HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use COPEGUS safely and effectively. See full prescribing information for COPEGUS.

COPEGUS® (ribavirin) Tablets, for oral use
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 COPEGUS, 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 COPEGUS (2.3, 5.2, 6.1).**
- **Significant teratogenic and embryocidal effects have been demonstrated in all animal species exposed to ribavirin. Therefore, COPEGUS 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 COPEGUS therapy (4, 5.1, 8.1).**

---------- RECENT MAJOR CHANGES ----------
Warnings and Precautions (5.8) 08/2015

---------- INDICATIONS AND USAGE ----------
COPEGUS is a nucleoside analogue indicated for the treatment of chronic hepatitis C (CHC) virus infection in combination with PEGASYS in patients 5 years of age and older with compensated liver disease not previously treated with interferon alpha, and in adult CHC patients coinfected with HIV (1)

---------- DOSAGE AND ADMINISTRATION ----------
- CHC: COPEGUS 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 (2.3, 2.4)

---------- DOSAGE FORMS AND STRENGTHS ----------
- COPEGUS tablets 200 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)

COPEGUS in combination with PEGASYS is contraindicated in patients with:
- Autoimmune hepatitis (4)
- Hepatic decompensation in cirrhotic patients (4, 5.3)

---------- 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)

PEGASYS/COPEGUS: 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 (5.5)
- Severe depression and suicidal ideation, autoimmune and infectious disorders, suppression of bone marrow function, pancreatitis, and diabetes (5)
- Bone marrow suppression with azathioprine coadministration (5.6)
- Growth impairment with combination therapy in pediatric patients (5.8)

---------- ADVERSE REACTIONS ----------
The most common adverse reactions (frequency greater than 40%) in adults receiving combination therapy are fatigue/asthenia, pyrexia, myalgia, and headache. (6.1)

The most common adverse reactions in pediatric subjects were similar to those seen in adults. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Genentech at 1-888-835-2555 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 (8.1)**
- Pediatrics: Safety and efficacy in pediatric patients less than 5 years old have not been established (8.4)
- Renal Impairment: Dose should be reduced in patients with creatinine clearance less than or equal to 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: 08/2015

FULL PRESCRIBING INFORMATION: CONTENTS*

*Sections or subsections omitted from the full prescribing information are not listed

FULL PRESCRIBING INFORMATION

WARNING: RISK OF SERIOUS DISORDERS AND RIBAVIRIN-ASSOCIATED EFFECTS

COPEGUS (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 COPEGUS *[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 COPEGUS, 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

COPEGUS in combination with PEGASYS (peginterferon alfa-2a) is indicated for the treatment of patients 5 years of age and older 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 COPEGUS combination therapy with PEGASYS:

- 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 adult patients with clinically stable HIV disease and CD4 count greater than 100 cells/mm^3.
- 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 COPEGUS and PEGASYS therapy have not been established in liver or other organ transplant recipients, patients with decompensated liver disease, or previous non-responders to interferon therapy.
- The safety and efficacy of COPEGUS therapy for the treatment of adenovirus, RSV, parainfluenza or influenza infections have not been established. COPEGUS 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

COPEGUS should be taken with food. COPEGUS should be given in combination with PEGASYS; it is important to note that COPEGUS should never be given as monotherapy. See PEGASYS Package Insert for all instructions regarding PEGASYS dosing and administration.

2.1 Chronic Hepatitis C Monoinfection

Adult Patients

The recommended dose of COPEGUS 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 COPEGUS 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**).

Table 1 PEGASYS and COPEGUS Dosing Recommendations

Hepatitis C Virus (HCV) Genotype	**PEGASYS Dose* (once weekly)**	**COPEGUS Dose (daily)**	**Duration**
Genotypes 1, 4	180 mcg	<75 kg = 1000 mg ≥75 kg = 1200 mg	48 weeks 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 10**).
Data on genotypes 5 and 6 are insufficient for dosing recommendations.
*See PEGASYS Package Insert for further details on PEGASYS dosing and administration, including dose modification in patients with renal impairment.

