HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use Ribasphere® (ribavirin capsules) safely and effectively. See full prescribing information for Ribasphere.
Ribasphere (ribavirin capsules) 200 mg
Initial U.S. Approval: 1998

WARNING: RISK OF SERIOUS DISORDERS AND RIBAVIRIN-ASSOCIATED EFFECTS
See full prescribing information for complete boxed warning

- **Ribavirin monotherapy is not effective for the treatment of chronic hepatitis C (*5.10*).**
- **The hemolytic anemia associated with Ribasphere therapy may result in worsening of cardiac disease that has led to fatal and nonfatal myocardial infarctions. Patients with a history of significant or unstable cardiac disease should not be treated with Ribasphere (*2.4, 5.2, 6.1*).**
- **Significant teratogenic and/or embryocidal effects have been demonstrated in all animal species exposed to ribavirin. Therefore, Ribasphere 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 the therapy and for 6 months after completion of treatment in both female patients and in female partners of male patients who are taking Ribasphere therapy (*4, 5.1, 8.1, 13.1, 17.2*).**

RECENT MAJOR CHANGES

Warnings and Precautions (*5.8*) [01/2011]

INDICATIONS AND USAGE

Ribasphere is a nucleoside analogue indicated in combination with interferon alfa-2b (pegylated and non pegylated) for the treatment of Chronic Hepatitis C (CHC) in patients 3 years of age or older with compensated liver disease. (*1.1*)

Patients with the following characteristics are less likely to benefit from retreatment after failing a course of therapy; previous nonresponse, previous pegylated interferon treatment, significant bridging fibrosis or cirrhosis, and genotype 1 infection.

DOSAGE AND ADMINISTRATION

Ribasphere is administered according to body weight. (*2.1, 2.2*)
Dose reduction or discontinuation is recommended in patients experiencing certain adverse reactions or renal dysfunction (*2.4, 2.5, 12.3*)

DOSAGE FORMS AND STRENGTHS

Ribasphere Capsules 200mg (*3*)

CONTRAINDICATIONS

- Pregnant women and men whose female partners are pregnant (*4, 8.1*)
- Known hypersensitivity reactions such as Stevens-Johnson syndrome, toxic epidermal necrolysis, and erythema multiforme to ribavirin or any component of the product (*4*)
- Autoimmune hepatitis (*4*)
- Hemoglobinopathies (*4*)
- Creatinine clearance < 50 mL/min (*4*)
- Coadministration with didanosine (*4, 7.1*)

WARNINGS AND PRECAUTIONS

- *Pregnancy Category X* (*5.1, 8.1, 8.3*)
- Birth Defects and fetal death with ribavirin: Patients must have a negative pregnancy test prior to therapy; use at least 2 forms of contraception and undergo monthly pregnancy tests.

Patients exhibiting the following conditions should be closely monitored and may require dose reduction or discontinuation of therapy:

- Monotherapy with ribavirin is not permitted. (*5.10*)
- Hemolytic anemia may occur with a significant initial drop in hemoglobin. (*5.2*)
- Pancreatitis. (*5.3*)
- Pulmonary infiltrates or pulmonary function impairment. (*5.4*)
- New or worsening ophthalmologic disorders. (*5.5*)
- Severe decreases in neutrophil and platelet counts, and hematologic, endocrine (e.g., TSH), and hepatic abnormalities. (*5.6*)
- Dental/periodontal disorders reported with combination therapy. (*5.7*)
- Concomitant administration of azathioprine. (*5.8*)
- Weight loss and growth inhibition reported with combination therapy in pediatric patients. (*5.9*)

ADVERSE REACTIONS

Hemolytic anemia. (*6.1*)
Most common adverse reactions (approximately 40%) in adult patients receiving ribavirin/peginterferon alfa-2b or interferon alfa-2b combination therapy are injection site reaction, fatigue/asthenia, headache, rigors, fevers, nausea, myalgia and anxiety/emotional lability/irritability. (*6.1, 6.2*)
Most common adverse reactions (>25%) in pediatric patients receiving ribavirin/peginterferon alfa-2b therapy are: pyrexia, headache, neutropenia, fatigue, anorexia, injection site erythema, and vomiting. (*6.1*)
To report SUSPECTED ADVERSE REACTIONS, contact Kadmon Pharmaceuticals at 1-877-377-7862 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch

To report SUSPECTED ADVERSE REACTIONS, contact at or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch

DRUG INTERACTIONS

Nucleoside analogues: closely monitor for toxicities. Discontinue nucleoside reverse transcriptase inhibitors or reduce dose or discontinue interferon, ribavirin or both with worsening toxicities. (*7.2*)

USE IN SPECIFIC POPULATIONS

- **Ribavirin Pregnancy Registry: 1-800-593-2214**
- Nursing mothers: potential adverse reactions from the drug in nursing infants. (*8.1, 8.3*)
- Pediatrics: Safety and efficacy in patients < 3 years old have not been established. (*8.4*)
- Organ transplant recipients: Safety and efficacy not studied. (*8.6*)
- Co-infected Patients: Safety and efficacy with HIV or HBV co-infection have not been established. (*8.7*)

See 17 for PATIENT COUNSELING INFORMATION and the FDA-approved Medication Guide

Revised: 12/2012

FULL PRESCRIBING INFORMATION: CONTENTS *

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FULL PRESCRIBING INFORMATION

WARNING: RISK OF SERIOUS DISORDERS AND RIBAVIRIN-ASSOCIATED EFFECTS

- **Ribasphere® (ribavirin capsules) monotherapy is not effective for the treatment of chronic hepatitis C virus infection and should not be used alone for this indication [see *Warnings and Precautions (5.10)*].**
- **The primary toxicity of ribavirin is hemolytic anemia. The anemia associated with Ribasphere therapy may result in worsening of cardiac disease that has led to fatal and nonfatal myocardial infarctions. Patients with a history of significant or unstable cardiac disease should not be treated with Ribasphere [see *Dosage and Administration (2.4)*, *Warnings and Precautions (5.2)*, and *Adverse Reactions (6.1)*].**
- **Significant teratogenic and 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, Ribasphere 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 Ribasphere therapy. At least two reliable forms of effective contraception must be utilized during treatment and during the 6-month posttreatment follow-up period [see *Contraindications (4)*, *Warnings and Precautions (5.1)*, *Use in Specific Populations (8.1)*, *Nonclinical Toxicology (13.1)*, and *Patient Counseling Information (17.2)*].**

1 INDICATIONS AND USAGE

1.1 Chronic Hepatitis C (CHC)

Ribasphere® (ribavirin capsules) in combination with interferon alfa-2b (pegylated and nonpegylated) is indicated for the treatment of Chronic Hepatitis C (CHC) in patients 3 years of age and older with compensated liver disease [see *Warnings and Precautions (5.9, 5.10)*, and *Use in Specific Populations (8.4)*].
The following points should be considered when initiating Ribasphere combination therapy with peginterferon alfa-2b or interferon alfa-2b:

- These indications are based on achieving undetectable HCV-RNA after treatment for 24 or 48 weeks and maintaining a Sustained Virologic Response (SVR) 24 weeks after the last dose.

- Combination therapy with Ribasphere/peginterferon alfa-2b is preferred over Ribasphere/interferon alfa-2b as this combination provides substantially better response rates [see *Clinical Studies (14)*].

- Patients with the following characteristics are less likely to benefit from retreatment after failing a course of therapy: previous nonresponse, previous pegylated interferon treatment, significant bridging fibrosis or cirrhosis, and genotype 1 infection [see *Clinical Studies (14)*].

- No safety and efficacy data are available for treatment of longer than one year.

2 DOSAGE AND ADMINISTRATION

Under no circumstances should Ribasphere Capsules be opened, crushed, or broken. Ribasphere should be taken with food [see *Clinical Pharmacology (12.3)*]. Ribasphere should not be used in patients with creatinine clearance < 50 mL/min.

2.1 Ribasphere/Peginterferon alfa-2b Combination Therapy

Adult Patients

The recommended dose of peginterferon alfa-2b is 1.5 mcg/kg/week subcutaneously in combination with 800 to 1400 mg Ribasphere Capsules orally based on patient body weight (see **Table 1**). The volume of peginterferon alfa-2b to be injected depends on the strength of peginterferon alfa-2b and patient's body weight (see **Table 1**).

Duration of Treatment – Interferon Alpha-naïve Patients

The treatment duration for patients with genotype 1 is 48 weeks. Discontinuation of therapy should be considered in patients who do not achieve at least a 2 $\log_{10}$ drop or loss of HCV-RNA at 12 weeks, or if HCV-RNA remains detectable after 24 weeks of therapy. Patients with genotype 2 and 3 should be treated for 24 weeks.

Duration of Treatment – Retreatment with Peginterferon alfa-2b/Ribavirin of Prior Treatment Failures

The treatment duration for patients who previously failed therapy is 48 weeks, regardless of HCV genotype. Re-treated patients who fail to achieve undetectable HCV-RNA at week 12 of therapy, or whose HCV-RNA remains detectable after 24 weeks of therapy, are highly unlikely to achieve SVR and discontinuation of therapy should be considered [see *Clinical Studies (14.1)*].

Table 1: Recommended Ribasphere/Peginterferon alfa-2b Combination Therapy Dosing (Adults)

Body weight kg (lbs)	Peginterferon alfa-2b Vial Strength to Use	Amount of Peginterferon alfa-2b (mcg) to Administer	Volume (mL)* of Peginterferon alfa-2b to Administer	Ribasphere Daily Dose	Ribasphere Number of Capsules
<40 (<87)	50 mcg per 0.5 mL	50	0.5	800 mg/day	2 x 200 mg capsules A.M. 2 x 200 mg capsules P.M.
40-50 (87-111)	80 mcg per 0.5 mL	64	0.4	800 mg/day	2 x 200 mg capsules A.M. 2 x 200 mg capsules P.M.
51-60 (112-133)	80 mcg per 0.5 mL	80	0.5	800 mg/day	2 x 200 mg capsules A.M. 2 x 200 mg capsules P.M.
61-65 (134-144)	120 mcg per 0.5 mL	96	0.4	800 mg/day	2 x 200 mg capsules A.M. 2 x 200 mg capsules P.M.
66-75 (145-166)	120 mcg per 0.5 mL	96	0.4	1000 mg/day	2 x 200 mg capsules A.M. 3 x 200 mg capsules P.M.
76-80 (167-177)	120 mcg per 0.5 mL	120	0.5	1000 mg/day	2 x 200 mg capsules A.M. 3 x 200 mg capsules P.M.
81-85 (178-187)	120 mcg per 0.5 mL	120	0.5	1200 mg/day	3 x 200 mg capsules A.M.

					3 x 200 mg capsules P.M.
86-105 (188-231)	150 mcg per 0.5 mL	150	0.5	1200 mg/day	3 x 200 mg capsules A.M. 3 x 200 mg capsules P.M
>105 (>231)	†	†	†	1400 mg/day	3 x 200 mg capsules A.M. 4 x 200 mg capsules P.M

*****When reconstituted as directed.
†For patients weighing >105 kg (>231 pounds), the peginterferon alfa-2b dose of 1.5 mcg/kg/week should be calculated based on individual patient weight. Two vials of peginterferon alfa-2b may be necessary to provide the dose.

Pediatric Patients
Dosing for pediatric patients is determined by body surface area for peginterferon alfa-2b and by body weight for Ribasphere. The recommended dose of peginterferon alfa-2b is 60 mcg/m^2/week subcutaneously in combination with 15 mg/kg/day of Ribasphere orally in two divided doses (see **Table 2**) for pediatric patients ages 3-17 years. Patients who reach their 18th birthday while receiving peginterferon alfa-2b/Ribasphere should remain on the pediatric dosing regimen. The treatment duration for patients with genotype 1 is 48 weeks. Patients with genotype 2 and 3 should be treated for 24 weeks.

Table 2: Recommended Ribasphere* Dosing in Combination Therapy (Pediatrics)

Body weight kg (lbs)	**Ribasphere Daily Dose**	**Ribasphere Number of Capsules**
47–59 (103–131)	800 mg/day	2 x 200 mg capsules A.M. 2 x 200 mg capsules P.M.
60–73 (132–162)	1000 mg/day	2 x 200 mg capsules A.M. 3 x 200 mg capsules P.M.
>73 (>162)	1200 mg/day	3 x 200 mg capsules A.M. 3 x 200 mg capsules P.M.

*****Ribasphere to be used in combination with Peginterferon alfa-2b 60 mcg/m^2 weekly.

2.2 Ribasphere/Interferon alfa-2b Combination Therapy
Adults
Duration of Treatment – Interferon Alpha-naïve Patients
The recommended dose of interferon alfa-2b is 3 million IU three times weekly subcutaneously. The recommended dose of Ribasphere Capsules depends on the patient's body weight (refer to **Table 3**). 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 *Indications and Usage (1.1)*, *Adverse Reactions (6.1)*, and *Clinical Studies (14)*]. 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.
Duration of Treatment – Retreatment with Interferon alfa-2b/Ribasphere in Relapse Patients
In patients who relapse following nonpegylated interferon monotherapy, the recommended duration of treatment is 24 weeks.
Table 3: Recommended Dosing

Body weight	**Ribasphere® (ribavirin capsules)**
≤75 kg	2 times 200 mg capsules AM 3 times 200 mg capsules PM daily orally
>75 kg	3 times 200 mg capsules AM 3 times 200 mg capsules PM daily orally

Pediatrics
The recommended dose of Ribasphere is 15 mg/kg per day orally (divided dose AM and PM). Refer to **Table 2** for Pediatric Dosing of Ribasphere in combination with interferon alfa-2b. Interferon alfa-2b for Injection by body weight of 25 kg to 61 kg is 3 million IU/m^2 three times weekly subcutaneously. Refer to adult dosing table for > 61 kg body weight. The recommended duration of treatment

is 48 weeks for pediatric patients with genotype 1. 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 this time. The recommended duration of treatment for pediatric patients with genotype 2/3 is 24 weeks.

