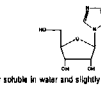
- **Ribavirin monotherapy is not effective for the treatment of chronic hepatitis C virus infection and should not be used alone for this indication. (See WARNING).**
- **The primary toxicity of ribavirin is hemolytic anemia. The anemia associated with ribavirin therapy may result in worsening of cardiac disease that has lead to fatal and nonfatal myocardial infarctions. Patients with a history of significant or unstable cardiac disease should not be treated with ribavirin. (See WARNINGS, ADVERSE REACTIONS, and DOSAGE AND ADMINISTRATION).**
- **Significant teratogenic and/or embryocidal effects have been demonstrated in all animal species exposed to ribavirin. In addition, ribavirin has a multiple dose half-life of 12 days, and so it may persist in nonplasma compartments for as long as 6 months. Therefore, ribavirin therapy is contraindicated in women who are pregnant and in the male partners of women who are pregnant. Extreme care must be taken to avoid pregnancy during therapy and for 6 months after completion of treatment in both female patients and in female partners of male patients who are taking ribavirin therapy. At least two reliable forms of effective contraception must be utilized during treatment and during the 6-month post-treatment follow-up period. (See CONTRAINDICATIONS, WARNINGS, PRECAUTIONS – Information for Patients and Pregnancy Category X).**

DESCRIPTION

Ribavirin

RIBASPHERE™ (Ribavirin capsules) is Three Rivers Pharmaceuticals' brand name for ribavirin, a nucleoside analog. 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 $C_8H_{12}N_4O_5$ and the molecular weight is 244.21.

RIBASPHERE™ (Ribavirin capsules) consist of white pellets in a white, opaque, gelatin capsule. Each capsule contains 200 mg ribavirin and the inactive ingredients: Croscarmellose Sodium, NF; Lactose Monohydrate, NF; Microcrystalline Cellulose, NF; and Povidone, USP. The capsule shell consists of gelatin and titanium dioxide. The capsule is printed horizontally with "rba 200" on both the body and the cap of the capsule using edible, green pharmaceutical ink which is made of Butyl Alcohol, NF; D&C Yellow #10 Aluminum Lake, Dehydrated Alcohol, USP; FD&C Blue #1 Aluminum Lake; Ferric Oxide, NF; Isopropyl Alcohol, USP; Propylene Glycol, USP; Shellac, NF; and Strong Ammonia Solution, NF.

Mechanism of Action

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

CLINICAL PHARMACOLOGY

Pharmacokinetics

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

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

Effect of Food on Absorption of Ribavirin Both AUC_∞ and C_{max} increased by 70% when ribavirin capsules were administered with a high-fat meal (941 kcal, 53.8 g fat, 31.6 g protein, and 57.4 g carbohydrate) in a single-dose pharmacokinetic study. There are insufficient data to address the clinical relevance of these results. Clinical efficacy studies with ribavirin/INTRON A® (interferon alfa-2b, recombinant) were conducted without instructions with respect to food consumption. (See DOSAGE AND ADMINISTRATION.)

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

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

Parameter	Ribavirin Capsules: Single Dose 600 mg Capsules (N=12)	Ribavirin Capsules: Multiple Dose 600 mg BID Capsules (N=12)
T_{max} (hr)	1.7 (46)***	3 (60)
C_{max}	782 (37)	3680 (65)
AUC_∞**	13400 (48)	228000 (25)
$T_{1/2}$ (hr)	43.5 (47)	298 (30)
Apparent Volume of Distribution (L)	2825 (97)	
Apparent Clearance (L/hr)	36.2 (40)	
Absolute Bioavailability	64% (44)††	

* ng/mL
** ng·hr/mL
*** N=11
† data obtained from a single-dose pharmacokinetic study using ^{14}C labeled ribavirin; N=5
†† N=6

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

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

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

No pharmacokinetic interactions were noted between INTRON A injection and ribavirin capsules in a multiple-dose pharmacokinetic study.

Drug Interactions

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

Special Populations

Renal Dysfunction The pharmacokinetics of ribavirin were assessed after administration of a single oral dose (400 mg) of ribavirin to non-HCV-infected subjects with varying degrees of renal dysfunction. The mean AUC_∞ value was three-fold greater in subjects with creatinine clearance values between 10 to 50 mL/min when compared to control subjects (creatinine clearance >80 mL/min). In subjects with creatinine clearance values between 30 to 60 mL/min, AUC_∞ was two-fold greater when compared to control subjects. The increased AUC_∞ appears to be due to reduction of renal and non-renal clearance in these patients. Phase III efficacy trials included subjects with creatinine clearance values > 50 mL/min. The multiple dose pharmacokinetics of ribavirin cannot be accurately predicted in patients with renal dysfunction. Ribavirin is not effectively removed by hemodialysis. Patients with creatinine clearance <50 mL/min should not be treated with RIBASPHERE™ (Ribavirin capsules) (See WARNINGS).

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

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

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

INDICATIONS AND USAGE

RIBASPHERE™ (Ribavirin capsules) are indicated in combination with INTRON A (interferon alfa-2b, recombinant) injection for the treatment of chronic hepatitis C in patients 18 years of age and older with compensated liver disease previously untreated with alpha interferon or in patients 18 years of age and older who have relapsed following alpha interferon therapy.

The safety and efficacy of RIBASPHERE™ (Ribavirin capsules) with non-pegylated interferons other than INTRON A product have not been established.

