

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use ribavirin safely and effectively. See full prescribing information for ribavirin.

Ribavirin Tablets

Initial U.S. Approval: 2002

WARNING: RISK OF SERIOUS DISORDERS AND RIBAVIRIN-ASSOCIATED EFFECTS

See full prescribing information for complete boxed warning.

- Ribavirin monotherapy, including ribavirin, is not effective for the treatment of chronic hepatitis C virus infection (Boxed Warning).
- The hemolytic anemia associated with ribavirin therapy may result in worsening of cardiac disease and lead to fatal and nonfatal myocardial infarctions. Patients with a history of significant or unstable cardiac disease should not be treated with ribavirin (2.3, 5.2, 6.1).
- Significant teratogenic and embryocidal effects have been demonstrated in all animal species exposed to ribavirin. Therefore, ribavirin is contraindicated in women who are pregnant and in the male partners of women who are pregnant. Extreme care must be taken to avoid pregnancy during therapy and for 6 months after completion of treatment in both female patients and in female partners of male patients who are taking ribavirin therapy (4, 5.1, 8.1).

RECENT MAJOR CHANGES

Boxed Warning	10/2010
Indications and Usage (1)	10/2010
Dosage and Administration (2.2, 2.3, 2.4, 2.5)	10/2010
Contraindications (4)	12/2010
Warnings and Precautions (5.1, 5.2, 5.3, 5.5, 5.6, 5.7, 5.8, 5.9)	10/2010
Warnings and Precautions, Hepatic Failure (5.3)	12/2010

INDICATIONS AND USAGE

Ribavirin is a nucleoside analogue indicated for the treatment of chronic hepatitis C (CHC) virus infection in combination with peginterferon alfa-2a in adults with compensated liver disease not previously treated with interferon alpha, and in CHC patients coinfecting with HIV (1)

DOSAGE AND ADMINISTRATION

- CHC: Ribavirin is administered according to body weight and genotype (2.1)
- CHC with HIV coinfection: 800 mg by mouth daily for a total of 48 weeks, regardless of genotype (2.2)
- Dose reduction or discontinuation is recommended in patients experiencing certain adverse reactions or renal impairment (2.4, 2.5)

DOSAGE FORMS AND STRENGTHS

- Ribavirin tablets 200 mg or 400 mg or 500 mg or 600 mg (3)

CONTRAINDICATIONS

- Pregnant women and men whose female partners are pregnant (4, 5.1, 8.1)
- Hemoglobinopathies (4)
- Coadministration with didanosine (4, 7.1)

Ribavirin in combination with peginterferon alfa-2a is contraindicated in patients with:

- Autoimmune hepatitis (4)
- Hepatic decompensation in cirrhotic patients (4, 5.3)

FULL PRESCRIBING INFORMATION

WARNING: RISK OF SERIOUS DISORDERS AND RIBAVIRIN-ASSOCIATED EFFECTS

Ribavirin monotherapy is not effective for the treatment of chronic hepatitis C virus infection and should not be used alone for this indication.

The primary clinical toxicity of ribavirin is hemolytic anemia. The anemia associated with ribavirin therapy may result in worsening of cardiac disease and lead to fatal and nonfatal myocardial infarctions. Patients with a history of significant or unstable cardiac disease should not be treated with ribavirin [see WARNINGS AND PRECAUTIONS (5.2), ADVERSE REACTIONS (6.1), and DOSAGE AND ADMINISTRATION (2.3)].

Significant teratogenic and/or embryocidal effects have been demonstrated in all animal species exposed to ribavirin. In addition, ribavirin has a multiple dose half-life of 12 days, and it may persist in non-plasma compartments for as long as 6 months. Therefore, ribavirin, including ribavirin, 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 therapy in both female patients and in female partners of male patients who are taking ribavirin therapy. At least two reliable forms of effective contraception must be utilized during treatment and during the 6 month post treatment follow-up period [see CONTRAINDICATIONS (4), WARNINGS AND PRECAUTIONS (5.1), and USE IN SPECIFIC POPULATIONS (8.1)].

1 INDICATIONS AND USAGE

Ribavirin in combination with peginterferon alfa-2a is indicated for the treatment of adults with chronic hepatitis C (CHC) virus infection who have compensated liver disease and have not been previously treated with interferon alpha.

- The following points should be considered when initiating ribavirin combination therapy with peginterferon alfa-2a:
 - This indication is based on clinical trials of combination therapy in patients with CHC and compensated liver disease, some of whom had histological evidence of cirrhosis (Child-Pugh class A), and in patients with clinically stable HIV disease and CD4 count > 100 cells/mm³.
 - This indication is based on achieving undetectable HCV-RNA after treatment for 24 or 48 weeks, based on HCV genotype, and maintaining a Sustained Virologic Response (SVR) 24 weeks after the last dose.
 - Safety and efficacy data are not available for treatment longer than 48 weeks.
 - The safety and efficacy of ribavirin and peginterferon alfa-2a therapy have not been established in liver or other transplant recipients, patients with decompensated liver disease, or previous non-responders to interferon therapy.
 - The safety and efficacy of ribavirin therapy for the treatment of adenovirus, RSV, parainfluenza or influenza infections have not been established. Ribavirin 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.