2.3 Laboratory Tests

The following laboratory tests are recommended for all patients treated with Ribasphere, 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 and Precautions (5.2, 5.7)*]), 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 and Precautions (5.2)*].

2.4 Dose Modifications

If severe adverse reactions or laboratory abnormalities develop during combination Ribasphere/interferon alfa-2b therapy or Ribasphere/peginterferon alfa-2b therapy, modified, or discontinue the dose until the adverse reaction abates or decreases in severity [see *Warnings and Precautions (5)*]. If intolerance persists after dose adjustment, combination therapy should be discontinued. Dose reduction of peginterferon alfa-2b in adult patients on Ribasphere/peginterferon alfa-2b combination therapy is accomplished in a two-step process from the original starting dose of 1.5 mcg/kg/week, to 1 mcg/kg/week, then to 0.5 mcg/kg/week, if needed. Dose reduction of peginterferon alfa-2b in adults may be accomplished by utilizing a lower dose strength or administering a lesser volume as shown in **Table 4.**

In the adult combination therapy study 2 dose reductions occurred in 42% of subjects receiving peginterferon alfa-2b 1.5 mcg/kg plus Ribasphere 800 mg daily including 57% of those subjects weighing 60 kg or less. In Study 4, 16% of subjects had a dose reduction of peginterferon alfa-2b to 1 mcg/kg in combination with Ribasphere, with an additional 4% requiring the second dose reduction of peginterferon alfa-2b to 0.5 mcg/kg due to adverse events [see *Adverse Reactions (6.1)*].

Table 4: Two-Step Dose Reduction of Peginterferon alfa-2b in Combination Therapy in Adults

First Dose Reduction to Peginterferon alfa-2b 1 mcg/kg				**Second Dose Reduction to Peginterferon alfa-2b 0.5 mcg/kg**			
Body weight kg (lbs)	**Peginterferon alfa-2b Vial Strength to Use**	**Amount of Peginterferon alfa-2b (mcg) to Administer**	**Volume (mL)* of Peginterferon alfa-2b to Administer**	**Body weight kg (lbs)**	**Peginterferon alfa-2b Vial Strength to Use**	**Amount of Peginterferon alfa-2b (mcg) to Administer**	**Volume (mL)* of Peginterferon alfa-2b to Administer**
<40 (<88)	50 mcg per 0.5 mL	35	0.35	<40 (<88)	50 mcg per 0.5 mL*†	20	0.2
40–50 (88–111)		45	0.45	40–50 (88–111)	50 mcg per 0.5 mL*†	25	0.25
51–60 (112–133)		50	0.5	51–60 (112–133)	50 mcg per 0.5 mL	30	0.3
61–75 (134–166)	80 mcg per 0.5 mL	64	0.4	61–75 (134–166)	50 mcg per 0.5 mL	35	0.35
76–85 (167–187)		80	0.5	76–85 (167–187)	50 mcg per 0.5 mL	45	0.45
86–104 (188–230)	120 mcg per 0.5 mL	96	0.4	86–104 (188–230)	50 mcg per 0.5 mL	50	0.5
105–125 (231–275)		108	0.45	105–125 (231–275)	80 mcg per 0.5 mL	64	0.4
>125 (>275)	150 mcg per 0.5 mL	135	0.45	>125 (>275)	80 mcg per 0.5 mL	72	0.45

*Must use vial. Minimum delivery for peginterferon alfa-2b 0.3 mL

†When reconstituted as directed

Dose reduction in pediatric patients is accomplished by modifying the recommended peginterferon alfa-2b dose in a two-step process from the original starting dose of 60 mcg/m^2/week, to 40 mcg/m^2/week, then to 20 mcg/m^2/week, if needed (see **Table 5**). In the pediatric combination therapy trial, dose reductions occurred in 25% of subjects receiving peginterferon alfa-2b 60 mcg/m^2 weekly plus Ribasphere 15 mg/kg daily. Dose reduction in pediatric patients is accomplished by modifying the recommended Ribasphere dose from the original starting dose of 15 mg/kg daily in a two-step process to 12 mg/kg/day, then to 8 mg/kg/day, if needed (see **Table 5**).
Ribasphere should not be used in patients with creatinine clearance < 50 mL/min. Subjects with impaired renal function and those over the age of 50 should be carefully monitored with respect to development of anemia [see *Warnings and Precautions (5.2)*, *Use in Specific Populations (8.5)*, and *Clinical Pharmacology (12.3)*].
Ribasphere 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 and Precautions (5.2)*].
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 therapy.
It is *recommended* that a patient whose hemoglobin level falls below 10 g/dL have his/her Ribasphere dose modified or discontinued per **Table 5**[see *Warnings and Precautions (5.2)*].
Table 5: Guidelines for Dose Modification and Discontinuation of Peginterferon alfa-2b, Interferon alfa-2b or Peginterferon alfa-2b/ Ribasphere Based on Laboratory Parameters in Adults and Pediatrics

Laboratory Values	**Adults**	**Pediatrics**		**Adults**	**Pediatrics**
	Peginterferon alfa-2b /Interferon alfa-2b	**Peginterferon alfa-2b**	**Interferon alfa-2b**	**Ribavirin**	
Hgb < 10g/dL	For patients with cardiac disease, reduce by 50%*	See footnote*	See footnote*	Adjust Dose†	1st reduction to 12 mg/kg/day 2nd reduction to 8 mg/kg/day
WBC < 1.5 x 10^9/L Neutrophils < 0.75 x 10^9/L Platelets< 50 x 10^9/L (Adults) < 70 x 10^9/L (Pediatrics)	Adjust Dose‡	1st reduction to 40 mcg/m^2/week 2nd reduction to 20 mcg/ m^2/week	Reduce by 50%	No Dose Change	No Dose Change
Hgb < 8.5g/dL WBC < 1 x 10^9/L Neutrophils < 0.5 x 10^9/L Creatinine > 2 mg/dL (Pediatrics) Platelets < 25 x 10^9/L (Adults) < 50 x 10^9/L (Pediatrics)	Permanently Discontinue	Permanently Discontinue	Permanently Discontinue	Permanently Discontinue	Permanently Discontinue

*****For adult patients with a history of stable cardiac disease receiving peginterferon alfa-2b or interferon alfa-2b in combination with ribavirin, the peginterferon alfa-2b or interferon alfa-2b dose should be reduced by half and the Ribasphere dose by 200 mg/day if a > 2 g/dL decrease in hemoglobin is observed during any 4-week period. Both peginterferon alfa-2b and Ribasphere or interferon alfa-2b and Ribasphere should be permanently discontinued if patients have hemoglobin levels < 12 g/dL after this Ribasphere dose reduction. Pediatric patients who have pre-existing cardiac conditions and experience a hemoglobin decrease ≥ 2 g/dL during any 4-week period during treatment should have weekly evaluations and hematology testing.

†1st dose reduction of Ribasphere is by 200 mg/day, except in patients receiving the 1400 mg dose it is by 400 mg/day; 2nd dose reduction of Ribasphere (if needed) is by an additional 200 mg/day.

‡For patients on Ribasphere/Peginterferon alfa-2b combination therapy: 1st dose reduction of peginterferon alfa-2b is to 1 mcg/kg/ week, 2nd dose reduction (if needed) of peginterferon alfa-2b is to 0.5 mcg/kg/week. For patients on Ribasphere/interferon alfa-2b combination therapy, reduce interferon alfa-2b dose by 50%.

Refer to the Intron A Package Insert or PegIntron Powder for Injection Package Insert for additional information about how to reduce an interferon alfa-2b or peginterferon alfa-2b dose.

2.5 Discontinuation of Dosing

Adults

It is recommended that HCV genotype 1 interferon-alfa-naïve patients receiving peginterferon alfa-2b in combination with ribavirin, be discontinued from therapy if there is not at least a 2 $\log_{10}$ drop or loss of HCV-RNA at 12 weeks of therapy, or whose HCV-RNA levels remain detectable (>10-20 IU/mL) after 24 weeks of therapy. Regardless of genotype, previously treated patients who have detectable HCV-RNA at week 12 or 24 are highly unlikely to achieve SVR and discontinuation of therapy should be considered.

Pediatrics (3-17 years of age)

It is recommended that patients receiving peginterferon alfa-2b/Ribasphere combination (excluding HCV Genotype 2 and 3) be discontinued from therapy at 12 weeks if their treatment Week 12 HCV-RNA dropped < 2 $\log_{10}$ compared to a pretreatment or at 24 weeks if they have detectable HCV-RNA (>10-20 IU/mL) at treatment Week 24.

3 DOSAGE FORMS AND STRENGTHS

Ribasphere 200 mg Capsules

4 CONTRAINDICATIONS

Ribasphere combination therapy is contraindicated in:

- women who are pregnant. Ribasphere may cause fetal harm when administered to a pregnant woman. Ribasphere is contraindicated in women who are or may become pregnant. If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to a fetus [see *Warnings and Precautions (5.1), Use in Specific Populations (8.1),* and *Patient Counseling Information (17.2)*]
- men whose female partners are pregnant
- patients with known hypersensitivity reactions such as Stevens-Johnson syndrome, toxic, epidermal necrolysis, and erythema multiforme to ribavirin or any component of the product
- patients with autoimmune hepatitis
- patients with hemoglobinopathies (e.g., thalassemia major, sickle-cell anemia)
- patients with creatinine clearance < 50 mL/min. [see *Use in Specific Populations (8.5)* and *Clinical Pharmacology (12.3)*]
- Coadministration of Ribasphere and didanosine is contraindicated as because exposure to the active metabolite of didanosine (dideoxyadenosine 5'-triphosphate) are increased. Fatal hepatic failure, as well as peripheral neuropathy, pancreatitis, and symptomatic hyperlactatemia/lactic acidosis have been reported in patients receiving both didanosine and ribavirin [see *Drug Interactions (7.1)*].

5 WARNINGS AND PRECAUTIONS

5.1 Pregnancy

Ribasphere (ribavirin capsules) may cause birth defects and death of the unborn child. Ribasphere therapy should not be started until a report of a negative pregnancy test has been obtained immediately prior to planned initiation of therapy. Patients should use at least two forms of contraception and have monthly pregnancy tests during treatment and during the 6-month period after treatment has been stopped. Extreme care must be taken to avoid pregnancy in female patients and in female partners of male patients. Ribavirin has demonstrated significant teratogenic and 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 of ribavirin. Ribasphere therapy should not be started until a report of a negative pregnancy test has been obtained immediately prior to planned initiation of therapy [see *Boxed Warning, Contraindications (4), Use in Specific Populations (8.1),* and *Patient Counseling Information (17.2)*].

5.2 Anemia

The primary toxicity of ribavirin is hemolytic anemia, which was observed in approximately 10% of Ribasphere/interferon alfa-2b-treated subjects in clinical trials. The anemia associated with Ribasphere capsules occurs within 1 to 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 [see *Dosage and Administration (2.4, 2.5)*].

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 before 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 (2.4, 2.5)*]. Because cardiac disease may be worsened by drug induced anemia, patients with a history of significant or unstable cardiac disease should not use Ribasphere.

5.3 Pancreatitis

Ribasphere and interferon alfa-2b or peginterferon alfa-2b therapy should be suspended in patients with signs and symptoms of pancreatitis and discontinued in patients with confirmed pancreatitis.

5.4 Pulmonary Disorders

Pulmonary symptoms, including dyspnea, pulmonary infiltrates, pneumonitis, pulmonary hypertension, and pneumonia, have been reported during therapy with ribavirin with alpha interferon combination therapy; 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 therapy should be discontinued.

5.5 Ophthalmologic Disorders

Ribavirin is used in combination therapy with alpha interferons. Decrease or loss of vision, retinopathy including macular edema, retinal artery or vein, thrombosis, retinal hemorrhages and cotton wool spots, optic neuritis, papilledema, and serous retinal detachment are induced or aggravated by treatment with alpha interferons. All patients should receive an eye examination at baseline. Patients with pre-existing ophthalmologic disorders (e.g., diabetic or hypertensive retinopathy) should receive periodic ophthalmologic exams during combination therapy with alpha interferon treatment. Any patient who develops ocular symptoms should receive a prompt and complete eye examination. Combination therapy with alpha interferons should be discontinued in patients who develop new or worsening ophthalmologic disorders.

5.6 Laboratory Tests

Peginterferon alfa-2b in combination with ribavirin may cause severe decreases in neutrophil and platelet counts, and hematologic, endocrine (e.g., TSH), and hepatic abnormalities.

Patients on peginterferon alfa-2b/Ribasphere combination therapy should have hematology and blood chemistry testing before the start of treatment and then periodically thereafter. In the adult clinical trial CBC (including hemoglobin, neutrophil, and platelet counts) and chemistries (including AST, ALT, bilirubin, and uric acid) were measured during the treatment period at weeks 2, 4, 8, 12, and then at 6-week intervals or more frequently if abnormalities developed. In pediatric subjects the same laboratory parameters were evaluated with additional assessment of hemoglobin at treatment week 6. TSH levels were measured every 12 weeks during the treatment period. HCV-RNA should be measured periodically during treatment [see *Dosage and Administration (2)*].