Pediatric Patients

PEGASYS is administered as 180 mcg/1.73m^2 x BSA once weekly subcutaneously, to a maximum dose of 180 mcg, and should be given in combination with ribavirin. The recommended treatment duration for patients with genotype 2 or 3 is 24 weeks and for other genotypes is 48 weeks.

COPEGUS should be given in combination with PEGASYS. COPEGUS is available only as a 200 mg tablet and therefore the healthcare provider should determine if this sized tablet can be swallowed by the pediatric patient. The recommended doses for COPEGUS are provided in **Table 2**. Patients who initiate treatment prior to their 18th birthday should maintain pediatric dosing through the completion of therapy.

Table 2 COPEGUS Dosing Recommendations for Pediatric Patients

Body Weight in kilograms (kg)	**COPEGUS Daily Dose***	**COPEGUS Number of Tablets**
23 – 33	400 mg/day	1 x 200 mg tablet A.M. 1 x 200 mg tablet P.M.
34 – 46	600 mg/day	1 x 200 mg tablet A.M. 2 x 200 mg tablets P.M.
47 – 59	800 mg/day	2 x 200 mg tablets A.M. 2 x 200 mg tablets P.M.
60 – 74	1000 mg/day	2 x 200 mg tablets A.M. 3 x 200 mg tablets P.M.
≥75	1200 mg/day	3 x 200 mg tablets A.M. 3 x 200 mg tablets P.M.

*approximately 15 mg/kg/day

2.2 Chronic Hepatitis C with HIV Coinfection

Adult Patients

The recommended dose for treatment of chronic hepatitis C in patients coinfected with HIV is PEGASYS 180 mcg subcutaneous once weekly and COPEGUS 800 mg by mouth daily for a total duration of 48 weeks, regardless of HCV genotype.

2.3 Dose Modifications

Adult and Pediatric Patients

If severe adverse reactions or laboratory abnormalities develop during combination COPEGUS/PEGASYS 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, COPEGUS/PEGASYS therapy should be discontinued. **Table 3** provides guidelines for dose modifications and discontinuation based on the patient's hemoglobin concentration and cardiac status.

COPEGUS 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 3 COPEGUS Dose Modification Guidelines in Adults and Pediatrics

Body weight in kilograms (kg)	**Laboratory Values**	
	Hemoglobin <10 g/dL in patients with no cardiac disease, or Decrease in hemoglobin of ≥2 g/dL during any 4 week period in patients with history of stable cardiac disease	Hemoglobin <8.5 g/dL in patients with no cardiac disease, or Hemoglobin <12 g/dL despite 4 weeks at reduced dose in patients with history of stable cardiac disease
Adult Patients older than 18 years of age		
Any weight	1 x 200 mg tablet A.M. 2 x 200 mg tablets P.M.	Discontinue COPEGUS
Pediatric Patients 5 to 18 years of age		
23 – 33 kg	1 x 200 mg tablet A.M.	Discontinue COPEGUS
34 – 46 kg	1 x 200 mg tablet A.M. 1 x 200 mg tablet P.M.	
47 – 59 kg	1 x 200 mg tablet A.M. 1 x 200 mg tablet P.M.	
60 – 74 kg	1 x 200 mg tablet A.M. 2 x 200 mg tablets P.M.	
≥75 kg	1 x 200 mg tablet A.M. 2 x 200 mg tablets P.M.	

The guidelines for COPEGUS dose modifications outlined in this table also apply to laboratory abnormalities or adverse reactions other than decreases in hemoglobin values.

Adult Patients

Once COPEGUS has been withheld due to either a laboratory abnormality or clinical adverse reaction, an attempt may be made to restart COPEGUS at 600 mg daily and further increase the dose to 800 mg daily. However, it is not recommended that COPEGUS be increased to the original assigned dose (1000 mg to 1200 mg).

Pediatric Patients

Upon resolution of a laboratory abnormality or clinical adverse reaction, an increase in COPEGUS dose to the original dose may be attempted depending upon the physician's judgment. If COPEGUS has been withheld due to a laboratory abnormality or clinical adverse reaction, an attempt may be made to restart COPEGUS at one-half the full dose.