Description of Clinical Studies

Ribavirin/INTRON A Combination Therapy

Adult Patients

Previously Untreated Patients

Adults with compensated chronic hepatitis C and detectable HCV RNA (assessed by a central laboratory using a research-based RT-PCR assay) who were previously untreated with alpha interferon therapy were enrolled into two multicenter, double-blind trials (US and International) and randomized to receive ribavirin capsules 1200 mg/day (1000 mg/day for patients weighing <75kg) plus INTRON A injection 3 MIU TIW or INTRON A injection plus placebo for 24 or 48 weeks followed by 24 weeks of off-therapy follow-up. The International study did not contain a 24-week INTRON A plus placebo treatment arm. The US study enrolled 912 patients who, at baseline, were 67% male, 89% Caucasian with a mean Knodell HAI score [I+II+III] of 7.5, and 72% genotype 1. The International study, conducted in Europe, Israel, Canada, and Australia, enrolled 799 patients (65% male, 96% Caucasian, mean Knodell score 6.8, and 58% genotype 1).

Study results are summarized in TABLE 2.

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

	US Study				International Study			
	24 weeks of treatment		48 weeks of treatment		24 weeks of treatment		48 weeks of treatment	
	INTRON A plus Ribavirin (N=228)	INTRON A plus Placebo (N=231)	INTRON A plus Ribavirin (N=226)	INTRON A plus Placebo (N=225)	INTRON A plus Ribavirin (N=245)	INTRON A plus Ribavirin (N=258)	INTRON A plus Placebo (N=266)
Virologic Response							
-Responder†	65 (29)	13 (6)	85 (37)	27 (12)	86 (32)	113 (42)	46 (17)
-Nonresponder	147 (54)	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†	102 (45)	77 (33)	96 (42)	65 (29)	103 (39)	102 (38)	89 (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)	66 (32)

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

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

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

Relapse Patients

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

Study results are summarized in TABLE 3.

TABLE 3. Virologic and Histologic Responses: Relapse Patients*

	US Study		International Study	
	INTRON A plus Ribavirin N=77	INTRON A plus Placebo N=76	INTRON A plus Ribavirin N=96	INTRON A plus Placebo N=96
Virologic Response				
-Responder†	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†	38 (49)	27 (36)	49 (51)	30 (31)
-No Improvement	23 (30)	37 (49)	29 (30)	44 (46)
-Missing Data	16 (21)	12 (16)	18 (19)	22 (23)

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

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

CONTRAINDICATIONS

Pregnancy

RIBASPHERE™ (Ribavirin capsules) may cause birth defects and/or death of the exposed fetus. Ribavirin therapy is contraindicated for use in women who are pregnant or in men whose female partners are pregnant. (See WARNINGS, PRECAUTIONS - Information for Patients and Pregnancy Category X).

RIBASPHERE™ (Ribavirin capsules) are contraindicated in patients with a history of hypersensitivity to ribavirin or any component of the capsule.

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

Patients with hemoglobinopathies (e.g., thalassemia major, sickle-cell anemia) should not be treated with RIBASPHERE™ (Ribavirin capsules)

WARNINGS

Based on results of clinical trials ribavirin monotherapy is not effective for the treatment of chronic hepatitis C virus infection; therefore, RIBASPHERE™ (Ribavirin capsules) must not be used alone. The safety and efficacy of RIBASPHERE™ (Ribavirin capsules) with non-pegylated interferons other than INTRON A product have not been established.

There are significant adverse events caused by ribavirin/INTRON A therapy, including severe depression and suicidal ideation, hemolytic anemia, suppression of bone marrow function, autoimmune and infectious disorders, pulmonary dysfunction, pancreatitis, and diabetes. Suicidal ideation or attempts occurred more frequently among pediatric patients, primarily adolescents, compared to adult patients (2.4% versus 1%) during treatment and off-therapy follow-up. The Appendix in this package insert should be reviewed in its entirety prior to initiation of therapy of RIBASPHERE™ (Ribavirin capsules) taken together with INTRON A for additional safety information.

Pregnancy

RIBASPHERE™ (Ribavirin capsules) may cause birth defects and/or death of the exposed fetus. Extreme care must be taken to avoid pregnancy in female patients and in female partners of male patients. RIBASPHERE™ (Ribavirin capsules) have demonstrated significant teratogenic and/or embryocidal effects in all animal species in which adequate studies have been conducted. These effects occurred at doses as low as one twentieth of the recommended human dose. If ribavirin THERAPY SHOULD NOT BE STARTED UNTIL A REPORT OF A NEGATIVE PREGNANCY TEST HAS BEEN OBTAINED IMMEDIATE- 7 PRIOR TO PLANNED INITIATION OF THERAPY. Patients should be instructed to use at least two forms of effective contraception during treatment and during the six month period after treatment has been stopped based on multiple dose half-life of ribavirin of 12 days. Pregnancy testing should occur monthly during ribavirin therapy and for six months after therapy has stopped (See CONTRAINDICATIONS and PRECAUTIONS: Information for Patients and Pregnancy Category X).

Anemia

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

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

Ribavirin and INTRON A therapy should be suspended in patients with signs and symptoms of pancreatitis and discontinued in patients with confirmed pancreatitis.

Ribavirin should not be used in patients with creatinine clearance <50 mL/min. (See CLINICAL PHARMACOLOGY, Special Populations).

