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**PRODUCT
INFORMATION**

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

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CONTRAINDICATIONS AND WARNINGS

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

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

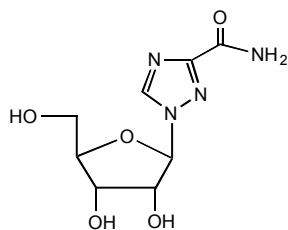
Alpha interferons, including INTRON® A, cause or aggravate fatal or life-threatening neuropsychiatric, autoimmune, ischemic, and infectious disorders. Patients should be monitored closely with periodic clinical and laboratory evaluations. Patients with persistently severe or worsening signs or symptoms of these conditions should be withdrawn from therapy.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

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DESCRIPTION

REBETOL®

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



Ribavirin is a white, crystalline powder. It is freely soluble in water and slightly soluble in anhydrous alcohol. The empirical formula is C₈H₁₂N₄O₅ and the molecular weight is 244.21.

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

45 monohydrate, croscarmellose sodium, and magnesium stearate. The capsule shell consists of
46 gelatin, sodium lauryl sulfate, silicon dioxide, and titanium dioxide. The capsule is printed with
47 edible blue pharmaceutical ink which is made of shellac, anhydrous ethyl alcohol, isopropyl
48 alcohol, n-butyl alcohol, propylene glycol, ammonium hydroxide, and FD&C Blue #2 aluminum
49 lake.

50

51 **INTRON[®] A**

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

54 Interferon alfa-2b, recombinant has been classified as an alpha interferon and is a water-
55 soluble protein composed of 165 amino acids with a molecular weight of 19,271 daltons
56 produced by recombinant DNA techniques. It is obtained from the bacterial fermentation of a
57 strain of *Escherichia coli* bearing a genetically engineered plasmid containing an interferon alfa-
58 2b gene from human leukocytes. The fermentation is carried out in a defined nutrient medium
59 containing the antibiotic tetracycline hydrochloride at a concentration of 5 to 10 mg/L; the
60 presence of this antibiotic is not detectable in the final product.

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

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

75

76 **Mechanism of Action**

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

79

80 **CLINICAL PHARMACOLOGY**

81 **Pharmacokinetics**

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

90

91 *Ribavirin* Single- and multiple-dose pharmacokinetic properties in adults with chronic hepatitis
92 C are summarized in **TABLE 1**. Ribavirin was rapidly and extensively absorbed following oral

93 administration. However, due to first-pass metabolism, the absolute bioavailability averaged
 94 64% (44%). There was a linear relationship between dose and AUC_{tf} (AUC from time zero to
 95 last measurable concentration) following single doses of 200-1200 mg ribavirin. The relationship
 96 between dose and C_{max} was curvilinear, tending to asymptote above single doses of 400-600 mg.

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

102

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

108

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

112

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

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

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 ¹⁴C labeled ribavirin; N = 5

116 †† N = 6

117 *** N = 11

118

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

123 Ribavirin has two pathways of metabolism: (i) a reversible phosphorylation pathway in
 124 nucleated cells; and (ii) a degradative pathway involving deribosylation and amide hydrolysis to
 125 yield a triazole carboxylic acid metabolite. Ribavirin and its triazole carboxamide and triazole

126 carboxylic acid metabolites are excreted renally. After oral administration of 600 mg of ¹⁴C-
127 ribavirin, approximately 61% and 12% of the radioactivity was eliminated in the urine and feces,
128 respectively, in 336 hours. Unchanged ribavirin accounted for 17% of the administered dose.

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

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

134

135 ***Special Populations***

136 ***Renal Dysfunction*** The pharmacokinetics of ribavirin were assessed after administration of a
137 single oral dose (400 mg) of ribavirin to subjects with varying degrees of renal dysfunction. The
138 mean AUC_{0-t} value was threefold greater in subjects with creatinine clearance values between 10
139 to 30 mL/min when compared to control subjects (creatinine clearance >90 mL/min). This
140 appears to be due to reduction of apparent clearance in these patients. Ribavirin was not
141 removed by hemodialysis. REBETOL is not recommended for patients with severe renal
142 impairment (see **WARNINGS**).