5.7 Dental and Periodontal Disorders

Dental and periodontal disorders have been reported in patients receiving ribavirin and interferon or peginterferon combination therapy. In addition, dry mouth could have a damaging effect on teeth and mucous membranes of the mouth during long-term treatment with the combination of ribavirin and interferon alfa-2b or pegylated interferon alfa-2b. Patients should brush their teeth thoroughly twice daily and have regular dental examinations. If vomiting occurs, they should be advised to rinse out their mouth thoroughly afterwards.

5.8 Concomitant Administration of Azathioprine

Pancytopenia (marked decreases in red blood cells, neutrophils and platelets) and bone marrow suppression have been reported in the literature to occur within 3 to 7 weeks after the concomitant administration of pegylated interferon/ribavirin and azathioprine. In this limited number of patients (n=8), myelotoxicity was reversible within 4 to 6 weeks upon withdrawal of both HCV antiviral therapy and concomitant azathioprine and did not recur upon reintroduction of either treatment alone. Peginterferon alfa-2b, Ribasphere and azathioprine should be discontinued for pancytopenia, and pegylated interferon/ribavirin should not be re-introduced with concomitant azathioprine [see *Drug Interaction (7.4)*].

5.9 Impact on Growth - Pediatric Use

Data on the effects of peginterferon alfa-2b plus ribavirin on growth come from an open-label study in subjects 3 through 17 years of age, and weight and height changes are compared to U.S. normative population data. In general, the weight and height gain of pediatric subjects treated with peginterferon alfa-2b plus ribavirin lags behind that predicted by normative population data for the entire length of treatment. After about 6 months posttreatment (Follow-Up Week 24), subjects had weight gain rebounds and regained their weight to 53rd percentile, above the average of the normative population and similar to that predicted by their average baseline weight (57th percentile). After about 6 months posttreatment, height gain stabilized and subjects treated with peginterferon alfa-2b plus ribavirin had an average height percentile of 44th percentile, which was less than the average of the normative population and less than their average baseline height (51st percentile). Severely inhibited growth velocity (< 3rd percentile) was observed in 70% of the

subjects while on treatment. Of the subjects experiencing severely inhibited growth, 20% had continued inhibited growth velocity (< 3rd percentile) after 6 months of follow-up.
Among the boys studied, the age groups of 3-11 years old and 12-17 years old had similar height percentile decreases of approximately 5 percentiles after 6 months posttreatment; weight gain continued to be similar to their average baseline percentile. Girls who were 3-11 years old and treated for 48 weeks had the largest average drop in height and weight percentiles (13 percentiles and 7 percentiles, respectively), whereas girls 12-17 years old continued along their average baseline height and weight percentiles after 6 months posttreatment.

5.10 Usage Safeguards
Based on results of clinical trials, ribavirin monotherapy is not effective for the treatment of chronic hepatitis C virus infection; therefore, Ribasphere Capsules must not be used alone. The safety and efficacy of ribavirin capsules have only been established when used together with interferon alfa-2b or peginterferon alfa-2b (not other interferons) as a combination therapy.
The safety and efficacy of ribavirin/interferon alfa-2b and peginterferon alfa-2b therapy for the treatment of HIV infection, adenovirus, RSV, parainfluenza, or influenza infections have not been established. Ribasphere 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.
There are significant adverse reactions caused by ribavirin/interferon alfa-2b or peginterferon alfa-2b 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 interferon alfa-2b and peginterferon alfa-2b package inserts should be reviewed in their entirety for additional safety information prior to initiation of combination treatment.

6 ADVERSE REACTIONS
Clinical trials with ribavirin in combination with peginterferon alfa-2b or interferon alfa-2b have been conducted in over 7800 subjects from 3 to 76 years of age.
The primary toxicity of ribavirin is hemolytic anemia. Reductions in hemoglobin levels occurred within the first 1 to 2 weeks of oral therapy. Cardiac and pulmonary reactions associated with anemia occurred in approximately 10% of patients [see *Warnings and Precautions (5.2)*].
Greater than 96% of all subjects in clinical trials experienced one or more adverse reactions. The most commonly reported adverse reactions in adult subjects receiving peginterferon alfa-2b or interferon alfa-2b in combination with ribavirin were injection site inflammation/reaction, fatigue/asthenia, headache, rigors, fevers, nausea, myalgia and anxiety/emotional lability/irritability. The most common adverse reactions in pediatric subjects, ages 3 and older, receiving ribavirin in combination with peginterferon alfa-2b or interferon alfa-2b were pyrexia, headache, neutropenia, fatigue, anorexia, injection site erythema, and vomiting.
The Adverse Reactions section references the following clinical studies:
- Ribavirin/peginterferon alfa-2b Combination therapy studies:
- Clinical Study 1 - evaluated peginterferon alfa-2b monotherapy (not further described in this label; see Peginterferon alfa-2b Powder for Injection Package Insert for information about this study).
- Study 2 - evaluated ribavirin 800 mg/day flat dose in combination with 1.5 mcg/kg/week peginterferon alfa-2b or with interferon alfa-2b.
- Study 3 - evaluated peginterferon alfa-2b/weight-based ribavirin in combination with peginterferon alfa-2b/flat dose ribavirin regimen.
- Study 4- compared two peginterferon alfa-2b (1.5 mcg/kg/week and 1 mcg/kg/week) doses in combination with ribavirin and a third treatment group receiving Pegasys® (180 mcg/week)/Copegus® (1000-1200 mg/day).
- Study 5 – evaluated peginterferon alfa-2b (1.5 mcg/kg/week) in combination with weight-based ribavirin in prior treatment failure subjects.

- Peginterferon alfa-2b/ribavirin Combination Therapy in Pediatric Patients.

- Ribavirin/interferon alfa-2b Combination Therapy studies for adults and pediatrics.

Serious adverse reactions have occurred in approximately 12% of subjects in clinical trials with peginterferon alfa-2b with or without ribavirin [see *BOXED WARNING, Warnings and Precautions (5)*]. The most common serious events occurring in subjects treated with peginterferon alfa-2b and ribavirin were depression and suicidal ideation [see *Warnings and Precautions (5.2)*], each occurring at a frequency of less than 1%. 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 and Precautions (5.10)*]. The most common fatal reaction occurring in subjects treated with peginterferon alfa-2b and ribavirin was cardiac arrest, suicide ideation, and suicide attempt [see *Warnings and Precautions (5.10)*], all occurring in less than 1% of subjects.
Because clinical trials are conducted under widely varying conditions, adverse reactions rates observed in the clinical trials of a drug cannot be directly compared to rated in the clinical trials of another drug and may not reflect the rates observed in clinical practice.

6.1 Clinical Studies Experience-Ribavirin/Peginterferon alfa-2b Combination Therapy

Adult Subjects

Adverse reactions that occurred in the clinical trial at > 5% incidence are provided by treatment group from the ribavirin/peginterferon alfa-2b Combination Therapy (Study 2) in **Table 6**.

Table 6: Adverse Reactions Occurring in >5% of Adult Subjects

	Percentage of Subjects Reporting Adverse Reactions*			***Percentage of Subjects Reporting Adverse Reactions****	
Adverse Reactions	**Peginterferon alfa-2b 1.5 mcg/kg/ Ribavirin (N=511)**	**Interferon alfa-2b/ Ribavirin (N=505)**	**Adverse Reactions**	**Peginterferon alfa-2b 1.5 mcg/kg/ Ribavirin (N=511)**	**Interferon alfa-2b/ Ribavirin (N=505)**
Application Site			**Musculoskeletal**		
Injection site Inflammation	25	18	Myalgia	56	50
Injection Site Reaction	58	36	Arthralgia	34	28
Autonomic Nervous System			Musculoskeletal Pain	21	19
Dry Mouth	12	8	**Psychiatric**		
Increased Sweating	11	7	Insomnia	40	41
Flushing	4	3	Depression	31	34
Body as a Whole			Anxiety/Emotional Lability/ Irritability	47	47
Fatigue/Asthenia	66	63	Concentration Impaired	17	21
Headache	62	58	Agitation	8	5
Rigors	48	41	Nervousness	6	6
Fever	46	33	**Reproductive, Female**		
Weight Loss	29	20	Menstrual Disorder	7	6
Right Upper Quadrant Pain	12	6	**Resistance Mechanism**		
Chest Pain	8	7	Viral Infection	12	12
Malaise	4	6	Fungal Infection	6	1
Central/Peripheral Nervous System			**Respiratory System**		
Dizziness	21	17	Dyspnea	26	24
Endocrine			Coughing	23	16
Hypothyroidism	5	4	Pharyngitis	12	13
Gastrointestinal			Rhinitis	8	6
Nausea	43	33	Sinusitis	6	5
Anorexia	32	27	**Skin and Appendages**		
Diarrhea	22	17	Alopecia	36	32
Vomiting	14	12	Pruritus	29	28
Abdominal Pain	13	13	Rash	24	23
Dyspepsia	9	8	Skin Dry	24	23
Constipation	5	5	**Special Senses, Other**		
Hematologic Disorders			Taste Perversion	9	4
Neutropenia	26	14	**Vision Disorders**		
Anemia	12	17	Vision Blurred	5	6
Leukopenia	6	5	Conjunctivitis	4	5
Thrombocytopenia	5	2			
Liver and Biliary System					
Hepatomegaly	4	4			

***A subject may have reported more than one adverse reaction within a body system/organ class category.

Table 7 summarizes the treatment related adverse reactions in Study 4 that occurred at a ≥10% incidence.

Table 7: Summary of Treatment-Related Adverse Reactions (≥10% Incidence) by Descending Frequency

	Study 4 *Percentage of Patients Reporting Treatment-Related Adverse Reactions*		
Adverse Reactions	**Peginterferon alfa-2b 1.5 mcg/kg with Ribavirin (n=1019)**	**Peginterferon alfa-2b 1 mcg/kg with Rbavirin (n=1016)**	**Peginterferon alfa-2a 180 mcg with Ribavirin Tablets (n=1035)**
Fatigue	67	68	64
Headache	50	47	41
Nausea	40	35	34
Chills	39	36	23
Insomnia	38	37	41
Anemia	35	30	34
Pyrexia	35	32	21
Injection Site Reactions	34	35	23
Anorexia	29	25	21
Rash	29	25	34
Myalgia	27	26	22
Neutropenia	26	19	31
Irritability	25	25	25
Depression	25	19	20
Alopecia	23	20	17
Dyspnea	21	20	22
Arthralgia	21	22	22
Pruritus	18	15	19
Influenza-like Illness	16	15	15
Dizziness	16	14	13
Diarrhea	15	16	14
Cough	15	16	17
Weight Decreased	13	10	10
Vomiting	12	10	9
Unspecified Pain	12	13	9
Dry Skin	11	11	12
Anxiety	11	11	10
Abdominal Pain	10	10	10
Leukopenia	9	7	10

The incidence of serious adverse reactions was comparable in all studies. In Study 3, there was a similar incidence of serious adverse reactions reported for the weight-based ribavirin group (12%) and with the flat-dose ribavirin regimen. In Study 2, the incidence of serious adverse reactions was 17% in the peginterferon alfa-2b/ribavirin groups compared to 14% in the interferon alfa-2b/ribavirin group.

In many but not all cases, adverse reactions resolved after dose reduction or discontinuation of therapy. Some subjects experienced ongoing or new serious adverse reactions during the 6-month follow-up period. In Study 2, many subjects continued to experience adverse reactions several months after discontinuation of therapy. By the end of the 6-month follow-up period, the incidence of ongoing adverse reactions by body class in the peginterferon alfa-2b 1.5/ribavirin group was 33% (psychiatric), 20% (musculoskeletal), and 10% (for endocrine and for GI). In approximately 10 to 15% of subjects' weight loss, fatigue, and headache had not resolved.