Pulmonary

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

PRECAUTIONS

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

The safety and efficacy of ribavirin/INTRON A therapy have not been established in liver or other organ transplant patients, patients with decompensated liver disease due to hepatitis C infection, patients who are nonresponders to interferon therapy, or patients coinfected with HBV or HIV.

Information for Patients

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

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

Patients receiving RIBASPHERE™ (Ribavirin capsules) should be informed of the benefits and risks associated with treatment, directed in its appropriate use, and referred to the patient MEDICATION GUIDE for RIBASPHERE™ (Ribavirin capsules). Patients should be informed that the effect of treatment of hepatitis C infection on transmission is not known, and that appropriate precautions to prevent transmission of the hepatitis C virus should be taken.

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

Laboratory Tests The following laboratory tests are recommended for all patients treated with RIBASPHERE™ (Ribavirin capsules), prior to beginning treatment and then periodically thereafter:

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

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

Ribavirin demonstrated increased incidences of mutation and cell transformation in multiple genotoxicity assays. Ribavirin was active in the Salls/373 *In Vitro* Cell Transformation Assay. Mutagenic activity was observed in the mouse lymphoma assay, and at doses of 20 - 200 mg/kg (estimated human equivalent of 1.67 - 16.7 mg/kg, based on body surface area adjustment for a 60 kg adult; 0.1 - 1 X the maximum recommended human 24-hour dose of ribavirin) in a mouse micronucleus assay. A dominant lethal assay in rats was negative, indicating that if mutations occurred in rats they were not transmitted through male gametes.

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

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

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

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

Pregnancy Category X (See CONTRAINDICATIONS)

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

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

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

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

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

Nursing Mothers It is not known whether the ribavirin product is excreted in human milk. Because of the potential for serious adverse reactions from the drug in nursing infants, a decision should be made whether to discontinue nursing or to delay or discontinue RIBASPHERE™ (Ribavirin capsules).

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

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

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

Pediatric Use

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

Drug Interactions

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

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

ADVERSE REACTIONS

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

Ribavirin/INTRON A Combination Therapy

In clinical trials, 19% and 6% of previously untreated and relapse patients, respectively, discontinued therapy due to adverse events in the combination arms compared to 13% and 3% in the interferon arms. Selected treatment-emergent adverse events that occurred in the US studies with ≥5% incidence are provided in TABLE 4 by treatment group. In general, the selected treatment-emergent adverse events were reported with lower incidence in the international studies as compared to the US studies with the exception of asthenia, influenza-like symptoms, nervousness, and pruritus.

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

	Percentage of Patients						
	US Previously Untreated Study				US Relapse Study		
	24 weeks of treatment		48 weeks of treatment		24 weeks of treatment		
Patients Reporting Adverse Events*	INTRON A plus Ribavirin (N=228)	INTRON A plus Placebo (N=231)	INTRON A plus Ribavirin (N=226)	INTRON A plus Placebo (N=225)	INTRON A plus Ribavirin (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	8	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	11	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	26	27	26	
-Rash	20	9	28	8	21	5	
-Pruritus	21	9	19	8	13	4	
Special Senses, Other Disorders							
-Taste Perversion	7	4	8	4	6	5	

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

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

Laboratory Values

Ribavirin/INTRON A Combination Therapy

Changes in selected hematologic values (hemoglobin, white blood cells, neutrophils, and platelets) during therapy are described below (See TABLE 5).

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

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

1 2 3

RIBASPHERE™ (Ribavirin capsules) 200 mg
PRODUCT INFORMATION 000197
APPROVED
RIBASPHERE™ (Ribavirin capsules) 200 mg
PRODUCT INFORMATION 000197
RX Only

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

	Percentage of Patients					
	US Previously Untreated Study				US Relapse Study	
	24 weeks of treatment		48 weeks of treatment		24 weeks of treatment	
	INTRON A plus Ribavirin (N=228)	INTRON A plus Placebo (N=231)	INTRON A plus Ribavirin (N=228)	INTRON A plus Placebo (N=225)	INTRON A plus Ribavirin (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

OVERDOSAGE

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

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

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

Ribavirin/INTRON A Combination Therapy

Adults

The recommended dose of RIBASPHERE™ (Ribavirin capsules) in patients 18 years of age and older depends on the patient's body weight. The recommended dose of ribavirin is provided in TABLE 6.

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

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

TABLE 6. Recommended Dosing for Patients 18 years of age and older

Body Weight	RIBASPHERE™ (Ribavirin capsules)
≤75 kg	2 X 200 mg capsules AM, 3 X 200 mg capsules PM daily p.o.
>75 kg	3 X 200 mg capsules AM, 3 X 200 mg capsules PM daily p.o.

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

***Dose Modifications* (TABLE 7)**

If severe adverse reactions or laboratory abnormalities develop during combination ribavirin/INTRON A therapy the dose should be modified, or discontinued if appropriate, until the adverse reactions abate. If intolerance persists after dose adjustment, ribavirin/INTRON A therapy should be discontinued. Ribavirin should not be used in patients with creatinine clearance <50 mL/min. (See WARNINGS and CLINICAL PHARMACOLOGY, Special populations). Ribavirin should be administered with caution to patients with pre-existing cardiac disease. Patients should be assessed before commencement of therapy and should be appropriately monitored during therapy. If there is any deterioration of cardiovascular status, therapy should be stopped. (See WARNINGS).