143

144 ***Hepatic Dysfunction*** The effect of hepatic dysfunction was assessed after a single oral dose of
145 ribavirin (600 mg). The mean AUC_{0-t} values were not significantly different in subjects with
146 mild, moderate, or severe hepatic dysfunction (Child-Pugh Classification A, B, or C), when
147 compared to control subjects. However, the mean C_{max} values increased with severity of hepatic
148 dysfunction and was twofold greater in subjects with severe hepatic dysfunction when compared
149 to control subjects.

150

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

153

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

154

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-dose
159 study of eighteen male and eighteen female subjects.

160

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

162

163 **INDICATIONS AND USAGE**

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

168

169 **Description of Clinical Studies**

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

181

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

183

TABLE 3. Virologic and Histologic Responses: Previously Untreated Patients*							
	US Study				International Study		
	24 weeks of treatment		48 weeks of treatment		24 weeks of treatment	48 weeks of treatment	
	INTRON A plus REBETOL (N=228)	INTRO N A plus Placebo (N=231)	INTRON A plus REBETOL (N=228)	INTRO N A plus Placebo (N=225)	INTRON A plus REBETOL (N=265)	INTRON A plus REBETOL (N=268)	INTRO N A plus Placebo (N=266)
Virologic Response							
-Responder ¹	65(29)	13(6)	85(37)	27(12)	86(32)	113(42)	46(17)
- Nonresponder	147(64)	194(84)	110(48)	168(75)	158(60)	120(45)	196(74)
-Missing Data	16(7)	24(10)	33(14)	30(13)	21(8)	35(13)	24(9)
Histologic Response							
-Improvement ²	102(45)	77(33)	96(42)	65(29)	103(39)	102(38)	69(26)
-No improvement	77(34)	99(43)	61(27)	93(41)	85(32)	58(22)	111(41)
-Missing Data	49(21)	55(24)	71(31)	67(30)	77(29)	108(40)	86(32)

184 * Number (%) of Patients.

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

187 ² Defined as posttreatment (end of follow-up) minus pretreatment liver biopsy Knodell
 188 HAI score (I+II+III) improvement of ≥ 2 points.

189

190 Of patients who had not achieved HCV RNA below the limit of detection of the research based
 191 assay by week 24 of REBETOL/INTRON A treatment, less than 5% responded to an additional
 192 24 weeks of combination treatment.

193

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

200

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

211 Study results are summarized in **TABLE 4**.

212

213

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

214 * Number (%) of Patients.

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

217 ² Defined as posttreatment (end of follow-up) minus pretreatment liver biopsy Knodell HAI
 218 score (I+II+III) improvement of ≥ 2 points.

219

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

222

223 **CONTRAINDICATIONS**

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

237

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

241

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

244

245 **WARNINGS**

246 **Pregnancy**

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

249

250 **Anemia**

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

260

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

268

269 Similarly, patients with hemoglobinopathies (eg, thalassemia, sickle-cell anemia) should
270 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. Rebetol/Intron**
277 **A therapy should be used with extreme caution in patients with a history of pre-existing**
278 **psychiatric disorders, and all patients should be carefully monitored for evidence of**
279 **depression and other psychiatric symptoms. Suspension of Rebetol/Intron A therapy**
280 **should be considered if psychiatric intervention and/or dose reduction is unsuccessful in**
281 **controlling psychiatric symptoms. In severe cases, therapy should be stopped immediately**
282 **and psychiatric intervention sought. (See ADVERSE REACTIONS.)**

283
284 **Pulmonary**

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

290
291 **Other**

292 •REBETOL Capsule monotherapy is not effective for the treatment of chronic hepatitis C and
293 should not be used for this indication.

294 •Fatal and nonfatal pancreatitis has been observed in patients treated with REBETOL/INTRON
295 A therapy. REBETOL/INTRON A therapy should be suspended in patients with signs and
296 symptoms of pancreatitis and discontinued in patients with confirmed pancreatitis.

297 •Combination REBETOL/INTRON A therapy should be used with caution in patients with
298 creatinine clearance <50 mL/min.

299 •Diabetes mellitus and hyperglycemia have been observed in patients treated with INTRON A.