2 DOSAGE AND ADMINISTRATION

2.1 Chronic Hepatitis C Monoinfection

The recommended dose of ribavirin tablets is provided in Table 1. The recommended duration of treatment for patients previously untreated with ribavirin and interferon is 24 to 48 weeks. The daily dose of ribavirin is 800 mg to 1200 mg administered orally in two divided doses. The dose should be individualized to the patient depending on baseline disease characteristics (e.g., genotype), response to therapy, and tolerability of the regimen (see Table 1). Ribavirin should be taken with food.

Table 1

Peginterferon alfa-2a and Ribavirin Dosing Recommendations			
Hepatitis C Virus (HCV) Genotype	Peginterferon Alfa-2a Dose*	Ribavirin Dose	Duration
Genotypes 1, 4	180 mcg	< 75 kg = 1000 mg > 75 kg = 1200 mg	48 weeks
Genotypes 2, 3	180 mcg	800 mg	24 weeks

Genotypes 2 and 3 showed no increased response to treatment beyond 24 weeks (see Table 6). Data on genotypes 5 and 6 are insufficient for dosing recommendations. *See Peginterferon alfa-2a Package Insert for further details on peginterferon alfa-2a dosing and administration.

2.2 Chronic Hepatitis C with HIV Coinfection

The recommended dose for treatment of chronic hepatitis C in patients coinfecting with HIV is peginterferon alfa-2a 180 mcg subcutaneous once weekly and ribavirin 800 mg by mouth daily for a total duration of 48 weeks, regardless of HCV genotype. Ribavirin should be taken with food.

2.3 Dose Modifications

If severe adverse reactions or laboratory abnormalities develop during combination ribavirin/peginterferon alfa-2a therapy, the dose should be modified or discontinued, if appropriate, until the adverse reactions abate or decrease in severity. If intolerance persists after dose adjustment, ribavirin/peginterferon alfa-2a therapy should be discontinued. Table 2 provides guidelines for dose modifications and discontinuation based on the patient's hemoglobin concentration and cardiac status. Ribavirin should be administered with caution to patients with pre-existing cardiac disease. Patients should be assessed before commencement of therapy and should be appropriately monitored during therapy. If there is any deterioration of cardiovascular status, therapy should be stopped [see WARNINGS AND PRECAUTIONS (5.2)].

Table 2

Ribavirin Dosage Modification Guidelines		
Laboratory Values	Reduce Only Ribavirin Dose to 600 mg/day* if:	Discontinue Ribavirin if:
Hemoglobin in patients with no cardiac disease	< 10 g/dL	< 8.5 g/dL
Hemoglobin in patients with history of stable cardiac disease	≥ 2 g/dL decrease in hemoglobin during any 4 week period treatment	< 12 g/dL despite 4 weeks at reduced dose

* One 200 mg tablet in the morning and two 200 mg tablets in the evening. Once ribavirin has been withheld due to either a laboratory abnormality or clinical manifestation, an attempt may be made to restart ribavirin at 800 mg daily and further increase the dose to 800 mg daily. However, it is not recommended that ribavirin be increased to the original assigned dose (1000 mg to 1200 mg). See peginterferon alfa-2a full prescribing information for recommendations on peginterferon alfa-2a dose modification.

2.4 Discontinuation of Dosing

Discontinuation of peginterferon alfa-2a/ribavirin therapy should be considered if the patient has failed to demonstrate at least a 2 log₁₀ reduction from baseline in HCV RNA by 12 weeks of therapy, or undetectable HCV RNA levels after 24 weeks of therapy. Peginterferon alfa-2a/ribavirin therapy should be discontinued in patients who develop hepatic decompensation during treatment [see WARNINGS AND PRECAUTIONS (5.3)].

2.5 Renal Impairment

Ribavirin should not be used in patients with creatinine clearance < 50 mL/min [see USE IN SPECIFIC POPULATIONS (8.1)].

3 DOSAGE FORMS AND STRENGTHS

Ribavirin tablets for oral administration are available as:

- 200 mg - light pink to pink, round, biconvex, beveled, film-coated tablets;
- 400 mg - light pink to pink, capsule shaped, biconvex, film-coated tablets;
- 500 mg - light pink to pink, modified capsule shaped, biconvex, film-coated tablets;
- 600 mg - light pink to pink, modified capsule shaped, biconvex, film-coated tablets

4 CONTRAINDICATIONS

Ribavirin is contraindicated in:

- Women who are pregnant. Ribavirin may cause fetal harm when administered to a pregnant woman. Ribavirin 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 the fetus [see WARNINGS AND PRECAUTIONS (5.1), USE IN SPECIFIC POPULATIONS (8.1), and PATIENT COUNSELING INFORMATION (7)].
- Men whose female partners are pregnant.