2.4 Renal Impairment

The total daily dose of COPEGUS should be reduced for patients with creatinine clearance less than or equal to 50 mL/min; and the weekly dose of PEGASYS should be reduced for creatinine clearance less than 30 mL/min as follows in **Table 4** *[see Use in Specific Populations (8.7), Pharmacokinetics (12.3), and PEGASYS Package Insert]*.

Table 4 Dosage Modification for Renal Impairment

Creatinine Clearance	PEGASYS Dose (once weekly)	COPEGUS Dose (daily)
30 to 50 mL/min	180 mcg	Alternating doses, 200 mg and 400 mg every other day
Less than 30 mL/min	135 mcg	200 mg daily
Hemodialysis	135 mcg	200 mg daily

The dose of COPEGUS should not be further modified in patients with renal impairment. If severe adverse reactions or laboratory abnormalities develop, COPEGUS should be discontinued, if appropriate, until the adverse reactions abate or decrease in severity. If intolerance persists after restarting COPEGUS, COPEGUS/PEGASYS therapy should be discontinued.

No data are available for pediatric subjects with renal impairment.

2.5 Discontinuation of Dosing

Discontinuation of PEGASYS/COPEGUS therapy should be considered if the patient has failed to demonstrate at least a 2 $\log_{10}$ reduction from baseline in HCV RNA by 12 weeks of therapy, or undetectable HCV RNA levels after 24 weeks of therapy.

PEGASYS/COPEGUS therapy should be discontinued in patients who develop hepatic decompensation during treatment *[see Warnings and Precautions (5.3)]*.

3 DOSAGE FORMS AND STRENGTHS

COPEGUS (ribavirin) is available as a light pink to pink colored, flat, oval-shaped, film-coated tablet for oral administration. Each tablet contains 200 mg of ribavirin.

4 CONTRAINDICATIONS

COPEGUS (ribavirin) is contraindicated in:

- Women who are pregnant. COPEGUS may cause fetal harm when administered to a pregnant woman. COPEGUS 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 (17)]*.
- Men whose female partners are pregnant.
- 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)]*.

COPEGUS and PEGASYS 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 coinfected with HIV before treatment *[see Warnings and Precautions (5.3)]*.

5 WARNINGS AND PRECAUTIONS

Significant adverse reactions associated with COPEGUS/PEGASYS 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 PEGASYS Package Insert should be reviewed in its entirety for additional safety information prior to initiation of combination treatment.

5.1 Pregnancy

COPEGUS 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.

COPEGUS 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 COPEGUS 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 COPEGUS/PEGASYS-treated subjects in clinical trials. Anemia associated with COPEGUS 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 COPEGUS. 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, patients with a history of significant or unstable cardiac disease should not use COPEGUS *[see Boxed Warning and Dosage and Administration (2.3)]*.

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 PEGASYS. Cirrhotic CHC patients coinfected 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, patients' clinical status and hepatic function should be closely monitored for signs and symptoms of hepatic decompensation. Treatment with PEGASYS/COPEGUS 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 PEGASYS and COPEGUS 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 PEGASYS with and without ribavirin. Patients developing signs or symptoms of severe skin reactions must discontinue therapy *[see Adverse Reactions (6.2)]*.

5.5 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 COPEGUS/PEGASYS treatment should be discontinued.

5.6 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. PEGASYS, COPEGUS, and azathioprine should be discontinued for pancytopenia, and pegylated interferon/ribavirin should not be re-introduced with concomitant azathioprine *[see Drug Interactions (7.3)]*.

5.7 Pancreatitis

COPEGUS and PEGASYS therapy should be suspended in patients with signs and symptoms of pancreatitis, and discontinued in patients with confirmed pancreatitis.

5.8 Impact on Growth in Pediatric Patients

During combination therapy for up to 48 weeks with PEGASYS plus ribavirin, growth inhibition was observed in pediatric subjects 5 to 17 years of age. Decreases in weight for age z-score and height for age z-score up to 48 weeks of therapy compared with baseline were observed. At 2 years post-treatment, 16% of pediatric subjects were more than 15 percentiles below their baseline weight curve and 11% were more than 15 percentiles below their baseline height curve.

The available longer term data on subjects who were followed up to 6 years post-treatment are too limited to determine the risk of reduced adult height in some patients *[see Clinical Studies Experience (6.1)]*.