300 •Ophthalmologic disorders have been reported with treatment with alpha interferons (including
301 INTRON A therapy). Investigators using alpha interferons have reported the occurrence of
302 retinal hemorrhages, cotton wool spots, and retinal artery or vein obstruction in rare instances.
303 Any patient complaining of loss of visual acuity or visual field should have an eye examination.
304 Because these ocular events may occur in conjunction with other disease states, a visual exam
305 prior to initiation of combination REBETOL/INTRON A therapy is recommended in patients
306 with diabetes mellitus or hypertension.

307 •Acute serious hypersensitivity reactions (eg, urticaria, angioedema, bronchoconstriction,
308 anaphylaxis) have been observed in INTRON A-treated patients; if such an acute reaction
309 develops, combination REBETOL/INTRON A therapy should be discontinued immediately and
310 appropriate medical therapy instituted.

311 •Combination REBETOL/INTRON A therapy should be discontinued for patients developing
312 thyroid abnormalities during treatment whose thyroid function cannot be controlled by
313 medication.

314

315 **PRECAUTIONS**

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

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

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

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

328 There is no information regarding the use of REBETOL Capsules with other interferons.
329

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

340 Patients (male and female) should be advised to notify the physician immediately in the event of
341 a pregnancy. (See **CONTRAINDICATIONS**.)

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

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

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

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

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

367
368 **Laboratory Tests** The following laboratory tests are recommended for all patients on
369 combination REBETOL/INTRON A therapy, prior to beginning treatment and then periodically
370 thereafter.

- 371 •Standard hematologic tests - including hemoglobin (pretreatment, week 2 and week
372 4 of therapy, and as clinically appropriate [see **WARNINGS**]), complete and
373 differential white blood cell counts, and platelet count.
- 374 •Blood chemistries - liver function tests and TSH.
- 375 •Pregnancy - including monthly monitoring for females of childbearing potential.

376
377 **Carcinogenesis and Mutagenesis** Carcinogenicity studies with interferon alfa-2b, recombinant
378 have not been performed because neutralizing activity appears in the serum after multiple dosing
379 in all of the animal species tested.

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

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

393
394 **Impairment of Fertility** No reproductive toxicology studies have been performed using
395 interferon alfa-2b, recombinant in combination with ribavirin. However, evidence provided
396 below for interferon alfa-2b, recombinant and ribavirin when administered alone indicate that
397 both agents have adverse effects on reproduction. It should be assumed that the effects produced
398 by either agent alone will also be caused by the combination of the two agents. Interferons may
399 impair human fertility. In studies of interferon alfa-2b recombinant administration in nonhuman
400 primates, menstrual cycle abnormalities have been observed. Decreases in serum estradiol and
401 progesterone concentrations have been reported in females treated with human leukocyte
402 interferon. In addition, ribavirin demonstrated significant embryocidal and/or teratogenic effects
403 at doses well below the recommended human dose in all animal species in which adequate
404 studies have been conducted.

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

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

413 12.5 mg/kg/day, based on body surface area adjustment for a 60 kg adult; 0.1 - 0.8 X the
414 maximum human 24-hour dose of ribavirin) administered for 3 or 6 months, abnormalities in
415 sperm occurred. Upon cessation of treatment, essentially total recovery from ribavirin-induced
416 testicular toxicity was apparent within 1 or 2 spermatogenesis cycles.

417

418 **Animal Toxicology** Long-term studies in the mouse and rat (18 - 24 months; doses of 20 - 75
419 and 10 - 40 mg/kg/day, respectively [estimated human equivalent doses of 1.67 - 6.25 and 1.43 -
420 5.71 mg/kg/day, respectively, based on body surface area adjustment for a 60 kg adult;
421 approximately 0.1 - 0.4 X the maximum human 24-hour dose of ribavirin]) have demonstrated a
422 relationship between chronic ribavirin exposure and increased incidences of vascular lesions
423 (microscopic hemorrhages) in mice. In rats, retinal degeneration occurred in controls, but the
424 incidence was increased in ribavirin-treated rats.

