the risk, and should not be administered to patients with creatinine clearance <30 mL/min (see **WARNINGS**).

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

#### **RECOMMENDED REGULATORY ACTION**

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

/s/

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

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



**MEMORANDUM OF TELEPHONE FACSIMILE CORRESPONDENCE**

**Date:** January 17, 2001

**To:** Rachel Steiner, Regulatory Affairs Associate  
Schering Corporation

**Address:** Galloping Hill Road  
Kenilworth, NJ 07033

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

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

**NDA** NDA 20-903, REBETRON™ COMBINATION THERAPY

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

---

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

- **Bone Marrow Toxicity**

\_\_\_\_\_

\_\_\_\_\_

- **Geriatric Use**

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

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

REBETOL (ribavirin) is known to be substantially excreted by the kidney, and the risk of adverse reactions to ribavirin may be greater in patients with impaired renal function. Because elderly patients often have decreased renal function, care should be taken in dose

selection. Renal function should be monitored and dosage adjustments of ribavirin should be made accordingly (see **DOSAGE AND ADMINISTRATION: Guidelines for Dosage Adjustment**). REBETOL (ribavirin) should be used in elderly patients with creatinine clearance <50 mL/min only if the potential benefit outweighs the risk, and should not be administered to patients with creatinine clearance <30 mL/min (see **WARNINGS**).

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

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

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

---

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

/s/

-----  
Destry Sullivan  
1/19/01 11:29:09 AM  
CSO

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

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



**MEMORANDUM OF TELEPHONE FACSIMILE CORRESPONDENCE**

**Date:** November 8, 2000

**To:** Rachel Steiner, Regulatory Affairs Associate  
Schering Corporation

**Address:** Galloping Hill Road  
Kenilworth, NJ 07033

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

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

**IND** NDA 20-903, REBETRON™

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

---

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

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

**BONE MARROW TOXICITY**

\_\_\_\_\_

\_\_\_\_\_

**4. III ADVERSE EVENTS SECTION.**

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

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

---

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

/s/

-----  
Destry Sullivan  
11/9/00 03:20:51 PM  
CSO

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

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



## Consumer Safety Officer Labeling Review

**NDA:** 20-903/S-006, S007

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

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

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

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

### Background:

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

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

### Label Revisions, S-006:

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

#### **Bone marrow toxicity:**

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

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

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

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

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

---

**Label Revisions, S-007:**

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

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

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

REBETOL (ribavirin) is known to be substantially excreted by the kidney, and the risk of adverse reactions to ribavirin may be greater in patients with impaired renal function. Because elderly patients often have decreased renal function, care should be taken in dose selection. Renal function should be monitored and dosage adjustments of ribavirin should be made accordingly (see **DOSAGE AND ADMINISTRATION: Guidelines for Dose Modifications**). REBETOL (ribavirin) should be used in elderly patients with creatinine clearance <50 mL/min only if the potential benefit outweighs the risk, and should not be administered to patients with creatinine clearance <30 mL/min (see **WARNINGS**).

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

**Conclusions/Recommendations:**

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

---

Destry M. Sullivan, MS

Regulatory Project Manager

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

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

---



**MEMORANDUM OF TELEPHONE FACSIMILE CORRESPONDENCE**

**Date:** November 15, 2000

**To:** Rachel Steiner, Regulatory Affairs Associate  
Schering Corporation

**Address:** Galloping Hill Road  
Kenilworth, NJ 07033

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

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

**IND** NDA 20-903, REBETRON™

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

---

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

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

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

---

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

/s/

-----  
Destry Sullivan  
11/16/00 11:44:23 AM  
CSO

Schering Geriatric labeling fax for Rebetrone

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