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

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

TABLE 7. Guidelines for Dose Modifications and Discontinuation for Anemia

	Dose Reduction* Ribavirin – 600 mg daily adults	Permanent Discontinuation of Ribavirin Treatment
Hemoglobin		
No Cardiac History	<10g/dL	<8.5g/dL
Cardiac History Patients	≥2g/dL decrease during any 4-week period during treatment	<12g/dL after 4 weeks of dose reduction

HOW SUPPLIED

RIBASPHERE™ (Ribavirin capsules), 200 mg are white, opaque gelatin capsules printed horizontally with "riba 200" on both the body and the cap of the capsule in green, edible ink. RIBASPHERE™ (Ribavirin capsules), 200 mg are packaged in HDPE bottles with child-resistant closures containing 180 capsules (NDC 66435-101-18).

Storage Conditions

The bottle of RIBASPHERE™ (Ribavirin capsules) should be stored at 25°C (77°F); excursions are permitted between 15°C and 30°C (59°F and 86°F) [see USP Controlled Room Temperature].

Manufactured by
DSM PHARMACEUTICALS, INC.
Greenville, NC 27834

Manufactured for
THREE RIVERS PHARMACEUTICALS, LLC
Cranberry Township, PA 16066

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Rev. 03/04 66435-101-18
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APPENDIX to Package Insert (Information on RIBASPHERE™ (Ribavirin capsules) taken together with INTRON A)

[Note: In addition to REBETOL®*(ribavirin) Capsules, Schering Corporation also markets REBETRON®*. REBETRON is a copackaged combination therapy containing REBETOL (ribavirin, USP) and INTRON A (interferon alfa-2b, recombinant) Injection. REBETRON has a package insert that provides information on the combination use of REBETOL (ribavirin, USP) and INTRON A. This Appendix provides information on ribavirin capsules taken together with INTRON A that corresponds to information in the package insert for REBETRON.]

CONTRAINDICATIONS AND WARNINGS

Combination RIBASPHERE™ (Ribavirin capsules)/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 RIBASPHERE™ (Ribavirin capsules)/INTRON A therapy. Females of childbearing potential and males must use two reliable forms of effective contraception during treatment and during the 6-month post-treatment follow-up period. Significant teratogenic and/or embryocidal effects have been demonstrated for ribavirin in all animal species studied. See CONTRAINDICATIONS and WARNINGS.

RIBASPHERE™ (Ribavirin capsules) 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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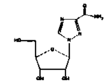
DESCRIPTION

Ribavirin capsules

RIBASPHERE™ (Ribavirin capsules) is Three Rivers Pharmaceuticals' 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 $C_8H_{12}N_4O_5$ and the molecular weight is 244.21.

Ribavirin capsules consist of white pellets in a white, opaque, gelatin capsule. Each capsule contains 200 mg ribavirin and the inactive ingredients: Croscarmellose Sodium, NF; Lactose Monohydrate, NF; Microcrystalline Cellulose, NF; and Povidone, USP. The capsule shell consists of gelatin and titanium dioxide. The capsule is printed horizontally with "riba 200" on both the body and the cap of the capsule using edible, green pharmaceutical ink which is made of Butyl Alcohol, NF; D&C Yellow #10 Aluminum Lake; Dehydrated Alcohol, USP; FD&C Blue #1 Aluminum Lake; Ferric Oxide, NF; Isopropyl Alcohol, USP; Propylene Glycol, USP; Shellac, NF; and Strong Ammonia Solution, NF.

INTRON A

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

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

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

Based on the specific activity of approximately 2.6 x 10⁸ IU/mg protein as measured by HPLC assay, the corresponding quantities of interferon alfa-2b, recombinant in the vials and pen described above are approximately 0.012 mg, 0.088 mg, and 0.087 mg protein, respectively.

Mechanism of Action

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

CLINICAL PHARMACOLOGY

Pharmacokinetics

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

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

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

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

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

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

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

* IU/mL for INTRON A and ng/mL for RIBAVIRIN CAPSULES
** IU.hr/mL for INTRON A and ng.hr/mL for RIBAVIRIN CAPSULES
† data obtained from a single-dose pharmacokinetic study using ¹⁴C labeled ribavirin, N = 5
†† N = 6
*** N = 11

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

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

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

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

Special Populations

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

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

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

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

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

Drug Interactions

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

INDICATIONS AND USAGE

RIBASPHERE™ (Ribavirin capsules) are indicated in combination with INTRON A (interferon alfa-2b, recombinant) Injection for the treatment of chronic hepatitis C in patients 18 years of age and older with compensated liver disease previously untreated with alpha interferon or in patients 18 years of age and older who have relapsed following alpha interferon therapy.

Description of Clinical Studies

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

Study results are summarized in TABLE 2.

[See reverse side]

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

	US Study: 24 weeks of treatment		US Study: 48 weeks of treatment		International Study: 24 weeks of treatment	International Study: 48 weeks of treatment	
	INTRON A plus Ribavirin capsules (N=228)	INTRON A plus Placebo (N=231)	INTRON A plus Ribavirin capsules (N=228)	INTRON A plus Placebo (N=225)	INTRON A plus Ribavirin capsules (N=265)	INTRON A plus Ribavirin capsules (N=268)	INTRON A plus Placebo (N=266)
Virologic Responses							
-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 Responses							
-Improvement[2]	102 (45)	77 (33)	96 (42)	65 (29)	103 (39)	102 (38)	69 (26)
-No improvement	77 (34)	99 (43)	61 (27)	93 (41)	85 (32)	58 (22)	111 (41)
-Missing Data	49 (21)	55 (24)	71 (31)	67 (30)	77 (29)	108 (40)	86 (32)

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

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

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

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

Study results are summarized in TABLE 3.