425

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

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

442 *Treatment and Posttreatment: Potential Risk to the Fetus* Ribavirin is known to accumulate in
443 intracellular components from where it is cleared very slowly. It is not known whether ribavirin
444 contained in sperm will exert a potential teratogenic effect upon fertilization of the ova. In a
445 study in rats, it was concluded that dominant lethality was not induced by ribavirin at doses up to
446 200 mg/kg for 5 days (estimated human equivalent doses of 7.14 - 28.6 mg/kg, based on body
447 surface area adjustment for a 60 kg adult; up to 1.7 X the maximum recommended human dose
448 of ribavirin). However, because of the potential human teratogenic effects of ribavirin, male
449 patients should be advised to take every precaution to avoid risk of pregnancy for their female
450 partners.

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

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

458 If pregnancy occurs in a patient or partner of a patient during treatment or during the 6
459 months after treatment cessation, physicians are encouraged to report such cases by calling (800)
460 727-7064.

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

466 **Pediatric Use**

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

471

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

480

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

485

486 **ADVERSE REACTIONS**

487 The safety of combination REBETOL/INTRON A therapy was evaluated in controlled trials of
488 1010 HCV-infected adults who were previously untreated with interferon therapy and were
489 subsequently treated for 24 or 48 weeks with combination REBETOL/INTRON A therapy and in
490 173 HCV-infected patients who had relapsed after interferon therapy and were subsequently
491 treated for 24 weeks with combination REBETOL/INTRON A therapy. (See **Description of**
492 **Clinical Studies.**) Overall, 19% and 6% of previously untreated and relapse patients,
493 respectively, discontinued therapy due to adverse events in the combination arms compared to
494 13% and 3% in the interferon arms.

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

499

500 The most common psychiatric events occurring in US studies of previously untreated and
501 relapse patients treated with REBETOL/INTRON A therapy, respectively, were insomnia (39%,
502 26%), depression (34%, 23%), and irritability (27%, 25%). Suicidal behavior (ideation,
503 attempts, and suicides) occurred in 1% of patients. (See **WARNINGS.**) In addition, the
504 following spontaneous adverse events have been reported during the marketing surveillance of
505 REBETOL/INTRON A therapy: hearing disorder and vertigo. Very rarely, combination
506 REBETOL/INTRON A therapy may be associated with aplastic anemia.

506

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

509 to the US studies with the exception of asthenia, influenza-like symptoms, nervousness, and
510 pruritus.
511

TABLE 5. 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)
Application Site Disorders						
injection site inflammation	13	10	12	14	6	8
injection site reaction	7	9	8	9	5	3
Body as a Whole - General Disorders						
headache	63	63	66	67	66	68
fatigue	68	62	70	72	60	53
rigors	40	32	42	39	43	37
fever	37	35	41	40	32	36
influenza-like symptoms	14	18	18	20	13	13
asthenia	9	4	9	9	10	4
chest pain	5	4	9	8	6	7
Central & Peripheral Nervous System Disorders						
dizziness	17	15	23	19	26	21
Gastrointestinal System Disorders						
nausea	38	35	46	33	47	33
anorexia	27	16	25	19	21	14
dyspepsia	14	6	16	9	16	9
vomiting	11	10	9	13	12	8
Musculoskeletal System Disorders						
myalgia	61	57	64	63	61	58
arthralgia	30	27	33	36	29	29
musculoskeletal pain	20	26	28	32	22	28
Psychiatric Disorders						
insomnia	39	27	39	30	26	25
irritability	23	19	32	27	25	20

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

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

514

515 **Laboratory Values**

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

519

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

526

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

534

535 *Platelets* In both previously untreated and relapse patients mean platelet counts generally
536 remained in the normal range in all treatment groups, however, mean platelet counts were 10% to
537 15% lower in the INTRON A plus placebo group than the REBETOL/INTRON A group. Mean
538 platelet counts returned to baseline levels within 4 weeks after treatment discontinuation.

539

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

543

544 *Bilirubin and Uric Acid* Increases in both bilirubin and uric acid, associated with hemolysis,
545 were noted in clinical trials. Most were moderate biochemical changes and were reversed within
546 4 weeks after treatment discontinuation. This observation occurs most frequently in patients with
547 a previous diagnosis of Gilbert's syndrome. This has not been associated with hepatic
548 dysfunction or clinical morbidity.