5.9 Laboratory Tests

Before beginning PEGASYS/COPEGUS 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 PEGASYS/COPEGUS.

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 adult 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. In the pediatric clinical trial, hematological and chemistry assessments were at 1, 3, 5, and 8 weeks, then every 4 weeks. 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 COPEGUS and PEGASYS may be considered as a guideline to acceptable baseline values for initiation of treatment:

- Platelet count greater than or equal to 90,000 cells/mm^3 (as low as 75,000 cells/mm^3 in HCV patients with cirrhosis or 70,000 cells/mm^3 in patients with CHC and HIV)
- Absolute neutrophil count (ANC) greater than or equal to 1500 cells/mm^3
- TSH and T_4 within normal limits or adequately controlled thyroid function
- CD4+ cell count greater than or equal to 200 cells/mm^3 or CD4+ cell count greater than or equal to 100 cells/mm^3 but less than 200 cells/mm^3 and HIV-1 RNA less than 5,000 copies/mL in patients coinfected with HIV
- Hemoglobin greater than or equal to 12 g/dL for women and greater than or equal to 13 g/dL for men in CHC monoinfected patients
- Hemoglobin greater than or equal to 11 g/dL for women and greater than or equal to 12 g/dL for men in patients with CHC and HIV

6 ADVERSE REACTIONS

PEGASYS in combination with COPEGUS causes a broad variety of serious adverse reactions *[see Boxed Warning and Warnings and Precautions (5)]*. The most common serious or life-threatening adverse reactions induced or aggravated by COPEGUS/PEGASYS include depression, suicide, relapse of drug abuse/overdose, and bacterial infections each occurring at a frequency of less than 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.

Adult Patients

In the pivotal registration trials NV15801 and NV15942, 886 patients received COPEGUS 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 PEGASYS alone or in combination with COPEGUS. 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 less than 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 5 shows rates of adverse events occurring in greater than or equal to 5% of 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 PEGASYS in combination with COPEGUS discontinued therapy; 16% of CHC/HIV coinfected 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 PEGASYS and/or COPEGUS therapy. The most common reason for dose modification of PEGASYS 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 COPEGUS in CHC and CHC/HIV patients was anemia (22% and 16%, respectively).

PEGASYS dose was reduced in 12% of patients receiving 1000 mg to 1200 mg COPEGUS for 48 weeks and in 7% of patients receiving 800 mg COPEGUS for 24 weeks. COPEGUS dose was reduced in 21% of patients receiving 1000 mg to 1200 mg COPEGUS for 48 weeks and in 12% of patients receiving 800 mg COPEGUS for 24 weeks.

Chronic hepatitis C monoinfected patients treated for 24 weeks with PEGASYS and 800 mg COPEGUS were observed to have lower incidence of serious adverse events (3% vs. 10%), hemoglobin less than 10 g/dL (3% vs. 15%), dose modification of PEGASYS (30% vs. 36%) and COPEGUS (19% vs. 38%), and of withdrawal from treatment (5% vs. 15%) compared to patients treated for 48 weeks with PEGASYS and 1000 mg or 1200 mg COPEGUS. On the other hand, the overall incidence of adverse events appeared to be similar in the two treatment groups.

Table 5 Adverse Reactions Occurring in greater than or equal to 5% of Patients in Chronic Hepatitis C Clinical Trials (Study NV15801)

Body System	**CHC Combination Therapy Study NV15801**	
	PEGASYS 180 mcg + 1000 mg or 1200 mg COPEGUS 48 weeks	**Intron A + 1000 mg or 1200 mg Rebetol• 48 weeks**
	N=451	**N=443**
	%	**%**
Application Site Disorders		
Injection site reaction	23	16
Endocrine Disorders		
Hypothyroidism	4	5
Flu-like Symptoms and Signs		
Fatigue/Asthenia	65	68
Pyrexia	41	55
Rigors	25	37
Pain	10	9
Gastrointestinal		
Nausea/Vomiting	25	29