TABLE 3. Virologic and Histologic Responses: Relapse Patients*

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

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

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

CONTRAINDICATIONS

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

RIBASPHERE™ (Ribavirin capsules) in combination with INTRON A Injection is contraindicated in patients with a history of hypersensitivity to ribavirin and/or alpha interferon or any component of the capsule and/or injection.

Patients with autoimmune hepatitis must not be treated with combination RIBASPHERE™ (Ribavirin capsules)/INTRON A therapy.

WARNINGS

Pregnancy

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

Anemia

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

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

Similarly, patients with hemoglobinopathies (e.g., thalassemia, sickle-cell anemia) should not be treated with combination RIBASPHERE™ (Ribavirin capsules)/INTRON A therapy.

Psychiatric

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

Bone marrow toxicity:

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

Pulmonary

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

Other

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

PRECAUTIONS

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

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

The safety and efficacy of RIBASPHERE™ (Ribavirin capsules)/INTRON A therapy has not been established in liver or other organ transplant patients, decompensated hepatitis C patients, patients who are nonresponders to interferon therapy, or patients coinfected with HBV or HIV.

The safety and efficacy of RIBASPHERE™ (Ribavirin capsules) monotherapy for the treatment of HIV infection, adenovirus, early RSV infection, parainfluenza, or influenza have not been established and RIBASPHERE™ (Ribavirin capsules) should not be used for these indications.

There is no information regarding the use of RIBASPHERE™ (Ribavirin capsules) with other interferons.

Triglycerides: Elevated triglyceride levels have been observed in patients treated with interferon including rib- [illegible] capsules/INTRON A therapy. E[illegible] triglyceride levels should be managed as clinically appropriate. Severe hypertriglyceridemia (triglyceride [illegible]g/dL) may result in pan[illegible] Discontinuation of RIBASPHERE™ (Ribavirin capsules)/INTRON A therapy should be considered for pa[illegible] persistently elevated tri[illegible] (triglycerides >1000 mg/dL) associated with symptoms of potential pancreatitis, such as abdominal pain, nau[illegible] vomiting (see **WARNINGS**).

Drug Interactions

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

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

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

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

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

Patients receiving combination RIBASPHERE™ (Ribavirin capsules)/INTRON A treatment should be directed in its appropriate use, informed of the benefits and risks associated with treatment, and referred to the Appendix of the Medication Guide on RIBASPHERE™ (Ribavirin capsules). There are no data evaluating whether RIBASPHERE™ (Ribavirin capsules)/INTRON A therapy will prevent transmission of infection to others. Also, it is not known if treatment with RIBASPHERE™ (Ribavirin capsules)/INTRON A therapy will cure hepatitis C or prevent cirrhosis, liver failure, or liver cancer that may be the result of infection with the hepatitis C virus.

If home use is prescribed, a puncture-resistant container for the disposal of used syringes and needles should be supplied to the patient. Patients should be thoroughly instructed in the importance of proper disposal and cautioned against any reuse of needles and syringes. The full container should be disposed of according to the directions provided by the physician. [See Appendix to the Medication Guide on RIBASPHERE™ (Ribavirin capsules).] To avoid possible transmission of disease, do not share your multidose pen with anyone, it is for you and you alone.

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

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

Laboratory Tests The following laboratory tests are recommended for all patients on combination RIBASPHERE™ (Ribavirin capsules)/INTRON A therapy, prior to beginning treatment and then periodically thereafter.

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

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

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

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

Impairment of Fertility No reproductive toxicology studies have been performed using interferon alfa-2b, recombinant in combination with ribavirin. However, evidence provided below for interferon alfa-2b, recombinant and ribavirin when administered alone indicate that both agents have adverse effects on reproduction. It should be assumed that the effects produced by either agent alone will also be caused by the combination of the two agents.

Interferons may impair human fertility. In studies of interferon administration in nonhuman primates, menstrual cycle abnormalities have been observed. Decreases in serum estradiol and progesterone concentrations have been reported in females treated with human leukocyte interferon. In addition, ribavirin demonstrated significant embryocidal and/or teratogenic effects at doses well below the recommended human dose in all animal species in which adequate studies have been conducted.

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

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

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

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

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

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

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

Male patients and their female partners must practice effective contraception (two reliable forms) during treatment with combination RIBASPHERE™ (Ribavirin capsules)/INTRON A therapy and for the 6-month post-therapy period (e.g., 15 half-lives for ribavirin clearance from the body).

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

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

Pediatric Use

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

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

Geriatric Use Clinical studies of combination therapy of ribavirin capsules taken together with INTRON A did not include sufficient numbers of subjects aged 65 and over to determine if they respond differently from younger subjects. In clinical trials, elderly subjects had a higher frequency of anemia (67%) than did younger patients (28%) (see **WARNINGS**).

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

RIBASPHERE™ (Ribavirin capsules) is known to be substantially excreted by the kidney, and the risk of adverse reactions to ribavirin may be greater in patients with impaired renal function. Because elderly patients often have decreased renal function, care sh[illegible] taken in dose selection. Renal fu[illegible] should be monitored and dosage adjustments of ribavirin should be made accordingly (see **DOSAGE [illegible]NISTRATION: Guidelines for Dose Modification**). RIBASPHERE™ (Ribavirin capsules) should not be used in elderly patients with creatinine c[illegible] 50mL/min (see **WARNINGS**).