WARNINGS AND PRECAUTIONS

- Birth defects and fetal death with ribavirin: Do not use in pregnancy and for 6 months after treatment. Patients must have a negative pregnancy test prior to therapy, use at least 2 forms of contraception and undergo monthly pregnancy tests (4, 5.1, 8.1)

Peginterferon alfa-2a/Ribavirin: Patients exhibiting the following conditions should be closely monitored and may require dose reduction or discontinuation of therapy:

- Hemolytic anemia may occur with a significant initial drop in hemoglobin. This may result in worsening cardiac disease leading to fatal or nonfatal myocardial infarctions (5.2, 6.1)
- Risk of hepatic failure and death: Monitor hepatic function during treatment and discontinue treatment for hepatic decompensation (5.3)
- Severe hypersensitivity reactions including urticaria, angioedema, bronchoconstriction, and anaphylaxis, and serious skin reactions such as Stevens-Johnson Syndrome (5.4)
- Pulmonary disorders, including pulmonary function impairment and pneumonitis, including fatal cases of pneumonia (5.6)
- Severe depression and suicidal ideation, autoimmune and Infectious disorders, suppression of bone marrow function, pancreatitis, and diabetes (5)
- Bone marrow suppression with azathioprine coadministration (5.7)

ADVERSE REACTIONS

The most common adverse reactions (frequency > 40%) in adults receiving combination therapy are fatigue/asthenia, pyrexia, myalgia, and headache (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Zydus Pharmaceuticals USA Inc. at 1-877-993-8779 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 (7.1)
- Azathioprine: Concomitant use of azathioprine with ribavirin has been reported to induce severe pancytopenia and may increase the risk of azathioprine-related myelotoxicity (7.3)

USE IN SPECIFIC POPULATIONS

- Ribavirin Pregnancy Registry: 1-800-593-2214
- Pediatrics: Safety and efficacy in patients < 18 years old have not been established (8.4)
- Renal Impairment: Do not use in patients with GFR < 50 mL/min (8.7)
- Organ transplant: Safety and efficacy have not been studied (8.10)

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

Revised: 04/2011

FULL PRESCRIBING INFORMATION: CONTENTS*

WARNING: RISK OF SERIOUS DISORDERS AND RIBAVIRIN-ASSOCIATED EFFECTS

1 INDICATIONS AND USAGE

- Patients with hemoglobinopathies (e.g., thalassemia major or sickle-cell anemia).
- In combination with didanosine. Reports of fatal hepatic failure, as well as peripheral neuropathy, pancreatitis, and symptomatic hyperlactatemia/lactic acidosis have been reported in clinical trials [see DRUG INTERACTIONS (7.1)].

Ribavirin and peginterferon alfa-2a combination therapy is contraindicated in patients with:

- Autoimmune hepatitis.
- Hepatic decompensation (Child-Pugh score greater than 6; class B and C) in cirrhotic CHC monoinfected patients before treatment [see WARNINGS AND PRECAUTIONS (5.3)].
- Hepatic decompensation (Child-Pugh score greater than or equal to 6) in cirrhotic CHC patients coinfecting with HIV before treatment [see WARNINGS AND PRECAUTIONS (5.3)].

5 WARNINGS AND PRECAUTIONS

Significant adverse reactions associated with ribavirin/peginterferon alfa-2a combination therapy include severe depression and suicidal ideation, hemolytic anemia, suppression of bone marrow function, autoimmune and infectious disorders, ophthalmologic disorders, cerebrovascular disorders, pulmonary dysfunction, colitis, pancreatitis, and diabetes. The Peginterferon alfa-2a Package Insert should be reviewed in its entirety for additional safety information prior to initiation of combination treatment.

5.1 Pregnancy

Ribavirin may cause birth defects and/or death of the exposed fetus. Ribavirin has demonstrated significant teratogenic and/or embryocidal effects in all animal species in which adequate studies have been conducted. These effects occurred at doses as low as one twentieth of the recommended human dose of ribavirin. Ribavirin therapy should not be started unless a report of a negative pregnancy test has been obtained immediately prior to planned initiation of therapy. Extreme care must be taken to avoid pregnancy in female patients and in female partners of male patients. Patients should be instructed to use at least two forms of effective contraception during treatment and for 6 months after treatment has been stopped. Pregnancy testing should occur monthly during ribavirin therapy and for 6 months after therapy has stopped. [see BOXED WARNING, CONTRAINDICATIONS (4), USE IN SPECIFIC POPULATIONS (8.1), and PATIENT COUNSELING INFORMATION (17)].

5.2 Anemia

The primary toxicity of ribavirin is hemolytic anemia, which was observed in approximately 13% of all ribavirin/peginterferon alfa-2a treated subjects in clinical trials. Anemia associated with ribavirin 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. Caution should be exercised in initiating treatment in any patient with baseline risk of severe anemia (e.g., spherocytosis, history of gastrointestinal bleeding) [see DOSAGE AND ADMINISTRATION (2.3)].