There have been 31 subject deaths which occurred during treatment or during follow-up in these clinical trials. In Study 1, there was 1 suicide in a subject receiving peginterferon alfa-2b monotherapy and 2 deaths among subjects receiving interferon alfa-2b monotherapy (1 murder/suicide and 1 sudden death). In Study 2, there was 1 suicide in a subject receiving peginterferon alfa-2b/ ribavirin combination therapy; and 1 subject death in the interferon alfa-2b/ribavirin group (motor vehicle accident). There have been 31 subject deaths which occurred during treatment or during follow-up in the three clinical trials. In Study 3, there were 14 deaths, 2 of which were probable suicides and 1 was an unexplained death in a person with a relevant medical history of depression. In Study

4, there were 12 deaths, 6 of which occurred in subjects who received peginterferon alfa-2b/ribavirin combination therapy, 5 in the peginterferon alfa-2b 1.5 mcg/ribavirin arm (N=1019) and 1 in the peginterferon alfa-2b 1 mcg/ribavirin arm (N=1016), and 6 of which occurred in subjects receiving peginterferon alfa-2a/ribavirin tablets (N=1035). There were 3 suicides which occurred during the off treatment follow-up period in subjects who received peginterferon alfa-2b (1.5 mcg/kg)/ribavirin combination therapy.
In studies 1 and 2, 10 to 14% of subjects receiving peginterferon alfa-2b, alone or in combination with ribavirin, discontinued therapy compared with 6% treated with interferon alfa-2b alone and 13% treated with interferon alfa-2b in combination with ribavirin. Similarly in Study 3, 15% of subjects receiving peginterferon alfa-2b in combination with weight-based ribavirin and 14% of subjects receiving peginterferon alfa-2b and flat dose ribavirin discontinued therapy due to an adverse reaction. The most common reasons for discontinuation of therapy were related to known interferon effects of psychiatric, systemic (e.g., fatigue, headache), or gastrointestinal adverse reactions. In study 4, 13% of subjects in the peginterferon alfa-2b 1.5 mcg/ribavirin arm, 10% in the peginterferon alfa-2b 1 mcg/ribavirin arm and 13% in the peginterferon alfa-2a 180 mcg/ribavirin tablets arm discontinued due to adverse events.
In Study 2, dose reductions due to adverse reactions occurred in 42% of subjects receiving peginterferon alfa-2b (1.5 mcg/kg)/ribavirin and in 34% of those receiving interferon alfa-2b/ribavirin. The majority of subjects (57%) weighing 60 kg or less receiving peginterferon alfa-2b (1.5 mcg/kg)/ribavirin required dose reduction. Reduction of interferon was dose related (peginterferon alfa-2b 1.5 mcg/kg > peginterferon alfa-2b 0.5 mcg/kg or interferon alfa-2b), 40%, 27%, 28%, respectively. Dose reduction for ribavirin was similar across all three groups, 33 to 35%. The most common reasons for dose modifications were neutropenia (18%), or anemia (9%) (see ***Laboratory Values***). Other common reasons include depression, fatigue, nausea, and thrombocytopenia. In Study 3, dose modifications due to adverse reactions occurred more frequently with WBD compared to flat dosing (29% and 23%, respectively). In Study 4, 16% of subjects had a dose reduction of peginterferon alfa-2b to 1 mcg/kg in combination with ribavirin, with an additional 4% requiring the second dose reduction of peginterferon alfa-2b to 0.5 mcg/kg due to adverse events compared to 15% of subjects in the peginterferon alfa-2a/ribavirin tablets arm, who required a dose reduction to 135 mcg/week with peginterferon alfa-2a, with an additional 7% in the peginterferon alfa-2a/ribavirin tablets arm requiring second dose reduction to 90 mcg/week with peginterferon alfa-2a.
In the peginterferon alfa-2b/ribavirin combination trials the most common adverse reactions were psychiatric which occurred among 77% of subjects in Study 2 and 68% to 69% of subjects in Study 3. These psychiatric adverse reactions included most commonly depression, irritability, and insomnia, each reported by approximately 30% to 40% of subjects in all treatment groups. Suicidal behavior (ideation, attempts, and suicides) occurred in 2% of all subjects during treatment or during follow-up after treatment cessation [see *Warnings and Precautions (5)*]. In study 4 psychiatric adverse reactions occurred in 58 % of subjects in the peginterferon alfa-2b 1.5 mcg/ribavirin arm, 55% of subjects in the peginterferon alfa-2b 1 mcg/ribavirin arm, 57% of subjects in the peginterferon alfa-2a 180 mcg/ribavirin tablets arm.
Peginterferon alfa-2b induced fatigue or headache in approximately two-thirds of subjects, with fever or rigors in approximately half of the subjects. The severity of some of these systemic symptoms (e.g., fever and headache) tends to decrease as treatment continues.
In Studies 1 and 2, application site inflammation and reaction (e.g., bruise, itchiness, and irritation) occurred at approximately twice the incidence with peginterferon alfa-2b therapies (in up to 75% of subjects) compared with interferon alfa-2b . However, injection site pain was infrequent (2 to 3%) in all groups. In Study 3 there was a 23 to 24% incidence overall for injection site reactions or inflammation.
Subjects receiving ribavirin/peginterferon alfa-2b retreatment after failing a previous interferon combination regimen reported adverse reactions similar to those previously associated with this regimen during clinical trials of treatment-naïve subjects.

Pediatric Subjects

In general, the adverse-reaction profile in the pediatric population was similar to that observed in adults. In the pediatric study, the most prevalent adverse reactions in all subjects were pyrexia (80%), headache (62%), neutropenia (33%), fatigue (30%), anorexia (29%), injection-site erythema (29%) and vomiting (27%). The majority of adverse reactions reported in the study were mild or moderate in severity. Severe adverse reactions were reported in 7% (8/107) of all subjects and included injection site pain (1%), pain in extremity (1%), headache (1%), neutropenia (1%), and pyrexia (4%). Important adverse reactions that occurred in this subject population were nervousness (7%; 7/107), aggression (3%; 3/107), anger (2%; 2/107), and depression (1%; 1/107). Five subjects received levothyroxine treatment, 3 with clinical hypothyroidism and 2 with asymptomatic TSH elevations.
Dose modifications of peginterferon alfa-2b and/or ribavirin were required in 25% of subjects due to treatment-related adverse reactions, most commonly for anemia, neutropenia and weight loss. Two subjects (2%; 2/107) discontinued therapy as the result of an adverse reaction.
Adverse reactions that occurred with a ≥ 10% incidence in the pediatric trial subjects are provided in **Table 8**.
Table 8: Percentage (%) of Pediatric Subjects With Treatment-Related Adverse Reactions (in at Least 10% of All Subjects)

System Organ Class **Preferred Term**	**All subjects** **(N=107)**
Blood and Lymphatic System Disorders	
Neutropenia	33%
Anemia	11%
Leukopenia	10%

Gastrointestinal Disorders	
Abdominal Pain	21%
Abdominal Pain Upper	12%
Vomiting	27%
Nausea	18%
General Disorders and Administration Site Conditions	
Pyrexia	80%
Fatigue	30%
Injection-Site Erythema	29%
Chills	21%
Asthenia	15%
Irritability	14%
Investigations	
Weight Loss	19%
Metabolism and Nutrition Disorders	
Anorexia	29%
Decreased Appetite	22%
Musculoskeletal and Connective Tissue Disorders	
Arthralgia	17%
Myalgia	17%
Nervous System Disorders	
Headache	62%
Dizziness	14%
Skin and Subcutaneous Tissue Disorders	
Alopecia	17%

Laboratory Values

Adult and Pediatric Subjects

The adverse reaction profile in Study 3, which compared peginterferon alfa-2b/weight-based ribavirin combination to a peginterferon alfa-2b/flat dose ribavirin regimen, revealed an increased rate of anemia with weight-based dosing (29% vs. 19% for weight-based vs. flat dose regimens, respectively). However, the majority of cases of anemia were mild and responded to dose reductions.

Changes in selected laboratory values during treatment in combination with ribavirin treatment are described below. **Decreases in hemoglobin, leukocytes, neutrophils, and platelets may require dose reduction or permanent discontinuation from therapy** [see *Dosage and Administration (2.4)*]. Changes in selected laboratory values during therapy are described in **Table 9**. Most of the changes in laboratory values in the peginterferon alfa-2b/ribavirin study with pediatric were mild or moderate.

Table 9: Selected Laboratory Values During Treatment With Ribavirin Plus Peginterferon alfa-2b or Ribavirin Capsules Plus Interferon alfa-2b in Previously Untreated Subjects

	Percent of Subjects		
	Adults (Study 2)		**Pediatrics**
Laboratory Parameters*	**Peginterferon alfa-2b plus Ribavirin Capsules (N=511)**	**Interferon alfa-2b plus Ribavirin Capsules (N=505)**	**Peginterferon alfa-2b plus Ribavirin Capsules (N=107)***
Hemoglobin (g/dL)			
9.5-<11.0	26	27	30
8.0-<9.5	3	3	2
6.5-7.9	0.2	0.2	-
Leukocytes ($x10^9$/L)			
2.0-2.9	46	41	39
1.5-<2.0	24	8	3
1.0-1.4	5	1	-
Neutrophils ($x10^9$/L)			
1.0-1.5	33	37	35

0.75-<1.0	25	13	26
0.5-<0.75	18	7	13
<0.5	4	2	3
Platelets (x10^9/L)			
70-100	15	5	1
50-<70	3	0.8	-
30-49	0.2	0.2	--
25-<50	--	--	1
Total Bilirubin		**(mg/dL)**	***(µmole/L)***
1.5 -3.0	10	13	--
1.26-2.59 x N†	--	--	7
3.1-6.0	0.6	0.2	--
2.6-5 x N†	--	--	-
6.1-12.0	0	0.2	--
ALT (U/L)			
2 x Baseline	0.6	0.2	1
2.1-5 x Baseline	3	1	5
5.1-10 x Baseline	0	0	3

*****The table summarizes the worst category observed within the period per subject per laboratory test. Only subjects with at least one treatment value for a given laboratory test are included.
†N=Upper limit of normal

Hemoglobin. Hemoglobin levels decreased to <11 g/dL in about 30% of subjects in Study 2. In Study 3, 47% of subjects receiving WBD ribavirin and 33% on flat dose ribavirin had decreases in hemoglobin levels <11 g/dL. Reductions in hemoglobin to < 9 g/dL occurred more frequently in subjects receiving WBD compared to flat dosing (4% and 2%, respectively). In Study 2, dose modification was required in 9% and 13% of subjects in the peginterferon alfa-2b/ribavirin and interferon alfa-2b/ribavirin groups. In Study 4, patients receiving peginterferon alfa-2b (1.5 mcg/kg)/ribavirin had decreases in hemoglobin levels to between 8.5 to <10 g/dL (28%) and to <8.5 g/dL (3%), whereas in patients receiving peginterferon alfa-2a 180 mcg/ribavirin tablets these decreases occurred in 26% and 4% of subjects respectively. Hemoglobin levels become stable by treatment Weeks 4-6 on average. The typical pattern observed was a decrease in hemoglobin levels by treatment Week 4 followed by stabilization and a plateau, which was maintained to the end of treatment. In the peginterferon alfa-2b monotherapy trial, hemoglobin decreases were generally mild and dose modifications were rarely necessary [see *Dosage and Administration (2.4)*].
Neutrophils. Decreases in neutrophil counts were observed in a majority of adult subjects treated with combination therapy with ribavirin in Study 2 (85%) and interferon alfa-2b/ribavirin (60%). Severe potentially life-threatening neutropenia (<0.5 x 10^9/L) occurred in 2% of subjects treated with interferon alfa-2b/ribavirin and in approximately 4% of subjects treated with peginterferon alfa-2b/ribavirin in Study 2. Eighteen percent of subjects receiving peginterferon alfa-2b/ribavirin in Study 2 required modification of interferon dosage. Few subjects (< 1%) required permanent discontinuation of treatment. Neutrophil counts generally return to pre-treatment levels 4 weeks after cessation of therapy [see *Dosage and Administration (2.4)*].
Platelets. Platelet counts decreased to < 100,000/mm^3 in approximately 20% of subjects treated with peginterferon alfa-2b alone or with ribavirin and in 6% of adult subjects treated with interferon alfa-2b/ribavirin. Severe decreases in platelet counts (< 50,000/mm^3) occur in < 4% of adult subjects. Subjects may require discontinuation or dose modification as a result of platelet decreases [see *Dosage and Administration (2.4)*]. In Study 2, 1% or 3% of subjects required dose modification of interferon alfa-2b or peginterferon alfa-2b, respectively. Platelet counts generally returned to pretreatment levels 4 weeks after the cessation of therapy.
Thyroid Function. Development of TSH abnormalities, with and without clinical manifestations, are associated with interferon therapies. In Study 2, clinically apparent thyroid disorders occur among subjects treated with either interferon alfa-2b or peginterferon alfa-2b (with or without ribavirin) at a similar incidence (5% for hypothyroidism and 3% for hyperthyroidism). Subjects developed new onset TSH abnormalities while on treatment and during the follow-up period. At the end of the follow-up period 7% of subjects still had abnormal TSH values.
Bilirubin and Uric acid. In Study 2, 10 to 14% of subjects developed hyperbilirubinemia and 33 to 38% developed hyperuricemia in association with hemolysis. Six subjects developed mild to moderate gout.

6.2 Clinical Studies Experience-Ribavirin/Interferon alfa-2b Combination Therapy
Adult Subjects
In clinical trials, 19% and 6% of previously untreated and relapse subjects, respectively, discontinued therapy due to adverse reactions in the combination arms compared to 13% and 3% in the interferon arms. Selected treatment-related adverse reactions that occurred in

the US studies with ≥5% incidence are provided by treatment group (see **Table 10**). In general, the selected treatment-related adverse reactions 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.

Pediatric Subjects

In clinical trials of 118 pediatric subjects 3 to 16 years of age, 6% discontinued therapy due to adverse reactions. Dose modifications were required in 30% of subjects, most commonly for anemia and neutropenia. In general, the adverse-reaction profile in the pediatric population was similar to that observed in adults. Injection site disorders, fever, anorexia, vomiting, and emotional lability occurred more frequently in pediatric subjects compared to adult subjects. Conversely, pediatric subjects experienced less fatigue, dyspepsia, arthralgia, insomnia, irritability, impaired concentration, dyspnea, and pruritus compared to adult subjects. Selected treatment-related adverse reactions that occurred with ≥5% incidence among all pediatric subjects who received the recommended dose of ribavirin/ interferon alfa-2b combination therapy are provided in **Table 10**.