549

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

	Percentage of Patients					
	US Previously Untreated Study				US Relapse Study	
	24 weeks of treatment		48 weeks of treatment		24 weeks of treatment	
	INTRO N A plus REBETOL (N=228)	INTRON A plus Placebo (N=231)	INTRON A plus REBETOL (N=228)	INTRON A plus Placebo (N=225)	INTRON A plus REBETOL (N=77)	INTRON A plus Placebo (N=76)
Hemoglobin (g/dL)						
9.5-10.9	24	1	32	1	21	3
8.0-9.4	5	0	4	0	4	0
6.5-7.9	0	0	0	0.4	0	0
<6.5	0	0	0	0	0	0
Leukocytes (x10⁹/L)						
2.0-2.9	40	20	38	23	45	26
1.5-1.9	4	1	9	2	5	3
1.0-1.4	0.9	0	2	0	0	0
<1.0	0	0	0	0	0	0
Neutrophils (x10⁹/L)						
1.0-1.49	30	32	31	44	42	34
0.75-0.99	14	15	14	11	16	18
0.5-0.74	9	9	14	7	8	4
<0.5	11	8	11	5	5	8
Platelets (x10⁹/L)						
70-99	9	11	11	14	6	12
50-69	2	3	2	3	0	5
30-49	0	0.4	0	0.4	0	0
<30	0.9	0	1	0.9	0	0
Total Bilirubin (mg/dL)						

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

550

551 **OVERDOSAGE**

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

557

558 **DOSAGE AND ADMINISTRATION**

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

562

563 **Adults**

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

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

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

577

TABLE 7. Recommended Adult Dosing		
Body weight	REBETOL Capsules	INTRON A Injection
≤ 75 kg	2 x 200 mg capsules AM, 3 x 200 mg capsules PM daily p.o.	3 million IU 3 times weekly s.c.
> 75 kg	3 x 200 mg capsules AM, 3 x 200 mg capsules PM daily p.o.	3 million IU 3 times weekly s.c.

578

579

580 **Pediatrics**

581

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

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

586

587

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

590

591 *Dose Modifications (TABLE 9)*

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

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

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

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

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

615

TABLE 9. Guidelines for Dose Modifications

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

*Study medication to be dose reduced is shown in parenthesis

616

617 Administration of INTRON A Injection

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

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

625

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

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

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

632

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

636 *Stability* INTRON A Injection provided in vials is stable at 35°C (95°F) for up to 7 days and at
 637 30°C (86°F) for up to 14 days. INTRON A Injection provided in a multidose pen is stable at
 638 30°C (86°F) for up to 2 days. The solution is clear and colorless.

639

640 **HOW SUPPLIED**

641 REBETOL 200-mg Capsules are white, opaque capsules with REBETOL, 200 mg, and the
 642 Schering Corporation logo imprinted on the capsule shell; the capsules are packaged in a bottle.
 643 INTRON A Injection is a clear, colorless solution packaged in single dose and multidose vials,
 644 and a multidose pen.

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

647

	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)

648

649

STORAGE CONDITIONS

650

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

651

652

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

653

654

655

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

656

657



Schering Corporation

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Kenilworth, NJ 07033 USA

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

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MEDICATION GUIDE

REBETRON

Combination Therapy

containing

REBETOL (ribavirin, USP) Capsules

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

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

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

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

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

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

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



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

What is REBETRON Combination Therapy?

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

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

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

Who should not take REBETRON Combination Therapy?

Do not use these medicines if:

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



breast-feeding.

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

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

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

How should I take REBETRON Combination Therapy?

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

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



table below.

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

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

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

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

What should I avoid while taking REBETRON Combination Therapy?

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

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



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

What are the possible side effects of REBETRON Combination Therapy?

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

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

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

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



- and tarry.
- high fever
- bruising
- bleeding
- decreased vision

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

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

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

What should I know about the hepatitis C virus?

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

How do I Inject INTRON A?