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 (2.3)]. Because cardiac disease may be worsened by drug-induced anemia, appropriate medical therapy instituted. Serious skin reactions including vesiculobullous eruptions, reactions in the spectrum of Stevens-Johnson Syndrome (erythema multiforme major) with varying degrees of skin and mucosal involvement and exfoliative dermatitis (erythroderma) have been reported in patients receiving peginterferon alfa-2a with and without ribavirin. Patients developing signs or symptoms of severe skin reactions must discontinue therapy [see ADVERSE REACTIONS (6.2)].

5.3 Hepatic Failure

Chronic hepatitis C (CHC) patients with cirrhosis may be at risk of hepatic decompensation and death when treated with alpha interferons, including peginterferon alfa-2a. Cirrhotic CHC patients coinfecting with HIV receiving highly active antiretroviral therapy (HAART) and interferon alfa-2a with or without ribavirin appear to be at increased risk for the development of hepatic decompensation compared to patients not receiving HAART. In Study NR15961 [see CLINICAL STUDIES (14.3)], among 129 CHC/HIV cirrhotic patients receiving HAART, 14 (11%) of these patients across all treatment arms developed hepatic decompensation resulting in 6 deaths. All 14 patients were on NRTIs, including stavudine, didanosine, abacavir, zidovudine, and lamivudine. These small numbers of patients do not permit discrimination between specific NRTIs or the associated risk. During treatment, hepatic decompensation and hepatic function should be closely monitored for signs and symptoms of hepatic decompensation. Treatment with peginterferon alfa-2a/ribavirin should be discontinued immediately in patients with hepatic decompensation [see CONTRAINDICATIONS (4)].

5.4 Hypersensitivity

Severe acute hypersensitivity reactions (e.g., urticaria, angioedema, bronchoconstriction, and anaphylaxis) have been observed during alpha interferon and ribavirin therapy. If such a reaction occurs, therapy with peginterferon alfa-2a and ribavirin should be discontinued immediately and appropriate medical therapy instituted. Serious skin reactions including vesiculobullous eruptions, reactions in the spectrum of Stevens-Johnson Syndrome (erythema multiforme major) with varying degrees of skin and mucosal involvement and exfoliative dermatitis (erythroderma) have been reported in patients receiving peginterferon alfa-2a with and without ribavirin. Patients developing signs or symptoms of severe skin reactions must discontinue therapy [see ADVERSE REACTIONS (6.2)].

5.5 Renal Impairment

Ribavirin should not be used in patients with creatinine clearance < 50 mL/min [see USE IN SPECIFIC POPULATIONS (8.7)].

5.6 Pulmonary Disorders

Dyspnea, pulmonary infiltrates, pneumonitis, pulmonary hypertension, and pneumonia have been reported during therapy with ribavirin and interferon. 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, patients should be closely monitored and, if appropriate, combination ribavirin/peginterferon alfa-2a treatment should be discontinued.

5.7 Bone Marrow Suppression

Pancytopenia (marked decreases in RBCs, 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-2a, ribavirin, and azathioprine should be discontinued for pancytopenia, and pegylated interferon/ribavirin should not be re-introduced with concomitant azathioprine [see DRUG INTERACTIONS (7.3)].

Ribavirin and peginterferon alfa-2a therapy should be suspended in patients with signs and symptoms of pancreatitis, and discontinued in patients with confirmed pancreatitis.

5.9 Laboratory Tests

Before beginning peginterferon alfa-2a/ribavirin combination therapy, standard hematological and biochemical laboratory tests are recommended for all patients. Pregnancy screening for women of childbearing potential must be performed. Patients who have pre-existing cardiac abnormalities should have electrocardiograms administered before treatment with peginterferon alfa-2a/ribavirin. After initiation of therapy, hematological tests should be performed at 2 weeks and 4 weeks and biochemical tests should be performed at 4 weeks. Additional testing should be performed periodically during therapy. In the clinical studies, the CBC (including hemoglobin level and white blood cell and platelet counts) and chemistries (including liver function tests and uric acid) were measured at 1, 2, 4, 6, and 8 weeks, and then every 4 to 6 weeks or more frequently if abnormalities were found. Thyroid stimulating hormone (TSH) was measured every 12 weeks. Monthly pregnancy testing should be performed during combination therapy and for 6 months after discontinuing therapy. The entrance criteria used for the clinical studies of ribavirin and peginterferon alfa-2a may be considered as a guideline to acceptable baseline values for initiation of treatment:

- Platelet count ≥ 90,000 cells/mm³ (as low as 75,000 cells/mm³ in HCV patients with cirrhosis or 70,000 cells/mm³ in patients with CHC and HIV)
- Absolute neutrophil count (ANC) ≥ 1500 cells/mm³
- TSH and T4 within normal limits or adequately controlled thyroid function
- CD4+ cell count ≥ 200 cells/mcL or CD4+ cell count ≥ 100 cells/mcL but < 200 cells/mcL and HIV-1 RNA < 5000 copies/mL in patients coinfecting with HIV
- Hemoglobin ≥ 12 g/dL for women and ≥ 13 g/dL for men in CHC monoinfected patients
- Hemoglobin ≥ 11 g/dL for women and ≥ 12 g/dL for men in patients with CHC and HIV

6 ADVERSE REACTIONS
Peginterferon alfa-2a in combination with ribavirin causes a broad variety of serious adverse reactions [see BOXED WARNING and WARNINGS AND PRECAUTIONS (5)]. The most common

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serious or life-threatening adverse reactions induced or aggravated by ribavirin/peginterferon alfa-2a include depression, suicide, relapse of drug abuse/overdose, and bacterial infections each occurring at a frequency of < 1%. Hepatic decompensation occurred in 2% (10/574 CHC/HIV patients [see WARNINGS AND PRECAUTIONS (5.3)]).