Table 10: Selected Treatment-Related Adverse Reactions: Previously Untreated and Relapse Adult Subjects and Previously Untreated Pediatric Subjects

	Percentage of Subjects						
	US Previously Untreated Study				**US Relapse Study**		**Pediatric Subjects**
Patients Reporting Adverse reactions*	**24 weeks of treatment**		**48 weeks of treatment**		**24 weeks of treatment**		**48 weeks of treatment**
	interferon alfa-2b plus ribavirin (N=228)	**interferon alfa-2b plus Placebo (N=231)**	**interferon alfa-2b plus ribavirin (N=228)**	**interferon alfa-2b plus Placebo (N=225)**	**interferon alfa-2b plus ribavirin (N=77)**	**interferon alfa-2b plus Placebo (N=76)**	**interferon alfa-2b plus ribavirin (N=118)**
Application Site Disorders							
Injection Site Inflammation	13	10	12	14	6	8	14
Injection Site Reaction	7	9	8	9	5	3	19
Body as a Whole - General Disorders							
Headache	63	63	66	67	66	68	69
Fatigue	68	62	70	72	60	53	58
Rigors	40	32	42	39	43	37	25
Fever	37	35	41	40	32	36	61
Influenza-like Symptoms	14	18	18	20	13	13	31
Asthenia	9	4	9	9	10	4	5
Chest Pain	5	4	9	8	6	7	5
Central & Peripheral Nervous System Disorders							
Dizziness	17	15	23	19	26	21	20
Gastrointestinal System Disorders							
Nausea	38	35	46	33	47	33	33
Anorexia	27	16	25	19	21	14	51
Dyspepsia	14	6	16	9	16	9	<1
Vomiting	11	10	9	13	12	8	42

Musculoskeletal System Disorders							
Myalgia	61	57	64	63	61	58	32
Arthralgia	30	27	33	36	29	29	15
Musculoskeletal Pain	20	26	28	32	22	28	21
Psychiatric Disorders							
Insomnia	39	27	39	30	26	25	14
Irritability	23	19	32	27	25	20	10
Depression	32	25	36	37	23	14	13
Emotional Lability	7	6	11	8	12	8	16
Concentration Impaired	11	14	14	14	10	12	5
Nervousness	4	2	4	4	5	4	3
Respiratory System Disorders							
Dyspnea	19	9	18	10	17	12	5
Sinusitis	9	7	10	14	12	7	<1
Skin and Appendages Disorders							
Alopecia	28	27	32	28	27	26	23
Rash	20	9	28	8	21	5	17
Pruritus	21	9	19	8	13	4	12
Special Senses, Other Disorders							
Taste Perversion	7	4	8	4	6	5	<1

*****Subjects reporting one or more adverse reactions. A patient may have reported more than one adverse reaction within a body system/ organ class category.

Laboratory Values

Changes in selected hematologic values (hemoglobin, white blood cells, neutrophils, and platelets) during therapy are described below (see **Table 11**).

Hemoglobin. Hemoglobin decreases among subjects receiving ribavirin therapy began at Week 1, with stabilization by Week 4. In previously untreated subjects 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 subjects 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 to 8 weeks of cessation of therapy in most subjects.

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 subjects with a previous diagnosis of Gilbert's syndrome. This has not been associated with hepatic dysfunction or clinical morbidity.

Table 11: Selected Hematologic Abnormalities During Treatment with Ribavirin Plus Interferon alfa-2b: Previously Untreated and Relapse Adult Subjects and Previously Untreated Pediatric Subjects

	Percentage of Subjects						
	US Previously Untreated Study				**US Relapse Study**		**Pediatric Subjects**
	24 weeks of treatment		**48 weeks of treatment**		**24 weeks of treatment**		**48 weeks of treatment**
	interferon alfa-2b plus	**interferon alfa-2b plus**	**interferon alfa-2b plus**	**interferon alfa-2b plus**	**interferon alfa-2b plus**	**interferon alfa-2b plus**	**interferon alfa-2b plus**

	ribavirin (N=228)	Placebo (N=231)	ribavirin (N=228)	Placebo (N=225)	ribavirin (N=77)	Placebo (N=76)	ribavirin (N=118)
Hemoglobin (g/dL)							
9.5 to 10.9	24	1	32	1	21	3	24
8.0 to 9.4	5	0	4	0	4	0	3
6.5 to 7.9	0	0	0	0.4	0	0	0
< 6.5	0	0	0	0	0	0	0
Leukocytes ($x10^9$/L)							
2.0 to 2.9	40	20	38	23	45	26	35
1.5 to 1.9	4	1	9	2	5	3	8
1.0 to 1.4	0.9	0	2	0	0	0	0
< 1.0	0	0	0	0	0	0	0
Neutrophils ($x10^9$/L)							
1.0 to 1.49	30	32	31	44	42	34	37
0.75 to 0.99	14	15	14	11	16	18	15
0.5 to 0.74	9	9	14	7	8	4	16
< 0.5	11	8	11	5	5	8	3
Platelets ($x10^9$/L)							
70 to 99	9	11	11	14	6	12	0.8
50 to 69	2	3	2	3	0	5	2
30 to 49	0	0.4	0	0.4	0	0	0
< 30	0.9	0	1	0.9	0	0	0
Total Bilirubin (mg/dL)							
1.5 to 3.0	27	13	32	13	21	7	2
3.1 to 6.0	0.9	0.4	2	0	3	0	0
6.1 to 12.0	0	0	0.4	0	0	0	0
> 12.0	0	0	0	0	0	0	0

6.3 Postmarketing Experiences

The following adverse reactions have been identified and reported during post approval use of ribavirin in combination with interferon alfa-2b or peginterferon alfa-2b. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Blood and Lymphatic System disorders

Pure red cell aplasia, aplastic anemia

Ear and Labyrinth disorders

Hearing disorder, vertigo

Respiratory, Thoracic and mediastinal disorders

Pulmonary hypertension

Eye disorders

Serous retinal detachment

Endocrine disorders

Diabetes

7 DRUG INTERACTIONS

7.1 Didanosine

Exposure to didanosine or its active metabolite (dideoxyadenosine 5’-triphosphate) is increased when didanosine is coadministered with ribavirin, which could cause or worsen clinical toxicities; therefore, coadministration of Ribasphere Capsules and didanosine is contraindicated. Reports of fatal hepatic failure, as well as peripheral neuropathy, pancreatitis, and symptomatic hyperlactatemia/lactic acidosis have been reported in clinical trials.

7.2 Nucleoside Analogues

Hepatic decompensation (some fatal) has occurred in cirrhotic HIV/HCV co-infected patients receiving combination antiretroviral therapy for HIV and interferon alpha and ribavirin. Adding treatment with alpha interferons alone or in combination with ribavirin may increase the risk in this patient subset. Patients receiving interferon with ribavirin and nucleoside reverse transcriptase inhibitors (NRTIs) should be closely monitored for treatment- associated toxicities, especially hepatic decompensation and anemia. Discontinuation of NRTIs should be considered as medically appropriate *[see Individual NRTI Product Information]*. Dose reduction or discontinuation of interferon, ribavirin, or both should also be considered if worsening clinical toxicities are observed, including hepatic decompensation (e.g., Child-Pugh >6).

Ribavirin may antagonize the *cell culture* antiviral activity of stavudine and zidovudine against HIV. Ribavirin has been shown in cell culture to inhibit phosphorylation of lamivudine, stavudine and zidovudine, which could lead to decreased antiretroviral activity. However, in a study with another pegylated interferon in combination with ribavirin, no pharmacokinetic (e.g., plasma concentrations or intracellular triphosphorylated active metabolite concentrations) or pharmacodynamic (e.g., loss of HIV/HCV virologic suppress) interaction was observed when ribavirin and lamivudine (n=18), stavudine (n=10), or zidovudine (n=6) were coadministered as part of a multidrug regimen to HIV/HCV co-infected subjects. Therefore, concomitant use of ribavirin with either of these drugs should be used with caution.

7.3 Drugs Metabolized by Cytochrome P-450

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 interferon alfa-2b for injection and ribavirin capsules in a multiple-dose pharmacokinetic study.

7.4 Azathioprine

The use of ribavirin for the treatment of chronic hepatitis C in patients receiving azathioprine has been reported to induce severe pancytopenia and may increase the risk of azathioprine-related myelotoxicity. Inosine monophosphate dehydrogenase (IMDH) is required for one of the metabolic pathways of azathioprine. Ribavirin is known to inhibit IMDH, thereby leading to accumulation of an azathioprine metabolite, 6-methylthioinosine monophosphate (6-MTITP), which is associated with myelotoxicity (neutropenia, thrombocytopenia, and anemia). Patients receiving azathioprine with ribavirin should have complete blood counts, including platelet counts, monitored weekly for the first month, twice monthly for the second and third months of treatment, then monthly or more frequently if dosage or other therapy changes are necessary [see *Warnings and Precautions (5.8)*].

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category X

[See *Contraindications (4), Warnings and Precautions (5.1), and Nonclinical Toxicology (13.1)*].

Treatment and Posttreatment

<u>Potential Risk to the Fetus</u>

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 to 28.6 mg/kg, based on body surface area adjustment for a 60 kg adult; up to 1.7 times 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 Ribasphere 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 Ribasphere and for the 6-month post-therapy period (e.g., 15 half-lives for ribavirin clearance from the body).

A Ribavirin Pregnancy Registry has been established to monitor maternal-fetal outcomes of pregnancies in female patients and female partners of male patients exposed to ribavirin during treatment and for 6 months following cessation of treatment. Physicians and patients are encouraged to report such cases by calling 1-800-593-2214.

8.3 Nursing Mothers

It is not known whether the Ribasphere 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.

8.4 Pediatric Use

Safety and effectiveness of Ribasphere in combination with peginterferon alfa-2b has not been established in pediatric patients below the age of 3 years. For treatment with ribavirin/interferon alfa-2b, evidence of disease progression, such as hepatic inflammation

and fibrosis, as well as prognostic factors for response, HCV genotype and viral load should be considered when deciding to treat a pediatric patient. The benefits of treatment should be weighed against the safety findings observed.
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 and Precautions (5.10)*]. As in adult patients, pediatric patients experienced other psychiatric adverse reactions (e.g., depression, emotional lability, somnolence), anemia, and neutropenia [see *Warnings and Precautions (5.2)*].

8.5 Geriatric Use
Clinical studies of ribavirin/interferon alfa-2b or peginterferon alfa-2b 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. Ribasphere should not be used in patients with creatinine clearance <50 mL/min [see *Contraindications (4)*].
In general, Ribasphere 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 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 and Precautions (5.2)*].

8.6 Organ Transplant Recipients
The safety and efficacy of interferon alfa-2b and peginterferon alfa-2b alone or in combination with Ribasphere for the treatment of hepatitis C in liver or other organ transplant recipients have not been established. In a small (n=16) single-center, uncontrolled case experience, renal failure in renal allograft recipients receiving interferon alpha and ribavirin combination therapy was more frequent than expected from the center's previous experience with renal allograft recipients not receiving combination therapy. The relationship of the renal failure to renal allograft rejection is not clear.

8.7 HIV or HBV Co-infection
The safety and efficacy of peginterferon alfa-2b/Ribasphere and interferon alfa-2b/Ribasphere for the treatment of patients with HCV co-infected with HIV or HBV have not been established.

10 OVERDOSAGE
There is limited experience with overdosage. Acute ingestion of up to 20 grams of ribavirin capsules, interferon alfa-2b ingestion up to 120 million units, and subcutaneous doses of interferon alfa-2b up to 10 times the recommended doses have been reported. Primary effects that have been observed are increased incidence and severity of the adverse reactions related to the therapeutic use of interferon alfa-2b and ribavirin. However, hepatic enzyme abnormalities, renal failure, hemorrhage, and myocardial infarction have been reported with administration of single subcutaneous doses of interferon alfa-2b that exceed dosing recommendations.
There is no specific antidote for interferon alfa-2b or Ribasphere overdose, and hemodialysis and peritoneal dialysis are not effective for treatment of overdose of these agents.

11 DESCRIPTION
Ribasphere® (ribavirin capsules) is Kadmon Pharmaceuticals' brand name for ribavirin, a synthetic nucleoside analogue (purine analogue). The chemical name of ribavirin is 1-ß-D-ribofuranosyl-1 *H*-1,2,4-triazole-3-carboxamide and has the following structural formula (see **Figure 1**):

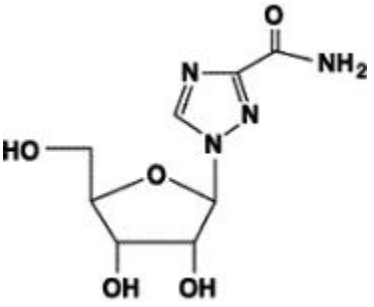

Figure 1: Structural Formula

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

Ribasphere® (ribavirin capsules) consists 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; Yellow Iron Oxide, NF; Dehydrated Alcohol, USP; FD&C Blue #2 Aluminum Lake; Isopropyl Alcohol, USP; Propylene Glycol, USP; Shellac, NF; Strong Ammonia Solution, NF; and Titanium Dioxide.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Ribavirin is an antiviral agent [see *Clinical Pharmacology (12.4)*].

12.3 Pharmacokinetics

Single- and multiple-dose pharmacokinetic properties in adults are summarized in **Table 12**. 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 to 1200 mg ribavirin. The relationship between dose and C_{max} was curvilinear, tending to asymptote above single doses of 400 to 600 mg.

Upon multiple oral dosing, based on $AUC12_{hr}$, a 6-fold accumulation of ribavirin was observed in plasma. Following oral dosing with 600 mg twice daily, steady-state was reached by approximately 4 weeks, with mean steady-state plasma concentrations of 2200 ng/mL (37%). Upon discontinuation of dosing, the mean half-life was 298 (30%) hours, which probably reflects slow elimination from nonplasma compartments.

Effect of Antacid on Absorption of Ribavirin

Coadministration of ribavirin capsules with an antacid containing magnesium, aluminum, and simethicone (Mylanta®[3]) resulted in a 14% decrease in mean ribavirin AUC_{tf}. The clinical relevance of results from this single-dose study is unknown.