RIBASPHERE™ (Ribavirin capsules) taken together with INTRON A should be used very cautiously in elderly p[illegible] with a history of psychiatric dis[illegible] (see **WARNINGS**).

ADVERSE REACTIONS

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

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

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

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

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

Percentage of Patients

Patients Reporting Adverse Events*	US Previously Untreated Study: 24 weeks of treatment		US Previously Untreated Study: 48 weeks of treatment		US Relapse Study: 24 weeks of treatment	
	INTRON A plus Ribavirin capsules (N=228)	INTRON A plus Placebo (N=231)	INTRON A plus Ribavirin capsules (N=228)	INTRON A plus Placebo (N=225)	INTRON A plus Ribavirin capsules (N=77)	INTRON A plus Placebo (N=76)
Application Site Disorders						
-Injection Site Inflammation	13	10	12	14	6	8
-Injection Site Reaction	7	9	8	9	5	3
Body as a Whole – General Disorders						
-Headache	63	63	66	67	66	68
-Fatigue	68	62	70	72	60	53
-Rigors	40	32	42	39	43	37
-Fever	37	35	41	40	32	36
-Influenza-like Symptoms	14	18	18	20	13	13
-Asthenia	9	4	9	9	10	4
-Chest pain	5	4	9	8	6	7
Central & Peripheral Nervous System Disorders						
-Dizziness	17	15	23	19	26	21
Gastrointestinal System Disorders						
-Nausea	38	35	46	33	47	33
-Anorexia	27	16	25	19	21	14
-Dyspepsia	14	6	16	9	16	9
-Vomiting	11	10	9	13	12	8
Musculoskeletal System Disorders						
-Myalgia	61	57	64	63	61	58
-Arthralgia	30	27	33	36	29	29
-Musculoskeletal Pain	20	26	28	32	22	28
Psychiatric Disorders						
-Insomnia	39	27	39	30	26	25
-Irritability	23	19	32	27	25	20
-Depression	32	25	36	37	23	14
-Emotional Lability	7	6	11	8	12	8
-Concentration Impaired	11	14	14	14	10	12
-Nervousness	4	2	4	4	5	4
Respiratory System Disorders						
-Dyspnea	19	9	18	10	17	12
-Sinusitis	9	7	10	14	12	7
Skin and Appendages Disorders						
-Alopecia	28	27	32	28	27	26
-Rash	20	9	28	8	21	5
-Pruritus	21	9	19	8	13	4
Special Senses, Other Disorders						
-Taste Perversion	7	4	8	4	6	5

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

Laboratory Values

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

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

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

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

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

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

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

Percentage of Patients

	US Previously Untreated Study: 24 weeks of treatment		US Previously Untreated Study: 48 weeks of treatment		US Relapse Study: 24 weeks of treatment	
	INTRON A plus Ribavirin capsules (N=228)	INTRON A plus Placebo (N=231)	INTRON A plus Ribavirin capsules (N=228)	INTRON A plus Placebo (N=225)	INTRON A plus Ribavirin capsules (N=77)	INTRON A plus Placebo (N=76)
Hemoglobin (g/dL)						
9.5 - 10.9	24	1	32	1	21	3
8.0 - 9.4	5	0	4	0	4	0
6.5 - 7.9	0	0	0	0.4	0	0
<6.5	0	0	0	0	0	0
Leukocytes (x10^9/L)						
2.0 - 2.9	40	20	38	23	45	26
1.5 - 1.9	4	1	9	2	5	3
1.0 - 1.4	0.9	0	2	0	0	0
<1.0	0	0	0	0	0	0
Neutrophils (x10^9/L)						
1.0 - 1.49	30	32	31	44	42	34
0.75 - 0.99	14	15	14	11	16	18
0.5 - 0.74	9	9	14	7	8	4
<0.5	11	8	11	5	5	8
Platelets (x10^9/L)						
70 - 99	9	11	11	14	6	12
50 - 69	2	3	2	3	0	5
30 - 49	0	0.4	0	0.4	0	0
<30	0.9	0	1	0.9	0	0
Total Bilirubin (mg/dL)						
1.5 - 3.0	27	13	32	13	21	7
3.1 - 6.0	0.9	0.4	2	0	3	0
6.1 - 12.0	0	0	0.4	0	0	0
>12.0	0	0	0	0	0	0

OVERDOSAGE

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

There is no specific antidote for INTRON A or RIBASPHERE™ (Ribavirin capsules), and hemodialysis and peritoneal dialysis are not effective for treatment of overdose of either agent.

DOSAGE AND ADMINISTRATION

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

Adults

The recommended dose of RIBASPHERE™ (Ribavirin capsules) in patients 18 years of age and older depends on the patient's body weight. The recommended doses of RIBASPHERE™ (Ribavirin capsules) and INTRON A for adults are given in **TABLE 6**.

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

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

TABLE 6. Recommended Adult Dosing

Body Weight	RIBASPHERE™ (Ribavirin 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.

Under no circumstances should RIBASPHERE™ (Ribavirin capsules) be opened, crushed or broken (see Contraindications an

Dose Modifications **(TABLE 7)**

In clinical trials, approximately 26% of patients required modification of their dose of ribavirin capsules, INTRON A Injection, or adverse reactions or laboratory abnormalities develop during combination RIBASPHERE™ (Ribavirin capsules)/INTRON A therap modified, or discontinued if appropriate, until the adverse reactions abate. If intolerance persists after dose adjustment, RIBASPH sules)/INTRON A therapy should be discontinued.