6.1 Clinical Studies Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice.

In the pivotal registration trials NV15801 and NV15942, 886 patients received ribavirin for 48 weeks at doses of 1000/1200 mg based on body weight. In these trials, one or more serious adverse reactions occurred in 10% of CHC monoinfected subjects and in 19% of CHC/HIV subjects receiving peginterferon alfa-2a alone or in combination with ribavirin. The most common serious adverse event (3% in CHC and 5% in CHC/HIV) was bacterial infection (e.g., sepsis, osteomyelitis, endocarditis, pyelonephritis, pneumonia).

Other serious adverse reactions occurred at a frequency of < 1% and included: suicide, suicidal ideation, psychosis, aggression, anxiety, drug abuse and drug overdose, angina, hepatic dysfunction, fatty liver, cholangitis, arrhythmia, diabetes mellitus, autoimmune phenomena (e.g., hyperthyroidism, hypothyroidism, sarcoidosis, systemic lupus erythematosus, rheumatoid arthritis), peripheral neuropathy, aplastic anemia, peptic ulcer, gastrointestinal bleeding, pancreatitis, colitis, corneal ulcer, pulmonary embolism, coma, myositis, cerebral hemorrhage, thrombotic thrombocytopenic purpura, psychotic disorder, and hallucination. The percentage of patients in clinical trials who experienced one or more adverse events was 98%. The most commonly reported adverse reactions were psychiatric reactions, including depression, insomnia, irritability, anxiety, and flu-like symptoms such as fatigue, pyrexia, myalgia, headache and rigors. Other common reactions were anorexia, nausea and vomiting, diarrhea, arthralgias, injection site reactions, alopecia, and pruritus. Table 3 shows rates of adverse events occurring in ≥ 5% subjects receiving pegylated interferon and ribavirin combination therapy in the CHC Clinical Trial, NV15801.

Ten percent of CHC monoinfected patients receiving 48 weeks of therapy with peginterferon alfa-2a in combination with ribavirin discontinued therapy; 16% of CHC/HIV coinfecting patients discontinued therapy. The most common reasons for discontinuation of therapy were psychiatric, flu-like syndrome (e.g., lethargy, fatigue, headache), dermatologic and gastrointestinal disorders and laboratory abnormalities (thrombocytopenia, neutropenia, and anemia). Overall 39% of patients with CHC or CHC/HIV required modification of peginterferon alfa-2a and/or ribavirin therapy. The most common reason for dose modification of peginterferon alfa-2a in CHC and CHC/HIV patients was for laboratory abnormalities; neutropenia (20% and 27%, respectively) and thrombocytopenia (4% and 6%, respectively). The most common reason for dose modification of ribavirin in CHC and CHC/HIV patients was anemia (22% and 16%, respectively).

Peginterferon alfa-2a dose was reduced in 12% of patients receiving 1000 mg to 1200 mg ribavirin for 48 weeks and in 7% of patients receiving 800 mg ribavirin for 24 weeks. Ribavirin dose was reduced in 21% of patients receiving 1000 mg to 1200 mg ribavirin for 4

* Severe hematologic abnormalities (lymphocyte <0.5 x 10⁹/L; hemoglobin < 10 g/dL; neutrophil < 0.75 x 10⁹/L; platelet < 50 x 10⁹/L).

Common Adverse Reactions in CHC with HIV Coinfection

The adverse event profile of coinfecting patients treated with peginterferon alfa-2a/ribavirin in Study NR15961 was generally similar to that shown for monoinfected patients in Study NV15801 (Table 3). Events occurring more frequently in coinfecting patients were neutropenia (40%), anemia (14%), thrombocytopenia (8%), weight decrease (16%), and mood alteration (9%).

Laboratory Test Abnormalities

Anemia due to hemolysis is the most significant toxicity of ribavirin therapy. Anemia (hemoglobin < 10 g/dL) was observed in 13% of all ribavirin and peginterferon alfa-2a combination-treated patients in clinical trials. The maximum drop in hemoglobin occurred during the first 8 weeks of initiation of ribavirin therapy [see DOSAGE AND ADMINISTRATION (2.3)].