Table 12: Mean (% CV) Pharmacokinetic Parameters for Ribavirin Capsules When Administered Individually to Adults

Parameter	Ribavirin Capsules	
	Single Dose 600 mg Capsules (N=12)	**Multiple Dose 600 mg Capsules (N=12)**
T_{max} (hr)	1.7 (46)*	3 (60)
C_{max} (ng/mL)	782 (37)	3680 (85)
AUC_{tf} (ng·hr/mL)	13400 (48)	228000 (25)
$T_{1/2}$ (hr)	43.6 (47)	298 (30)
Apparent Volume of Distribution (L)	2825 (9)†	
Apparent Clearance (L/hr)	38.2 (40)	
Absolute Bioavailability	64% (44)‡	

*N=11

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

‡N=6

Tissue Distribution

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.

Metabolism and Excretion

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

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_{tf} value was threefold greater in subjects with creatinine clearance values between 10 to 30 mL/min when compared to control subjects (creatinine clearance >90 mL/min). In subjects with creatinine clearance values between 30 to 60 mL/min, AUC_{tf} was twofold greater when compared to control subjects. The increased AUC_{tf} appears to be due to reduction of renal and nonrenal clearance in these subjects. 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 [see *Contraindications (4)*].

Hepatic Dysfunction

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

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 18 male and 18 female subjects.

Pediatric Patients

Multiple-dose pharmacokinetic properties for Ribavirin capsules and interferon alfa-2b in pediatric subjects with chronic hepatitis C between 5 and 16 years of age are summarized in **Table 13.** The pharmacokinetics of ribavirin and interferon alfa-2b (dose-normalized) are similar in adults and pediatric subjects.

Table 13: Mean (% CV) Multiple-dose Pharmacokinetic Parameters for Interferon alfa-2b and Ribavirin Capsules When Administered to Pediatric Subjects with Chronic Hepatitis C

Parameter	**Ribavirin 15 mg/kg/day as 2 divided doses (N=17)**	**Interferon alfa-2b 3 MIU/m^2 three times weekly (N=54)**
T_{max} (hr)	1.9 (83)	5.9 (36)
C_{max} (ng/mL)	3275 (25)	51 (48)
AUC*	29774 (26)	622 (48)
Apparent clearance L/hr/kg	0.27 (27)	ND†

Note: numbers in parenthesis indicate % coefficient of variation.

*AUC_{12} (ng hr/mL) for ribavirin; AUC_{0-24} (IU-hr/mL) for interferon alfa-2b

†ND=not done

A clinical study in pediatric subjects with chronic hepatitis C between 3 and 17 years of age was conducted in which pharmacokinetics for Peginterferon alfa-2b and ribavirin capsules were evaluated. In pediatric subjects receiving body surface area-adjusted dosing of peginterferon alfa-2b at 60 mcg/m^2/week, the log transformed ratio estimate of exposure during the dosing interval is predicted to be 58% [90% CI: 141%, 177%] higher than observed in adults receiving 1.5 mcg/kg/week. The pharmacokinetics of ribavirin (dose-normalized) in this trial were similar to those reported in a prior study of ribavirin in combination with interferon alfa-2b in pediatric subjects and in adult subjects.

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 [see *Dosage and Administration (2)*].

12.4 Microbiology

Mechanism of Action

The mechanism by which ribavirin contributes to its antiviral efficacy in the clinic is not fully understood. Ribavirin has direct antiviral activity in tissue culture against many RNA viruses. Ribavirin increases the mutation frequency in the genomes of several viruses and ribavirin triphosphate inhibits HCV polymerase in a biochemical reaction.

Antiviral Activity in Cell Culture

The anti-viral activity of ribavirin in the HCV-replicon is not well understood and has not been defined because of the cellular toxicity of ribavirin. Direct anti-viral activity has been observed in tissue culture of other RNA viruses. The anti-HCV activity of interferon was demonstrated in cell containing self-replicating HCV-RNS (HCV replicon cells) or HCV infection.

Resistance

HCV genotypes show wide variability in their response to pegylated recombinant human interferon/ribavirin therapy. Genetic changes associated with the variable response have not been identified.

Cross-resistance

There is no reported cross-resistance between pegylated/non-pegylated interferons and ribavirin.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis, 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 noncarcinogenic 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 Balb/3T3 *In Vitro* Cell Transformation Assay. Mutagenic activity was observed in the mouse lymphoma assay, and at doses of 20 to 200 mg/kg (estimated human equivalent of 1.67 to 16.7 mg/kg, based on body surface area adjustment for a 60 kg adult; 0.1 to 1 times 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 teratogenic effects at doses well below the recommended human dose 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 times 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 times the maximum recommended human 24-hour dose of ribavirin) [see *Contraindications (4)*, and *Warnings and Precautions (5.1)*].

Fertile women and partners of fertile women should not receive Ribasphere unless the patient and his/her partner are using effective contraception (two reliable forms). Based on a multiple-dose half-life (t1/2) of ribavirin of 12 days, effective contraception must be utilized for 6 months post-therapy (e.g., 15 half-lives of clearance for ribavirin).

Ribasphere 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 to 12.5 mg/kg/day, based on body surface area adjustment for a 60kg adult; 0.1-0.8 times 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.

13.2 Animal Toxicology and/or Pharmacology

Long-term studies in the mouse and rat [18 to 24 months; doses of 20 to 75 and 10 to 40 mg/kg/day, respectively, estimated human equivalent doses of 1.67 to 6.25 and 1.43 to 5.71 mg/kg/day, respectively, based on body surface area adjustment for a 60 kg adult; approximately 0.1 to 0.4 times 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.

In a study in which rat pups were dosed postnatally with ribavirin at doses of 10, 25, and 50 mg/kg/day, drug-related deaths occurred at 50 mg/kg (at rat pup plasma concentrations below human plasma concentrations at the human therapeutic dose) between study Days 13 and 48. Rat pups dosed from postnatal Day 7 through 63 demonstrated a minor, dose-related decrease in overall growth at all doses, which was subsequently manifested as slight decreases in body weight, crown-rump length, and bone length. These effects showed evidence of reversibility, and no histopathological effects on bone were observed. No ribavirin effects were observed regarding neurobehavioral or reproductive development.

14 CLINICAL STUDIES

Clinical Study 1 evaluated peginterferon alfa-2b monotherapy. See PegIntron Powder for Injection Package Insert for information about this study.

14.1 Ribavirin/Peginterferon alfa-2b Combination Therapy

Adult Subjects

<u>*Study 2*</u>

A randomized study compared treatment with two peginterferon alfa-2b/ribavirin regimens [peginterferon alfa-2b 1.5 mcg/kg subcutaneously once weekly/ribavirin 800 mg orally daily (in divided doses); peginterferon alfa-2b 1.5 mcg/kg subcutaneously once weekly for 4 weeks then 0.5 mcg/kg subcutaneously once weekly for 44 weeks/ribavirin 1000 or 1200 mg orally daily (in divided doses)] with interferon alfa-2b [3 MIU subcutaneously three times weekly/ribavirin 1000 or 1200 mg orally daily (in divided doses)]

in 1530 adults with chronic hepatitis C. Interferon-naïve subjects were treated for 48 weeks and followed for 24 weeks posttreatment. Eligible subjects had compensated liver disease, detectable HCV-RNA, elevated ALT, and liver histopathology consistent with chronic hepatitis.

Response to treatment was defined as undetectable HCV-RNA at 24 weeks posttreatment (see **Table 14**). The response rate to the peginterferon alfa-2b 1.5 mcg/kg plus ribavirin 800 mg dose was higher than the response rate to interferon alfa-2b/ribavirin (see **Table 14**).The response rate to peginterferon alfa-2b 1.5#0.5 mcg/kg/ribavirin was essentially the same as the response to interferon alfa-2b/ribavirin (data not shown).

Table 14: Rates of Response to Combination Treatment

	Peginterferon alfa-2b 1.5 mcg/kg once weekly Ribavirin 800 mg once daily	**Interferon alfa-2b 3 MIU three times weekly Ribavirin 1000/1200 mg**
Overall Response*, †	52% (264/511)	46% (231/505)
Genotype 1	41% (141/348)	33% (112/343)
Genotype 2 to 6	75% (123/163)	73% (119/162)

*****Serum HCV-RNA was measured with a research-based quantitative polymerase chain reaction assay by a central laboratory.
†Difference in overall treatment response (Peginterferon alfa-2b/ribavirin vs. interferon alfa-2b/ ribavirin) is 6% with 95% confidence interval of (0.18, 11.63) adjusted for viral genotype and presence of cirrhosis at baseline. Response to treatment was defined as undetectable HCV-RNA at 24 weeks posttreatment.

Subjects with viral genotype 1, regardless of viral load, had a lower response rate to peginterferon alfa-2b (1.5 mcg/kg)/ribavirin (800 mg) compared to subjects with other viral genotypes. Subjects with both poor prognostic factors (genotype 1 and high viral load) had a response rate of 30% (78/256) compared to a response rate of 29% (71/247) with interferon alfa-2b/ribavirin combination therapy. Subjects with lower body weight tended to have higher adverse-reaction rates [see *Adverse Reactions (6.1)*] and higher response rates than subjects with higher body weights. Differences in response rates between treatment arms did not substantially vary with body weight.

Treatment response rates with peginterferon alfa-2b/ribavirin combination therapy were 49% in men and 56% in women. Response rates were lower in African American and Hispanic subjects and higher in Asians compared to Caucasians. Although African Americans had a higher proportion of poor prognostic factors compared to Caucasians, the number of non-Caucasians studied (11% of the total) was insufficient to allow meaningful conclusions about differences in response rates after adjusting for prognostic factors in this study.

Liver biopsies were obtained before and after treatment in 68% of subjects. Compared to baseline approximately two-thirds of subjects in all treatment groups were observed to have a modest reduction in inflammation.

Study 3

In a large, United States, community-based study (Study 3), 4913 subjects with chronic hepatitis C were randomized to receive peginterferon alfa-2b 1.5 mcg/kg subcutaneously once weekly in combination with a ribavirin dose of 800 to 1400 mg (weight-based dosing [WBD]) or 800 mg (flat) orally daily (in divided doses) for 24 or 48 weeks based on genotype. Response to treatment was defined as undetectable HCV-RNA (based on an assay with a lower limit of detection of 125 IU/mL) at 24 weeks posttreatment. Treatment with peginterferon alfa-2b 1.5 mcg/kg and ribavirin 800 to 1400 mg resulted in a higher sustained virologic response compared to peginterferon alfa-2b in combination with a flat 800 mg daily dose of ribavirin. Subjects weighing > 105 kg obtained the greatest benefit with WBD, although a modest benefit was also observed in subjects weighing > 85 to 105 kg (see **Table 15**). The benefit of WBD in subjects weighing > 85 kg was observed with HCV genotypes 1-3. Insufficient data were available to reach conclusions regarding other genotypes. Use of WBD resulted in an increased incidence of anemia [see *Adverse Reactions (6.1)*].

Table 15: SVR Rate by Treatment and Baseline Weight - Study 3

Treatment Group	**Subject Baseline Weight**			
	<65 kg (<143 lb)	**65-85 kg (143-188 lb)**	**>85-105 kg (>188-231 lb)**	**>105 kg (>231 lb)**
WBD*	50% (173/348)	45% (449/994)	42% (351/835)	47% (138/292)
Flat	51% (173/342)	44% (443/1011)	39% (318/819)	33% (91/272)

*****p=0.01, primary efficacy comparison (based on data from subjects weighing 65 kg or higher at baseline and utilizing a logistic regression analysis that includes treatment [WBD or Flat], genotype and presence/absence of advanced fibrosis, in the model).

A total of 1552 subjects weighing > 65 kg in Study 3 had genotype 2 or 3 and were randomized to 24 or 48 weeks of therapy. No additional benefit was observed with the longer treatment duration.

Study 4

A large randomized study compared the safety and efficacy of treatment for 48 weeks with two peginterferon alfa-2b/ribavirin regimens [peginterferon alfa-2b 1.5 mcg/kg and 1 mcg/kg subcutaneously once weekly both in combination with ribavirin 800 to 1400 mg PO daily (in two divided doses)] and Pegasys 180 mcg subcutaneously once weekly in combination with Copegus 1000 to 1200 mg PO daily (in two divided doses) in 3070 treatment-naïve adults with chronic hepatitis C genotype 1. In this study, lack of early

virologic response by treatment Week 12 (subjects who do not achieve undetectable HCV-RNA or ≥2 $\log_{10}$ reduction from baseline) was the criteria for discontinuation of treatment. Sustained Virologic Response (SVR) to the treatment was defined as undetectable HCV-RNA (Roche COBAS TaqMan assay, a lower limit of quantitation of 27 IU/mL) at 24 weeks posttreatment [see **Table 16**].

Table 16: Response Rate by Treatment

	% (number) of Patients		
Treatment Group	**Peginterferon alfa-2b 1.5 mcg/kg/Ribavirin**	**Peginterferon alfa-2b 1 mcg/kg/Ribavirin**	**Pegasys 180 mcg/Copegus**
SVR	40 (406/1019)	38 (386/1016)	41 (423/1035)

In all three treatment groups, overall SVR rates were similar. In subjects with poor prognostic factors, subjects randomized to peginterferon alfa-2b (1.5 mcg/kg)/ribavirin or Pegasys/Copegus achieved higher SVR rates compared to those randomized to the peginterferon alfa-2b 1 mcg/kg/ribavirin arm. In all arms, SVR rates were lower in subjects with poor prognostic factors compared to those without. For the peginterferon alfa-2b 1.5 mcg/kg plus ribavirin dose, SVR rates for those with and without, respectively, the following baseline factors were as follows: cirrhosis (10% vs. 42%), normal ALT levels (32% vs. 42%), baseline viral load >600,000 IU/mL (35% vs. 61%), >40 years old (38% vs. 50%), and African American subjects (23% vs. 44%). In subjects with undetectable HCV-RNA at treatment week 12 who received peginterferon alfa-2b (1.5 mcg/kg)/ribavirin, the SVR rate was 81% (328/407).