RIBASPHERE™ (Ribavirin capsules)/INTRON A therapy should be administered with caution to patients with pre-existing cardiac di be assessed before commencement of therapy and should be appropriately monitored during therapy. If there is any deterioration tus, therapy should be stopped. (See **WARNINGS**).

For patients with a history of stable cardiovascular disease, a permanent dose reduction is required if the hemoglobin decreases 4-week period. In addition, for these cardiac history patients, if the hemoglobin remains <12 g/dL after 4 weeks on a reduced do discontinue combination RIBASPHERE™ (Ribavirin capsules)/INTRON A therapy.

It is recommended that a patient whose hemoglobin level falls below 10 g/dL have his/her RIBASPHERE™ (Ribavirin capsules) do daily (1 x 200 mg capsule AM, 2 x 200 mg capsules PM). A patient whose hemoglobin level falls below 8.5 g/dL should be perm from RIBASPHERE™ (Ribavirin capsules)/INTRON A therapy. (See **WARNINGS**).

It is recommended that a patient who experiences moderate depression (persistent low mood, loss of interest, poor self image, and/ his/her INTRON A dose temporarily reduced and/or be considered for medical therapy. A patient experiencing severe depression or su should be discontinued from RIBASPHERE™ (Ribavirin capsules)/INTRON A therapy and followed closely with appropriate medic **WARNINGS**).

TABLE 7. Guidelines for Dose Modifications

	Dose Reduction* RIBASPHERE™ (Ribavirin capsules) – Adults 600 mg daily; INTRON A – Adults 1.5 million IU TIW	Permanent Discontinuation o Treatment RIBASPHERE™ (Ribavirin capsu and INTRON A
Hemoglobin	<10g/dL RIBASPHERE™ (Ribavirin capsules) Cardiac History Patients only. ≥2g/dL decrease during any 4-week period during treatment RIBASPHERE™ (Ribavirin capsules)/INTRON A)	<8.5g/dL Cardiac History Patients only. <12g/dL after 4 weeks of dose redu
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)	Adults: <25 x 10^9/L

*Study medication to be dose reduced is shown in parenthesis

Administration of INTRON A Injection

At the discretion of the physician, the patient may self-administer the INTRON A. [See Illustrated Appendix to Medication Guid (Ribavirin capsules) for instructions.]

The Intron A Injection is supplied as a clear and colorless solution. The appropriate INTRON A dose should be withdrawn from the tidose pen and injected subcutaneously. The INTRON A injection supplied with the B-D Safety Lok™ syringes contain a plastic sle the needle after use. The syringe locks with an audible click when the green stripe on the safety sleeve covers the red stripe on the istration of INTRON A Injection, it is essential to follow the procedure for proper disposal of syringes and needles. [See Appendix on RIBASPHERE™ (Ribavirin capsules) for detailed instructions.]

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

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

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

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

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

HOW SUPPLIED

RIBASPHERE™ (Ribavirin capsules), 200 mg are white, opaque gelatin capsules printed horizontally with "riba 200" on both the bo capsule in green, edible ink. RIBASPHERE™ (Ribavirin capsules), 200 mg are packaged in HDPE bottles with child-resistant closures sules (NDC 66435-101-18).

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

STORAGE CONDITIONS

The bottle of RIBASPHERE™ (Ribavirin capsules) should be stored at 25°C (77°F); excursions are permitted between 15°C and 3 [see USP Controlled Room Temperature].

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

Manufactured by
DSM PHARMACEUTICALS, INC.
Greenville, NC 27834

Manufactured for
THREE RIVERS PHARMACEUTICALS, LLC
Cranberry Township, PA 16066

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tance of ribavirin capsules/INTRON A therapy, hearing disorder and vertigo. Very rarely, combination ribavirin capsules/INTRON A therapy may be associated with aplastic anemia.

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

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

	Percentage of Patients					
	US Previously Untreated Study				US Relapse Study	
	24 weeks of treatment		48 weeks of treatment		24 weeks of treatment	
Patients Reporting Adverse Events*	INTRON A plus Ribavirin capsules (N=228)	INTRON A plus Placebo (N=231)	INTRON A plus Ribavirin capsules (N=228)	INTRON A plus Placebo (N=225)	INTRON A plus Ribavirin capsules (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	26	32	22	28
Psychiatric Disorders						
-Insomnia	39	27	39	30	26	25
-Irritability	23	15	32	27	25	20
-Depression	32	25	36	37	23	14
-Emotional Lability	7	6	11	8	12	8
-Concentration Impaired	11	14	14	14	10	12
-Nervousness	4	2	4	4	5	4
Respiratory System Disorders						
-Dyspnea	19	9	18	10	17	12
-Sinusitis	9	7	10	14	12	7
Skin and Appendages Disorders						
-Alopecia	28	27	32	28	27	26
-Rash	20	9	28	8	21	5
-Pruritus	21	9	19	8	13	4
Special Senses, Other Disorders						
-Taste Perversion	7	4	8	4	6	5

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

Laboratory Values

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

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

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

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

Thyroid Function Of patients who entered the previously untreated (24 and 48 week treatment) and relapse (24 week treatment) studies without thyroid abnormalities, approximately 3% to 5% and 1% to 2%, respectively, developed thyroid abnormalities requiring clinical intervention.