Body System	CHC Combination Therapy Study NV15801	
	PEGASYS 180 mcg + 1000 mg or 1200 mg COPEGUS 48 weeks	Intron A + 1000 mg or 1200 mg Rebetol• 48 weeks
	N=451	N=443
	%	%
Diarrhea	11	10
Abdominal pain	8	9
Dry mouth	4	7
Dyspepsia	6	5
Hematologic*		
Lymphopenia	14	12
Anemia	11	11
Neutropenia	27	8
Thrombocytopenia	5	<1
Metabolic and Nutritional		
Anorexia	24	26
Weight decrease	10	10
Musculoskeletal, Connective Tissue and Bone		
Myalgia	40	49
Arthralgia	22	23
Back pain	5	5
Neurological		
Headache	43	49
Dizziness (excluding vertigo)	14	14
Memory impairment	6	5
Psychiatric		
Irritability/Anxiety/Nervousness	33	38
Insomnia	30	37
Depression	20	28
Concentration impairment	10	13
Mood alteration	5	6
Resistance Mechanism Disorders		
Overall	12	10
Respiratory, Thoracic and Mediastinal		
Dyspnea	13	14

Body System	CHC Combination Therapy Study NV15801	
	PEGASYS 180 mcg + 1000 mg or 1200 mg COPEGUS 48 weeks	Intron A + 1000 mg or 1200 mg Rebetol• 48 weeks
	N=451	N=443
	%	%
Cough	10	7
Dyspnea exertional	4	7
Skin and Subcutaneous Tissue		
Alopecia	28	33
Pruritus	19	18
Dermatitis	16	13
Dry skin	10	13
Rash	8	5
Sweating increased	6	5
Eczema	5	4
Visual Disorders		
Vision blurred	5	2

* Severe hematologic abnormalities (lymphocyte less than 500 cells/mm^3; hemoglobin less than 10 g/dL; neutrophil less than 750 cells/mm^3; platelet less than 50,000 cells/mm^3).

Pediatric Patients

In a clinical trial with 114 pediatric subjects (5 to 17 years of age) treated with PEGASYS alone or in combination with COPEGUS, dose modifications were required in approximately one-third of subjects, most commonly for neutropenia and anemia. In general, the safety profile observed in pediatric subjects was similar to that seen in adults. In the pediatric study, the most common adverse events in subjects treated with combination therapy PEGASYS and COPEGUS for up to 48 weeks were influenza-like illness (91%), upper respiratory tract infection (60%), headache (64%), gastrointestinal disorder (56%), skin disorder (47%), and injection-site reaction (45%). Seven subjects receiving combination PEGASYS and COPEGUS treatment for 48 weeks discontinued therapy for safety reasons (depression, psychiatric evaluation abnormal, transient blindness, retinal exudates, hyperglycemia, type 1 diabetes mellitus, and anemia). Severe adverse events were reported in 2 subjects in the PEGASYS plus COPEGUS combination therapy group (hyperglycemia and cholecystectomy).

Table 6 Percentage of Pediatric Subjects with Adverse Reactions* During First 24 Weeks of Treatment by Treatment Group and for 24 Weeks Post-treatment (in at Least 10% of Subjects)

	Study NV17424	
System Organ Class	**PEGASYS 180 mcg/1.73 m² x BSA + COPEGUS 15 mg/kg (N=55)**	**PEGASYS 180 mcg/1.73 m² x BSA + Placebo** (N=59)**
	%	%
General disorders and administration site conditions		
Influenza like illness	91	81
Injection site reaction	44	42
Fatigue	25	20
Irritability	24	14
Gastrointestinal disorders		
Gastrointestinal disorder	49	44
Nervous system disorders		
Headache	51	39
Skin and subcutaneous tissue disorders		
Rash	15	10
Pruritus	11	12
Musculoskeletal, connective tissue and bone disorders		
Musculoskeletal pain	35	29
Psychiatric disorders		
Insomnia	9	12
Metabolism and nutrition disorders		
Decreased appetite	11	14

* Displayed adverse drug reactions include all grades of reported adverse clinical events considered possibly, probably, or definitely related to study drug.

**Subjects in the PEGASYS plus placebo arm who did not achieve undetectable viral load at week 24 switched to combination treatment thereafter. Therefore, only the first 24 weeks are presented for the comparison of combination therapy with monotherapy.