Study 5 - Ribavirin/Peginterferon alfa-2b Combination Therapy in Prior Treatment Failures

In a noncomparative trial, 2293 patients with moderate to severe fibrosis who failed previous treatment with combination alpha interferon/ribavirin were re-treated with peginterferon alfa-2b, 1.5 mcg/kg subcutaneously, once weekly, in combination with weight adjusted ribavirin. Eligible patients included prior nonresponders (patients who were HCV-RNA positive at the end of a minimum 12 weeks of treatment) and prior relapsers (patients who were HCV-RNA negative at the end of a minimum 12 weeks of treatment and subsequently relapsed after posttreatment follow-up). Patients who were negative at Week 12 were treated for 48 weeks and followed for 24 weeks posttreatment. Response to treatment was defined as undetectable HCV-RNA at 24 weeks posttreatment (measured using a research-based test, limit of detection 125 IU/mL). The overall response rate was 22% (497/2293) (99% CI: 19.5, 23.9). Patients with the following characteristics were less likely to benefit from retreatment: previous nonresponse, previous pegylated interferon treatment, significant bridging fibrosis or cirrhosis, and genotype 1 infection.

The retreatment sustained virologic response rates by baseline characteristics are summarized in **Table 17.**

Table 17: SVR Rates by Baseline Characteristics of Prior Treatment Failures

		Overall SVR by Previous Response and Treatment			
		Nonresponder		Relapser	
HCV Genotype/ Metavir Fibrosis Score		**alfa interferon/ Ribavirin % (number of patients)**	**peginterferon (2a and 2b combined)/ Ribavirin % (number of patients)**	**alfa interferon/ Ribavirin % (number of patients)**	**peginterferon (2a and 2b combined)/ Ribavirin % (number of patients)**
Overall		18 (158/903)	6 (30/476)	43 (130/300)	35 (113/344)
HCV 1		13 (98/761)	4 (19/431)	32 (67/208)	23 (56/243)
	F2	18 (36/202)	6 (7/117)	42 (33/79)	32 (23/72)
	F3	16 (38/233)	4 (4/112)	28 (16/58)	21 (14/67)
	F4	7 (24/325)	4 (8/202)	26 (18/70)	18 (19/104)
HCV 2/3		49 (53/109)	36 (10/28)	67 (54/81)	57 (52/92)
	F2	68 (23/34)	56 (5/9)	76 (19/25)	61 (11/18)
	F3	39 (11/28)	38 (3/8)	67 (18/27)	62 (18/29)
	F4	40 (19/47)	18 (2/11)	59 (17/29)	51 (23/45)
HCV 4		17 (5/29)	7 (1/15)	88 (7/8)	50 (4/8)

Achievement of an undetectable HCV-RNA at treatment week 12 was a strong predictor of sustained virologic response (SVR). In this trial, 1470 (64%) subjects did not achieve an undetectable HCV-RNA at treatment week 12, and were offered enrollment into long-term treatment trials, due to an inadequate treatment response. Of the 823 (36%) subjects who were HCV-RNA undetectable at treatment week 12, those infected with genotype 1 had an SVR of 48% (245/507), with a range of responses by fibrosis scores (F4-F2) of 39-55%. Subjects infected with genotype 2/3 who were HCV-RNA undetectable at treatment week 12 had an overall SVR of 70% (196/281), with a range of responses by fibrosis scores (F4-F2) of 60-83%. For all genotypes, higher fibrosis scores were associated with a decreased likelihood of achieving SVR.

Pediatric Subjects

Previously untreated pediatric subjects 3 to 17 years of age with compensated chronic hepatitis C and detectable HCV-RNA were treated with ribavirin 15 mg/kg per day plus peginterferon alfa-2b 60 mcg/m^2 once weekly for 24 or 48 weeks based on HCV genotype and baseline viral load. All subjects were to be followed for 24 weeks posttreatment. A total of 107 subjects received

treatment of whom 52% were female, 89% were Caucasian, and 67% were infected with HCV Genotype 1. Subjects infected with Genotypes 1, 4 or Genotype 3 with HCV-RNA ≥ 600,000 IU/mL received 48 weeks of therapy while those infected with Genotype 2 or Genotype 3 with HCV-RNA < 600,000 IU/mL received 24 weeks of therapy. The study results are summarized in **Table 18**.

Table 18: Sustained Virologic Response Rates by Genotype and Assigned Treatment Duration - Pediatric Study

	All Subjects N = 107	
	24 Weeks Virologic Response	**48 Weeks Virologic Response**
Genotype	**n*,† (%)**	**n*,† (%)**
All	26/27 (96.3)	44/80 (55.0)
1	-	38/72 (52.8)
2	14/15 (93.3)	-
3‡	12/12 (100)	2/3 (66.7)
4	-	4/5 (80.0)

*Response to treatment was defined as undetectable HCV-RNA at 24 weeks posttreatment.
†n = number of responders/number of subjects with given genotype, and assigned treatment duration.
‡Subjects with genotype 3 low viral load (<600,000 IU/mL) were to receive 24 weeks of treatment while those with genotype 3 and high viral load were to receive 48 weeks of treatment.

14.2 Ribavirin/Interferon alfa-2b Combination Therapy

Adult Subjects

Previously Untreated Subjects

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 subjects weighing ≤ 75 kg) plus interferon alfa-2b for injection 3 MIU three times weekly or interferon alfa-2b for 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 interferon alfa-2b plus placebo treatment arm. The US study enrolled 912 subjects 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 subjects (65% male, 95% Caucasian, mean Knodell score 6.8, and 58% genotype 1).

Study results are summarized in **Table 19**.

Table 19: Virologic and Histologic Responses: Previously Untreated Subjects*

	US Study				**International Study**		
	24 weeks of treatment		**48 weeks of treatment**		**24 weeks of treatment**	**48 weeks of treatment**	
	interferon alfa-2b plus ribavirin (N=228)	**Interferon alfa-2b plus Placebo (N=231)**	**interferon alfa-2b plus ribavirin (N=228)**	**Interferon alfa-2b plus Placebo (N=225)**	**interferon alfa-2b plus ribavirin (N=265)**	**interferon alfa-2b plus ribavirin (N=268)**	**interferon alfa-2b plus Placebo (N=266)**
Virologic Response							
Responder†	65 (29)	13 (6)	85 (37)	27 (12)	86 (32)	113 (42)	46 (17)
Nonresponder	147 (64)	194 (84)	110 (48)	168 (75)	158 (60)	120 (45)	196 (74)
Missing Data	16 (7)	24 (10)	33 (14)	30 (13)	21 (8)	35 (13)	24 (9)
Histologic Response							
Improvement‡	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 subjects.
†Defined as HCV-RNA below limit of detection using a research-based RT-PCR assay at end of treatment and during follow-up period.
‡Defined as posttreatment (end of follow-up) minus pretreatment liver biopsy Knodell HAI score (I+II+III) improvement of ≥2 points.

Of subjects who had not achieved HCV-RNA below the limit of detection of the research-based assay by Week 24 of ribavirin/ interferon alfa-2b treatment, less than 5% responded to an additional 24 weeks of combination treatment.
Among subjects with HCV Genotype 1 treated with ribavirin/interferon alfa-2b 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 subjects with HCV nongenotype 1 randomized to ribavirin/interferon alfa-2b therapy for 48 weeks compared to 24 weeks.
Relapse Subjects
Subjects 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 subjects weighing ≤ 75 kg) plus interferon alfa-2b 3 MIU three times weekly or interferon alfa-2b plus placebo for 24 weeks followed by 24 weeks of off-therapy follow-up. The US study enrolled 153 subjects 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 subjects (64% male, 95% Caucasian, mean Knodell score 6.6, and 56% genotype 1). Study results are summarized in **Table 20.**

Table 20: Virologic and Histologic Responses: Relapse Subjects*

	US Study		**International Study**	
	interferon alfa-2b plus ribavirin (N=77)	**interferon alfa-2b plus Placebo (N=76)**	**interferon alfa-2b plus ribasphere (N=96)**	**interferon alfa-2b 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 subjects.
†Defined as HCV-RNA below limit of detection using a research-based RT-PCR assay at end of treatment and during follow-up period.
‡Defined as posttreatment (end of follow-up) minus pretreatment liver biopsy Knodell HAI score (I+II+III) improvement of ≥2 points.

Virologic and histologic responses were similar among male and female subjects in both the previously untreated and relapse studies.
Pediatric Subjects
Pediatric subjects 3 to 16 years of age with compensated chronic hepatitis C and detectable HCV-RNA (assessed by a central laboratory using a research-based RT-PCR assay) were treated with ribavirin 15 mg/kg per day plus interferon alfa-2b 3 MIU/m^2 three times weekly for 48 weeks followed by 24 weeks of off-therapy follow-up. A total of 118 subjects received treatment who were 57% male, 80% Caucasian, and 78% genotype 1. Subjects <5 years of age received ribavirin oral solution and those ≥5 years of age received either ribavirin oral solution or capsules.
Study results are summarized in **Table 21**.

Table 21: Virologic Response: Previously Untreated Pediatric Subjects*

	interferon alfa-2b 3 MIU/m^2 three times weekly plus Ribavirin 15 mg/kg/day
Overall Response† (N=118)	54 (46)
Genotype 1 (N=92)	33 (36)
Genotype non-1 (N=26)	21 (81)

*Number (%) of subjects
†Defined as HCV-RNA below limit of detection using a research-based RT-PCR assay at end of treatment and during follow-up period.

Subjects with viral genotype 1, regardless of viral load, had a lower response rate to interferon alfa-2b/ribavirin combination therapy compared to subjects with genotype non-1, 36% vs. 81%. Subjects with both poor prognostic factors (genotype 1 and high viral load) had a response rate of 26% (13/50).

16 HOW SUPPLIED/STORAGE AND HANDLING

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 edible, green pharmaceutical ink. Ribasphere® (Ribavirin capsules), 200 mg are packaged in HDPE bottles with child-resistant closures containing 42 capsules (NDC 66435-101-42), 56 capsules (NDC 66435-101-56), 70 capsules (NDC 66435-101-70), 84 capsules (NDC 66435-101-84), 140 capsules (NDC 66435-101-14), 168 capsules (NDC 66435-101-16) and 180 capsules (NDC 66435-101-18).
The bottle of Ribasphere Capsules should be stored at 25°C (77°F); excursions permitted to 15° to 30°C (59° to 86°F) [see USP Controlled Room Temperature].

17 PATIENT COUNSELING INFORMATION

[See FDA-Approved Medication Guide]

17.1 Anemia

The most common adverse experience occurring with Ribasphere Capsules is anemia, which may be severe [see *Warnings and Precautions (5.2)* and *Adverse Reactions (6)*]. Patients should be advised that laboratory evaluations are required prior to starting therapy and periodically thereafter [see *Dosage and Administration (2.3)*]. It is advised that patients be well hydrated, especially during the initial stages of treatment.

17.2 Pregnancy

Patients must be informed that Ribasphere Capsules may cause birth defects and death of the unborn child. Ribasphere 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 Ribasphere. Ribasphere 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 Ribasphere 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 (4)*, *Warnings and Precautions (5.1)*, and *Use in Specific Populations (8.1)*].
If pregnancy does occur during treatment or during 6 months post therapy, the patient must be advised of the teratogenic risk of Ribasphere 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 1-800-593-2214.

17.3 Risks versus Benefits

Patients receiving Ribasphere Capsules should be informed of the benefits and risks associated with treatment, directed in its appropriate use, and referred to the patient **MEDICATION GUIDE**. 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.
Patients should be informed about what to do in the event they miss a dose of Ribasphere; the missed dose should be taken as soon as possible during the same day. Patients should not double the next dose. Patients should be advised to contact their healthcare provider if they have questions.

Manufactured by
DSM PHARMACEUTICALS, INC.
Greenville, NC 27834, USA
Manufactured for
Kadmon Pharmaceuticals, LLC
Warrendale, PA 15086, USA

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MEDICATION GUIDE

Ribasphere® (R#b-a-sphere) (ribavirin capsules)

Rx Only

Read this Medication Guide before you start taking Ribasphere® (ribavirin capsules), and each time you get a refill. There may be new information. This information does not take the place of talking to your healthcare provider about your medical condition or your treatment.

What is the most important information I should know about Ribasphere (ribavirin capsules)?

1. **Do Not take Ribasphere (ribavirin capsules) alone to treat chronic hepatitis C infection.** Ribasphere (ribavirin capsules) should be used in combination with **either interferon alfa-2b (Intron A®[1]) or peginterferon alfa-2b (PegIntron®[2])** to treat chronic hepatitis C infection.