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



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

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

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

Description of your INTRON A multidose pen

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

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



INTRON A Pen

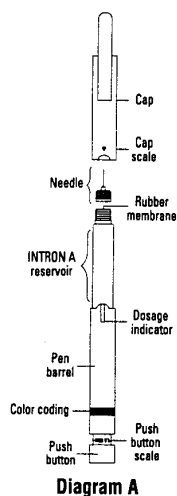


Diagram A

Novofine* Needle Assembly



Diagram B

HOW TO USE YOUR INTRON A Multidose Pen

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

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

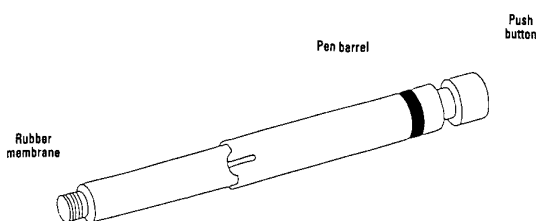


Diagram C

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

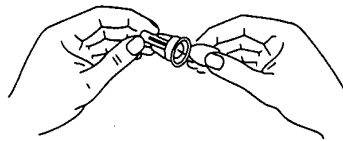


Diagram D

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

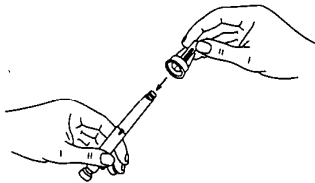


Diagram E

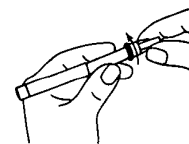


Diagram F

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



outer needle cap for later use.

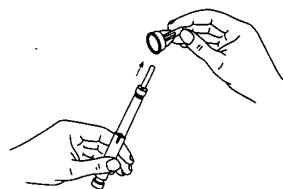


Diagram G

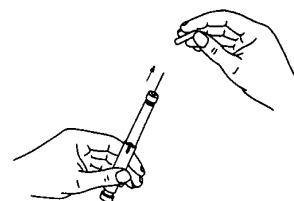


Diagram H

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

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

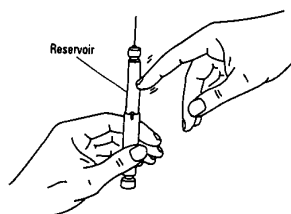


Diagram I

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

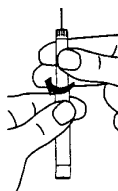


Diagram J

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

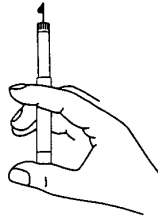


Diagram K

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

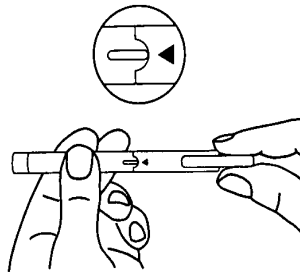


Diagram L

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

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

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

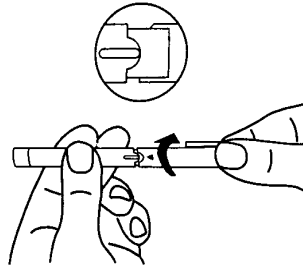


Diagram M

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

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

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

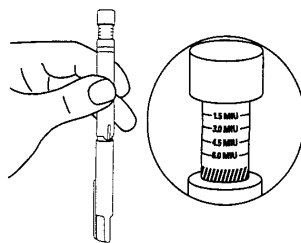


Diagram N



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

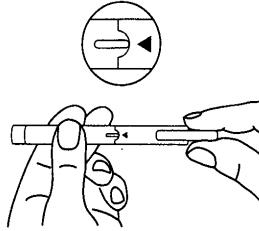


Diagram O

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

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



Diagram P

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



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

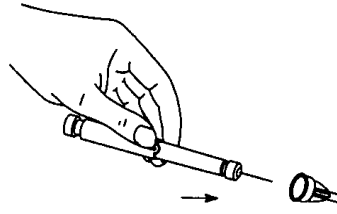


Diagram Q

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

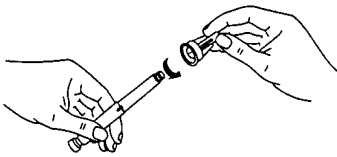


Diagram R

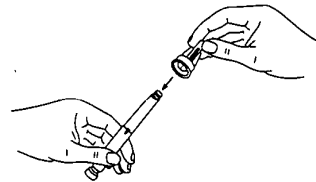


Diagram S

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

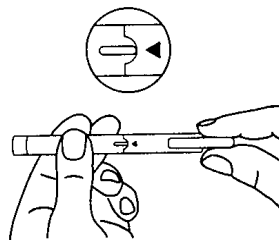


Diagram T

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

How do I store my medications?