Laboratory Parameter	Peginterferon Alfa-2a + Ribavirin 1000/1200 mg 48 weeks (N=887)	Interferon Alfa-2b + Ribavirin 1000/1200 mg 48 weeks (N=443)
Neutrophils (x10⁹/L)		
1.0 to 1.48	34%	38%
0.5 to 0.99	49%	21%
< 0.5	5%	1%
Platelets (x10⁹/L)		
50 to 74.9	11%	4%
20 to 49.9	5%	< 1%
< 20	0	0
Hemoglobin (g/dL)		
8.5 to 9.9	11%	11%
< 8.5	2%	< 1%

6.2 Postmarketing Experience

The following adverse reactions have been identified and reported during post-approval use of peginterferon alfa-2a/ribavirin combination therapy. 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

Ear and Labyrinth disorders

Hearing impairment, hearing loss

Eye disorders

Serous retinal detachment

Immune disorders

Liver and renal graft rejection

Metabolism and Nutrition disorders

Dehydration

Skin and Subcutaneous Tissue disorders

Stevens-Johnson Syndrome (SJS)

Toxic epidermal necrolysis (TEN)

7 DRUG INTERACTIONS

Results from a pharmacokinetic sub-study demonstrated no pharmacokinetic interaction between peginterferon alfa-2a and ribavirin.

7.1 Nucleoside Reverse Transcriptase Inhibitors (NRTIs)

In vitro data indicate ribavirin reduces phosphorylation of lamivudine, stavudine, and zidovudine. However, no pharmacokinetic (e.g., plasma concentrations or intracellular triphosphorylated active metabolite concentrations) or pharmacodynamic (e.g., loss of HIV/HCV virologic suppression) interaction was observed when ribavirin and lamivudine (n=18), stavudine (n=10), or zidovudine (n=6) were co-administered as part of a multi-drug regimen to HCV/HIV coinfecting patients.

In Study NR15961 among the CHC/HIV coinfecting cirrhotic patients receiving NRTIs cases of hepatic decompensation (some fatal) were observed [see WARNINGS AND PRECAUTIONS (5.3)]. Patients receiving peginterferon alfa-2a/ribavirin and NRTIs should be closely monitored for treatment associated toxicities. Physicians should refer to prescribing information for the respective NRTIs for guidance regarding toxicity management. In addition, dose reduction or discontinuation of peginterferon alfa-2a, ribavirin, or both should also be considered if worsening toxicities are observed, including hepatic decompensation (e.g., Child-Pugh ≥ 6) [see WARNINGS AND PRECAUTIONS (5.3) and DOSAGE AND ADMINISTRATION (2.3)].

Didanosine

Co-administration of ribavirin and didanosine is contraindicated. Didanosine or its active metabolite (dideoxyadenosine 5'-triphosphate) concentrations are increased when didanosine is co-administered with ribavirin, which could cause or worsen clinical toxicities. Reports of fatal hepatic failure, as well as peripheral neuropathy, pancreatitis, and symptomatic hypercalcemia/lactic acidosis have been reported in clinical trials [see CONTRAINDICATIONS (4)].

Zidovudine

In Study NR15961, patients who were administered zidovudine in combination with peginterferon alfa-2a/ribavirin developed severe neutropenia (ANC < 500) and severe anemia (hemoglobin < 8 g/dL) more frequently than similar patients not receiving zidovudine (neutropenia 15% vs 9% [anemia 5% vs. 1%]). Discontinuation of zidovudine should be considered as medically appropriate.

7.2 Drugs Metabolized by Cytochrome P450

In vitro studies indicate that ribavirin does not inhibit CYP2C9, CYP2C19, CYP2D6 or CYP3A4.

7.3 Azathioprine

The use of ribavirin to treat 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-MITTP), 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 (5.7)].

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy: Category X [see CONTRAINDICATIONS (4)].

Ribavirin produced significant and/or teratogenic effects in all animal species in which adequate studies have been conducted. Malformations of the skull, palate, eye, jaw, limbs, skeleton, and gastrointestinal tract were noted. The incidence and severity of teratogenic effects increased with escalation of the drug dose. Survival of fetuses and offspring was reduced [see CONTRAINDICATIONS (4), WARNINGS AND PRECAUTIONS (5.1)].

In conventional embryotoxicity/teratogenicity studies in rats and rabbits, observed no-effect dose levels were well below those proposed clinically use (0.3 mg/kg/day for both the rat and rabbit approximately 0.06 times the recommended daily human dose of ribavirin). No maternal toxicity or effects on offspring were observed in a perinatal/toxicity study in rats dosed orally at up to 1 mg/kg/day (approximately 0.01 times the maximum recommended daily human dose of ribavirin).

Treatment and Post-treatment Potential Risk to the Fetus

Ribavirin is known to accumulate in intraocular components from where it is cleared very slowly. It is not known whether ribavirin is contained in sperm, and if so, will exert a potential teratogenic effect upon fertilization of the ova. 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. Ribavirin should not be used by pregnant women or by men whose female partners are pregnant. Female patients of childbearing potential and male patients with female partners of childbearing potential should not receive ribavirin unless the patient and his/her partner are using effective contraception (two reliable forms) during therapy and for 6 months post therapy [see CONTRAINDICATIONS (4)].