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

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

	Percentage of Patients					
	US Previously Untreated Study				US Relapse Study	
	24 weeks of treatment		48 weeks of treatment		24 weeks of treatment	
	INTRON A plus Ribavirin capsules (N=228)	INTRON A plus Placebo (N=231)	INTRON A plus Ribavirin capsules (N=228)	INTRON A plus Placebo (N=225)	INTRON A plus Ribavirin capsules (N=77)	INTRON A plus Placebo (N=76)
Hemoglobin (g/dL)						
9.5 - 10.9	24	1	32	1	21	3
8.0 - 9.4	5	0	4	0	4	0
6.5 - 7.9	0	0	0	0.4	0	0
<6.5	0	0	0	0	0	0
Leukocytes (x10^9/L)						
2.0 - 2.9	40	20	38	23	45	26
1.5 - 1.9	4	1	9	2	5	3
1.0 - 1.4	0.9	0	2	0	0	0
<1.0	0	0	0	0	0	0
Neutrophils (x10^9/L)						
1.0 - 1.49	30	32	31	44	42	34
0.75 - 0.99	14	15	14	11	16	18
0.5 - 0.74	9	9	14	7	6	4
<0.5	11	8	11	5	5	8
Platelets (x10^9/L)						
70 - 99	9	11	11	14	6	12
50 - 69	2	3	2	3	0	5
30 - 49	0	0.4	0	0.4	0	0
<30	0.9	0	1	0.9	0	0
Total Bilirubin (mg/dL)						
1.5 - 3.0	27	13	32	13	21	7
3.1 - 6.0	0.9	0.4	2	0	3	0
6.1 - 12.0	0	0	0.4	0	0	0
>12.0	0	0	0	0	0	0

OVERDOSAGE

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

There is no specific antidote for INTRON A or RIBASPHERE™ (Ribavirin capsules), and hemodialysis and peritoneal dialysis are not effective for treatment of overdose of either agent.

DOSAGE AND ADMINISTRATION

INTRON A Injection should be administered subcutaneously and RIBASPHERE™ (Ribavirin capsules) should be administered orally. RIBASPHERE™ (Ribavirin capsules)may be administered without regard to food, but should be administered in a consistent manner. (See CLINICAL PHARMACOLOGY).

Adults

The recommended dose of RIBASPHERE™ (Ribavirin capsules) in patients 18 years of age and older depends on the patient's body weight. The recommended doses of RIBASPHERE™ (Ribavirin capsules) and INTRON A for adults are given in TABLE 6.

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

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

TABLE 6. Recommended Adult Dosing

Body Weight	RIBASPHERE™ (Ribavirin 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.

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

Dose Modifications **(TABLE 7)**

In clinical trials, approximately 26% of patients required modification of their dose of ribavirin capsules, INTRON A injection, or both agents. If severe adverse reactions or laboratory abnormalities develop during combination RIBASPHERE™ (Ribavirin capsules)/INTRON A therapy the dose should be modified, or discontinued if appropriate, until the adverse reactions abate. If intolerance persists after dose adjustment, RIBASPHERE™ (Ribavirin capsules)/INTRON A therapy should be discontinued.

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

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

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

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

TABLE 7. Guidelines for Dose Modifications

	Dose Reduction*	Permanent Discontinuation of Treatment
	RIBASPHERE™ (Ribavirin capsules) - Adults 800 mg daily INTRON A - Adults 1.5 million IU TIW	RIBASPHERE™ (Ribavirin capsules) and INTRON A
Hemoglobin	<10g/dL RIBASPHERE™ (Ribavirin capsules)	<8 g/dL
	Cardiac History Patients only. ≥2g/dL decrease during any 4-week period during treatment RIBASPHERE™ (Ribavirin capsules)/INTRON A)	Cardiac History Patients only. <12g/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)	Adults <25 x 10^9/L

*Study medication to be dose reduced is shown in parenthesis

Administration of INTRON A Injection

At the discretion of the physician, the patient may self-administer the INTRON A. [See Illustrated Appendix to Medication Guide on RIBASPHERE™ (Ribavirin capsules) for instructions.]

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

Vial/Pen Label Strength	Fill Volume	Concentration
3 million IU vial	0.5 mL	3 million IU/0.5 mL
18 million IU multidose vial†	3.6 mL	3 million IU/0.5 mL
18 million IU multidose pen††	1.5 mL	3 million IU/0.2 mL

† This is a multidose vial which contains a total of 22.5 million IU of interferon alfa-2b, recombinant per 3.6 mL in order to provide the delivery of six 0.5-mL doses, each containing 3 million IU of interferon alfa-2b, recombinant (for a label strength of 18 million IU).

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

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

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

HOW SUPPLIED

RIBASPHERE™ (Ribavirin capsules), 200 mg are white, opaque gelatin capsules printed horizontally with "rba 200" on both the body and the cap of the capsule in green, edible ink. RIBASPHERE™ (Ribavirin capsules), 200 mg are packaged in HDPE bottles with child-resistant closures containing 180 capsules (NDC 66435-101-18)

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

STORAGE CONDITIONS

The bottle of RIBASPHERE™ (Ribavirin capsules) should be stored at 25°C (77°F); excursions are permitted between 15°C and 30°C (59°F and 86°F) (see USP Controlled Room Temperature)

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

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