2. **Ribasphere (ribavirin capsules) may cause a significant drop in your red blood cell count and cause anemia in some cases. Anemia has been associated with worsening of Heart Problems, and in rare cases can cause a Heart Attack and Death.** Tell your healthcare provider if you have ever had any heart problems. Ribasphere **(ribavirin capsules)** may not be right for you. **Seek medical attention right away if you experience chest pain.**

3. **Ribasphere (ribavirin capsules) may cause Birth Defects or Death of your unborn baby. Do Not Take Ribasphere (ribavirin capsules) if you or your sexual partner is pregnant or plan to become pregnant. Do Not become Pregnant within 6 months after discontinuing Ribasphere (ribavirin capsules) therapy.** You must use 2 forms of birth control when you take Ribasphere **(ribavirin capsules)** and for the 6 months after treatment.
   # Females must have a pregnancy test before starting Ribasphere (ribavirin capsules), every month while taking Ribasphere (ribavirin capsules), and every month for the 6 months after the last dose of Ribasphere (ribavirin capsules).
   # **If you or your female sexual partner becomes pregnant while taking Ribasphere (ribavirin capsules), tell your healthcare provider right away. You or your healthcare provider should contact the Ribavirin Pregnancy Registry by calling 1-800-593-2214. The Ribavirin Pregnancy Registry collects information about what happens to mothers and their babies if the mother takes Ribasphere (ribavirin capsules) while she is pregnant.**

What is Ribasphere (ribavirin capsules)?

Ribasphere is a medicine used with either interferon alfa-2b or peginterferon alfa-2b to treat chronic (lasting a long time) hepatitis C infection in people 3 years and older with liver disease.
It is not known if Ribasphere (ribavirin capsules) use for longer than one year is safe and will work.
It is not known if Ribasphere (ribavirin capsules) use in children younger than 3 years old is safe and will work.

Who should not take Ribasphere (ribavirin capsules)?

See "**What is the most important information I should know about Ribasphere (ribavirin capsules)?"**
Do not take Ribasphere (ribavirin capsules) if you have:

- or ever had serious allergic reactions to the ingredients in Ribasphere (ribavirin capsules). See the end of this Medication Guide for a complete list of ingredients.
- certain types of hepatitis (autoimmune hepatitis).
- certain blood disorders (hemoglobinopathies).
- severe kidney disease.
- take didanosine (VIDEX®[3]).

Talk to your healthcare provider before taking Ribasphere (ribavirin capsules) if you have any of these conditions.

What should I tell my healthcare provider before taking Ribasphere (ribavirin capsules)?

Before you take Ribasphere (ribavirin capsules), tell your healthcare provider if you have or ever had:

- treatment for hepatitis C that did not work for you.
- breathing problems. Ribasphere (ribavirin capsules) may cause or worsen breathing problems you already have.
- vision problems. Ribasphere (ribavirin capsules) may cause eye problems or worsen eye problems you already have. You should have an eye exam before you start treatment with Ribasphere (ribavirin capsules).

- certain blood disorders such as anemia (low red blood cell count).
- high blood pressure, heart problems, or have had a heart attack. Your healthcare provider should check your blood and heart before you start treatment with Ribasphere (ribavirin capsules).
- thyroid problems
- liver problems other than hepatitis C infection
- human immunodeficiency virus (HIV) or any immunity problems
- mental health problems, including depression or thoughts of suicide
- kidney problems
- an organ transplant
- diabetes. Ribasphere (ribavirin capsules) may make your diabetes worse or harder to treat.
- any other medical condition
- are breast feeding. It is not known if Ribasphere (ribavirin capsules) passes into your breast milk. You and your healthcare provider should decide if you will take Ribasphere (ribavirin capsules) or breast feed.

Tell your healthcare provider about all the medicines you take, including prescription medicines, vitamins, and herbal supplements. Ribasphere may affect the way other medicines work.
Especially tell your healthcare provider if you take didanosine (VIDEX) or azathioprine (Imuran® and Azasan®).
Know the medicines you take. Keep a list of them to show your healthcare provider or pharmacist when you get a new medicine.

How should I take Ribasphere (ribavirin capsules)?

- Take Ribasphere (ribavirin capsules) exactly as your healthcare provider tells you. Your healthcare provider will tell you how much Ribasphere (ribavirin capsules) to take and when to take it.
- Take Ribasphere (ribavirin capsules) with food.
- Take **Ribasphere Capsules** whole. Do not open, break, or crush Ribasphere Capsules before swallowing. If you cannot swallow **Ribasphere Capsules** whole, tell your healthcare provider.
- If you miss a dose of Ribasphere (ribavirin capsules), take the missed dose as soon as possible during the same day. Do not double the next dose. If you have questions about what to do, call your healthcare provider.
- If you take too much Ribasphere (ribavirin capsules), call your healthcare provider or Poison Control Center at 1-800-222-1222, or go to the nearest hospital emergency room right away.

What are the possible side effects of Ribasphere (ribavirin capsules)?
Ribasphere (ribavirin capsules) may cause serious side effects, including:
See "What is the most important information I should know about Ribasphere (ribavirin capsules)?"

- **Swelling and irritation of your pancreas (pancreatitis)**. You may have stomach pain, nausea, vomiting, or diarrhea.
- **Serious breathing problems.** Difficulty breathing may be a sign of a serious lung infection (pneumonia) that can lead to death.
- **Serious eye problems** that may lead to vision loss or blindness.
- **Dental problems.** Your mouth may be very dry, which can lead to problems with your teeth and gums.
- **Severe depression**
- **Suicidal thoughts and attempts.** Adults and children who take Ribasphere (ribavirin capsules), especially teenagers are more likely to have suicidal thoughts or attempt to hurt themselves while taking Ribasphere (ribavirin capsules). Call your healthcare provider right away or go to the nearest hospital emergency room if you have new or worse depression or thoughts about suicide or dying.
- **Severe blood disorders.** An increased risk when used in combination with pegylated alpha interferons and azathioprine.
- **Weight loss and slowed growth in children**

Tell your provider right away if you have any side effect that bothers you or that does not go away.
The most common side effects of Ribasphere (ribavirin capsules) include:
- flu-like symptoms - feeling tired, headache, shaking along with high temperature (fever), nausea, and muscle aches.

- mood changes, feeling irritable.

The most common side effects of Ribasphere (ribavirin capsules) in children include:
- a decrease in the blood cells that fight infection (neutropenia).

- a decrease in appetite.

- stomach pain and vomiting.

Tell your healthcare provider if you have any side effect that bothers you or that does not go away.
These are not all the possible side effects of Ribasphere (ribavirin capsules). For more information ask your healthcare provider or pharmacist.
Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

How should I store Ribasphere (ribavirin capsules)?

Store **Ribasphere (ribavirin capsules)** between 59#F to 86#F (15#C to 30#C).
Keep Ribasphere (ribavirin capsules) and all medicines out of the reach of children.

GENERAL INFORMATION ABOUT THE SAFE AND EFFECTIVE USE OF RIBASPHERE (RIBAVIRIN CAPSULES).

It is not known if treatment with Ribasphere (ribavirin capsules) will cure hepatitis C virus infections or prevent cirrhosis, liver failure, or liver cancer that can be caused by hepatitis C virus infections. It is not known if taking Ribasphere (ribavirin capsules) will prevent you from infecting another person with the hepatitis C virus.
Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. Do not use Ribasphere (ribavirin capsules) for a condition for which it was not prescribed. Do not give Ribasphere (ribavirin capsules) to other people, even if they have the same symptoms that you have. It may harm them.
This Medication Guide summarizes the most important information about Ribasphere (ribavirin capsules). If you would like more information, talk with your healthcare provider. You can ask your pharmacist or health care provider for information about Ribasphere (ribavirin capsules) that is written for health professionals.

What are the ingredients in Ribasphere (ribavirin capsules)?

Active ingredients: ribavirin
Ribasphere (ribavirin capsules)
Inactive ingredients: croscarmellose sodium, lactose monohydrate, microcrystalline cellulose, and povidone. 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, Yellow Iron Oxide, NF, dehydrated alcohol USP, FD&C Blue #2 Aluminum Lake, isopropyl alcohol USP, propylene glycol USP, Shellac, NF, strong ammonia solution, NF and titanium dioxide.
This Medication Guide has been approved by the U.S. Food and Drug Administration

Manufactured by:
DSM PHARMACEUTICALS, INC.
Greenville, NC 27834, USA
for
Kadmon Pharmaceuticals, LLC
Warrendale, PA 15086, USA
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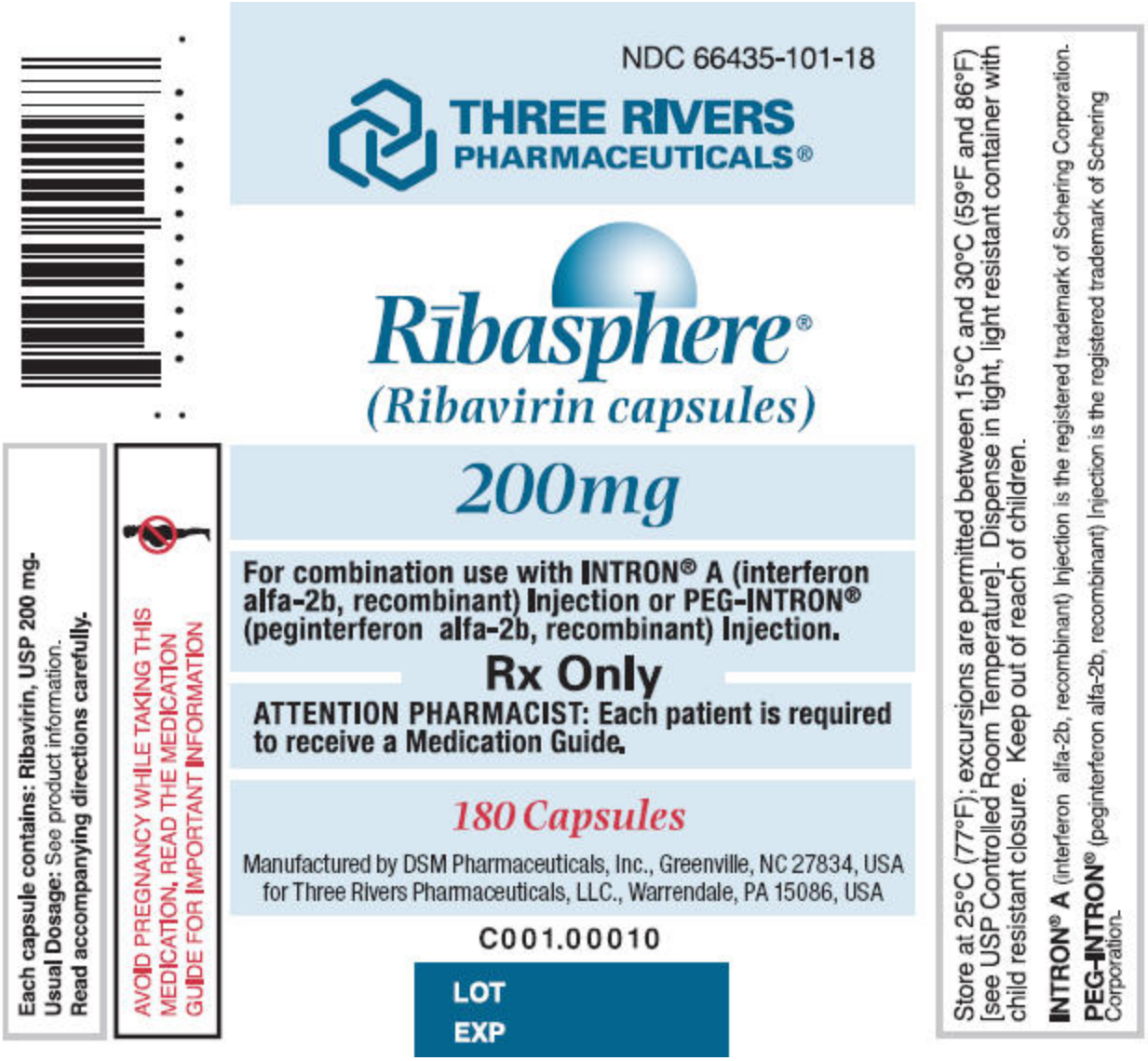
U.S. Patent No. 6,720,000
C001.00068-01/11
Issued: 09/12
1. INTRON A is a registered trademark of Schering Corporation
2. PegIntron is a registered trademark of Schering Corporation
3. VIDEX® is a registered trademark of Bristol-Myers Squibb Company.
4. Imuran® is a registered trademark of Prometheus Laboratories, Inc.
5. Azasan® is a registered trademark of AAI Properties, Inc.

PRINCIPAL DISPLAY PANEL - BOTTLE LABEL



Bottle Label

NDC 66435-101-18
Kadmon Pharmaceuticals
Ribasphere®
(Ribavirin capsules)
200 mg
For combination use with INTRON® A (interferon alfa-2b, recombinant) Injection or PEG-INTRON® (peginterferon alfa-2b, recombinant) Injection.
Rx Only
ATTENTION PHARMACIST: Each patient is required to receive a Medication Guide.
180 Capsules
Manufactured by DSM Pharmaceuticals, Inc., Greenville, NC 27834, USA
for Kadmon Pharmaceuticals, LLC., Warrendale, PA 15086, USA
C001.00109
Each capsule contains: Ribavirin, USP 200 mg.
Usual Dosage: See product information.
Read accompanying directions carefully.
AVOID PREGNANCY WHILE TAKING THIS

MEDICATION. READ THE MEDICATION
GUIDE FOR IMPORTANT INFORMATION
Store at 25°C (77°F); excursions are permitted between 15°C and 30°C (59°F and 86°F)
[see USP controlled Room Temperature]. Dispense in tight, light resistant container with
child resistant closure. Keep out of reach of children.

INTRON® A (interferon alfa-2b, recombinant) Injection is the registered trademark of Schering Corporation.

PEG-INTERON® (peginterferon alfa-2b, recombinant) Injection is the registered trademark of Schering Corporation.

Revised: 12/2012 Distributed by: Kadmon Pharmaceuticals, LLC