Ribavirin Pregnancy Registry

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

8.3 Nursing Mothers

It is not known whether ribavirin is excreted in human milk. Because many drugs are excreted in human milk and to avoid any potential for serious adverse reactions in nursing infants from ribavirin, a decision should be made either to discontinue nursing or therapy with ribavirin, based on the importance of the therapy to the mother.

8.4 Pediatric Use

Pharmacokinetic evaluations in pediatric patients have not been performed. Safety and effectiveness of ribavirin have not been established in patients below the age of 18.

8.5 Geriatric Use

Clinical studies of ribavirin and peginterferon alfa-2a did not include sufficient numbers of subjects aged 65 or over to determine whether they respond differently from younger subjects. Specific pharmacokinetic evaluations for ribavirin in the elderly have not been performed. The risk of toxic reactions to this drug may be greater in patients with impaired renal function. Ribavirin should not be administered to patients with creatinine clearance < 50 mL/min.

8.6 Race

A pharmacokinetic study in 42 subjects demonstrated there is no clinically significant difference in ribavirin pharmacokinetics among Black (n=14), Hispanic (n=13) and Caucasian (n=15) subjects.

8.7 Renal Impairment

The pharmacokinetics of ribavirin following administration of ribavirin have not been studied in patients with renal impairment and there are limited data from clinical trials on administration of ribavirin in patients with creatinine clearance < 50 mL/min. Therefore, patients with creatinine clearance < 50 mL/min should not be treated with ribavirin [see WARNINGS AND PRECAUTIONS (5.8) and DOSAGE AND ADMINISTRATION (2.5)].

8.8 Hepatic Impairment

The effect of hepatic impairment on the pharmacokinetics of ribavirin following administration of ribavirin has not been evaluated. The clinical trials of ribavirin were restricted to patients with Child-Pugh class A disease.

8.9 Gender

No clinically significant differences in the pharmacokinetics of ribavirin were observed between male and female subjects. Ribavirin pharmacokinetics, when corrected for weight, are similar in male and female patients.

8.10 Organ Transplant Recipients

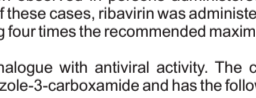
The safety and efficacy of peginterferon alfa-2a and ribavirin treatment have not been established in patients with liver and other transplantations. As with other alpha interferons, liver and renal graft rejections have been reported on peginterferon alfa-2a, alone or in combination with ribavirin [see ADVERSE REACTIONS (6.2)].

10 OVERDOSAGE

No cases of overdose with ribavirin have been reported in clinical trials. Hypocalcemia and hypomagnesemia have been observed in persons administered greater than the recommended dosage of ribavirin. In most of these cases, ribavirin was administered intravenously at dosages up to and in some cases exceeding four times the recommended maximum oral daily dose.

11 DESCRIPTION

Ribavirin is a nucleoside analogue with antiviral activity. The chemical name of ribavirin is 1-β-D-ribofuranosyl-1H-1,2,4-triazole-3-carboxamide and has the following structural formula:



The molecular formula of ribavirin is C₈H₁₀N₄O₅ and the molecular weight is 244.2. Ribavirin is a white to off-white powder. It is freely soluble in water and slightly soluble in anhydrous alcohol. Each film-coated ribavirin tablet inflected for oral administration contains 200 mg or 400 mg or 500 mg or 600 mg of ribavirin. In addition, each tablet contains the following inactive ingredients: croscollidone, hypromellose, iron oxide red, iron oxide yellow, magnesium stearate, microcrystalline cellulose, polyethylene glycol, povidone, silicon dioxide, talc and titanium dioxide.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Ribavirin is an antiviral drug [see CLINICAL PHARMACOLOGY (12.4)].

12.2 Pharmacokinetics

Multiple dose ribavirin pharmacokinetic data are available for HCV patients who received ribavirin in combination with peginterferon alfa-2a. Following administration of 1200 mg/day with food for 12 weeks mean SD (n=39; body weight > 75 kg) AUC₀₋₂₄ was 25,361±7110 ng·hr/mL and C_{max} was 2748±818 ng/mL. The average time to reach C_{max} was 2 hours. Trough ribavirin plasma concentrations following 12 weeks of dosing with food were 1662±545 ng/mL in HCV infected patients who received 800 mg/day (n=89), and 2112±810 ng/mL in patients who received 1200 mg/day (n=75; body weight > 75 kg).

The terminal half-life of ribavirin following administration of a single oral dose of ribavirin is about 120 to 170 hours. The total apparent clearance following administration of a single oral dose of ribavirin is about 26 L/h. There is extensive accumulation of ribavirin after multiple dosing (twice daily) such that the C_{max} at steady state was four-fold higher than that of a single dose.

Effect of Food on Absorption of Ribavirin

Bioavailability of a single oral dose of ribavirin was increased by co-administration with a high-fat meal. The absorption was slowed (T_{max} was doubled) and the AUC₀₋₂₄ and C_{max} increased by 42% and 66%, respectively, when ribavirin was taken with a high-fat meal compared with fasting conditions [see DOSAGE AND ADMINISTRATION (2.1) and PATIENT COUNSELING INFORMATION (17)].