STORAGE OF REBETOL CAPSULES

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

STORAGE OF INTRON A INJECTION MULTIDOSE PEN

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

* Novofine is a registered trademark of Novo Nordisk.

General advice about prescription medicines

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

Ingredients:

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

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

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

Manufactured by:

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Kenilworth, NJ 07033 USA

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Rev. X/01

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MEDICATION GUIDE

REBETRON

Combination Therapy
containing

REBETOL (ribavirin, USP) Capsules

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

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

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

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

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

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

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



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

What is REBETRON Combination Therapy?

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

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

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

Who should not take REBETRON Combination Therapy?

Do not use these medicines if:

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



breast-feeding.

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

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

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

How should I take REBETRON Combination Therapy?

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

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



table below.

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

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

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

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

What should I avoid while taking REBETRON Combination Therapy?

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

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



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

What are the possible side effects of REBETRON Combination Therapy?

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

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

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

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



- and tarry.
- high fever
- bruising
- bleeding
- decreased vision

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

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

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

What should I know about the hepatitis C virus?

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

How do I Inject INTRON A?

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



Preparing the INTRON A Dose

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

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

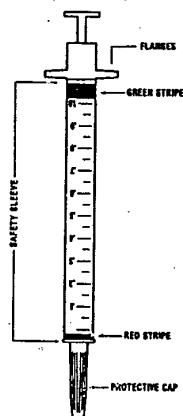


Figure A

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

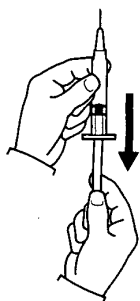


Figure B



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

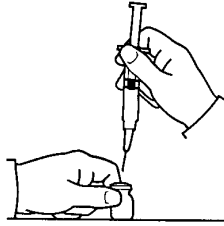


Figure C

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

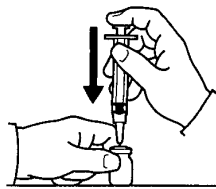


Figure D

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

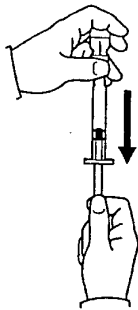


Figure E

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



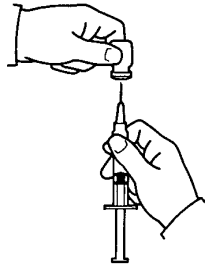


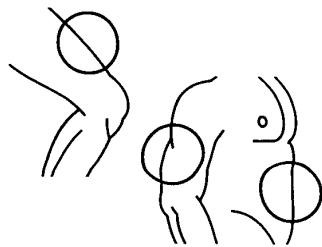
Figure F

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

Subcutaneous (under the skin) Injection

1. Select the site for injection

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

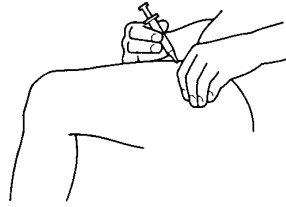


Use an alcohol swab to cleanse the skin where the injection is to be made. Wait for area to dry.

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

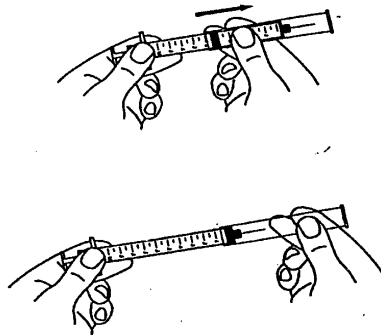


3. With a quick dart-like motion, push the needle about 1/4 inch into the pinched skin at an angle of 45° to 90°.



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

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



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

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



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

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

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

How do I store my medications?

STORAGE OF REBETOL CAPSULES

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

STORAGE OF INTRON A INJECTION VIAL

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

General advice about prescription medicines

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

Ingredients:

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

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

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

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