Elimination and Metabolism

The contribution of renal and hepatic pathways to ribavirin elimination after administration of ribavirin is not known. *In vitro* studies indicate that ribavirin is not a substrate of CYP450 enzymes.

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 RNA viruses and ribavirin triphosphate inhibits HCV polymerase in a biochemical reaction.

Antiviral Activity in Cell Culture

In the stable HCV cell culture model system (HCV replicon), ribavirin inhibited autonomous HCV RNA replication with a 50% effective concentration (EC₅₀) value of 11 to 21 mcM. In the same model,

PEG-IFN α-2a also inhibited HCV RNA replication, with an EC₅₀ value of 0.1 to 3 ng/mL. The combination of PEG-IFN α-2a and ribavirin was more effective at inhibiting HCV RNA replication than either agent alone.

Resistance

Different HCV genotypes display considerable clinical variability in their response to PEG-IFN α and ribavirin therapy. Viral genetic determinants associated with the variable response have not been definitively identified.

Cross-resistance

Cross-resistance between IFN α and ribavirin has not been observed.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

In a p53 (+/-) mouse carcinogenicity study up to the maximum tolerated dose of 100 mg/kg/day, ribavirin was not oncogenic. Ribavirin was also not oncogenic in a rat 2 year carcinogenicity study at doses up to the maximum tolerated dose of 60 mg/kg/day. On a body surface area basis, these doses are approximately 0.5 and 0.6 times the maximum recommended daily human dose of ribavirin, respectively.

Mutagenesis

Ribavirin demonstrated mutagenic activity in the *in vitro* mouse lymphoma assay. No clastogenic activity was observed in an *in vivo* mouse micronucleus assay at doses up to 2000 mg/kg. However, results from studies published in the literature show clastogenic activity in the *in vivo* mouse micronucleus assay at oral doses up to 2000 mg/kg. A dominant lethal assay in rats was negative, indicating that if mutations occurred in rats they were not transmitted through male gametes. However, potential carcinogenic risk to humans cannot be excluded.

Impairment of Fertility

In a fertility study in rats, ribavirin showed a marginal reduction in sperm counts at the dose of 100 mg/kg/day with no effect on fertility. Upon cessation of treatment, total recovery occurred after 1 spermatogenesis cycle. Abnormalities in sperm were observed in studies in mice designed to evaluate the time course and reversibility of ribavirin-induced testicular degeneration at doses of 15 to 150 mg/kg/day (approximately 0.1 to 0.8 times the maximum recommended daily human dose of ribavirin) administered for 3 to 6 months. Upon cessation of treatment, essentially total recovery from ribavirin-induced testicular toxicity was apparent within 1 or 2 spermatogenic cycles.

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

No reproductive toxicology studies have been performed using peginterferon alfa-2a in combination with ribavirin. However, peginterferon alfa-2a and ribavirin when administered separately, each has adverse effects on reproduction. It should be assumed that the effects produced by either agent alone would also be caused by the combination of the two agents.

13.2 Animal Toxicology

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 (up to 1.7 times the maximum recommended human dose of ribavirin). Long-term studies in the mouse and rat (18 to 24 months; dose 20 to 75, and 10 to 40 mg/kg/day, respectively, approximately 0.1 to 0.4 times the maximum daily human dose of ribavirin) have demonstrated a relationship between chronic ribavirin exposure and an increased incidence of vascular lesions (microscopic hemorrhages) in mice. In rats, retinal degeneration occurred in controls, but the incidence was increased in ribavirin-treated rats.

14 CLINICAL STUDIES

14.1 Chronic Hepatitis C Patients

The safety and effectiveness of peginterferon alfa-2a in combination with ribavirin for the treatment of hepatitis C virus infection were assessed in two randomized controlled clinical trials. All patients were adults, had compensated liver disease, detectable hepatitis C virus, liver biopsy diagnosis of chronic hepatitis, and were previously untreated with interferon. Approximately 20% of patients in both studies had compensated cirrhosis (Child-Pugh class A). Patients coinfecting with HIV were excluded from these studies.

In Study NV15801, patients were randomized to receive either peginterferon alfa-2a 180 mcg subcutaneous once weekly with an oral placebo, peginterferon alfa-2a 180 mcg once weekly with ribavirin 1000 mg by mouth (body weight < 75 kg) or 1200 mg by mouth (body weight ≥ 75 kg) or interferon alfa-2b 3 MIU subcutaneous three times a week plus ribavirin 1000 mg or 1200 mg by mouth. All patients received 48 weeks of therapy followed by 24 weeks of treatment-free follow-up. Ribavirin or placebo treatment assignment was blinded. Sustained virologic response was defined as undetectable (< 50 IU/mL) HCV RNA on or after study week 68. Peginterferon alfa-2a in combination with ribavirin resulted in a higher SVR compared to peginterferon alfa-2a alone or interferon alfa-2b plus ribavirin (Table 5). In all treatment arms, patients with viral genotype 1, regardless of viral load, had a lower response rate to peginterferon alfa-2a in combination with ribavirin compared to patients with other viral genotypes.

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