In pediatric subjects randomized to combination therapy, the incidence of most adverse reactions was similar for the entire treatment period (up to 48 weeks plus 24 weeks follow-up) in comparison to the first 24 weeks, and increased only slightly for headache, gastrointestinal disorder, irritability and rash. The majority of adverse reactions occurred in the first 24 weeks of treatment.

Growth Inhibition in Pediatric Subjects *[see Warnings and Precautions (5.8)]*.

Pediatric subjects treated with PEGASYS plus ribavirin combination therapy showed a delay in weight and height increases with up to 48 weeks of therapy compared with baseline. Both weight for age and height for age z-scores as well as the percentiles of the normative population for subject weight and height decreased during treatment. At the end of 2 years follow-up after treatment, most subjects had returned to baseline normative curve percentiles for weight (64^{th} mean percentile at baseline, 60^{th} mean percentile at 2 years post-treatment) and height (54^{th} mean percentile at baseline, 56^{th} mean percentile at 2 years post-treatment). At the end of treatment, 43% (23 of 53) of subjects experienced a weight percentile decrease of more than 15 percentiles, and 25% (13 of 53) experienced a height percentile decrease of more than 15 percentiles on the normative growth curves. At 2 years post-treatment, 16% (6 of 38) of subjects were more than 15 percentiles below their baseline weight curve and 11% (4 of 38) were more than 15 percentiles below their baseline height curve.

Thirty-eight of the 114 subjects enrolled in the long-term follow-up study, extending up to 6 years post-treatment. For most subjects, post-treatment recovery in growth at 2 years post-treatment was maintained to 6 years post-treatment.

Common Adverse Reactions in CHC with HIV Coinfection (Adults)

The adverse event profile of coinfected patients treated with PEGASYS/COPEGUS in Study NR15961 was generally similar to that shown for monoinfected patients in Study NV15801 (**Table 5**). Events occurring more frequently in coinfected patients were neutropenia (40%), anemia (14%), thrombocytopenia (8%), weight decrease (16%), and mood alteration (9%).

Laboratory Test Abnormalities

Adult Patients

Anemia due to hemolysis is the most significant toxicity of ribavirin therapy. Anemia (hemoglobin less than 10 g/dL) was observed in 13% of all COPEGUS and PEGASYS 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)]*.

Table 7 Selected Laboratory Abnormalities During Treatment with COPEGUS in Combination With Either PEGASYS or Intron A

Laboratory Parameter	**PEGASYS + Ribavirin 1000/1200 mg 48 wks**	**Intron A + Ribavirin 1000/1200 mg 48 wks**
	(N=887)	**(N=443)**
Neutrophils (cells/mm^3)		
1,000 <1,500	34%	38%
500 <1,000	49%	21%
<500	5%	1%
Platelets (cells/mm^3)		
50,000 - <75,000	11%	4%
20,000 - <50,000	5%	< 1%
<20,000	0	0
Hemoglobin (g/dL)		
8.5 - 9.9	11%	11%
<8.5	2%	< 1%

Pediatric Patients

Decreases in hemoglobin, neutrophils and platelets may require dose reduction or permanent discontinuation from treatment *[see Dosage and Administration (2.4)]*. Most laboratory abnormalities noted during the clinical trial returned to baseline levels shortly after discontinuation of treatment.

Table 8 Selected Hematologic Abnormalities During First 24 Weeks of Treatment by Treatment Group in Previously Untreated Pediatric Subjects

Laboratory Parameter	**PEGASYS 180 mcg/1.73 m² x BSA + COPEGUS 15 mg/kg (N=55)**	**PEGASYS 180 mcg/1.73 m² x BSA + Placebo* (N=59)**
Neutrophils (cells/mm^3)		
1,000 - <1,500	31%	39%
750 - <1,000	27%	17%
500 - <750	25%	15%
<500	7%	5%
Platelets (cells/mm^3)		
75,000 - <100,000	4%	2%
50,000 - <75,000	0%	2%
<50,000	0%	0%
Hemoglobin (g/dL)		
8.5 - <10	7%	3%
<8.5	0%	0%

* Subjects in the PEGASYS plus placebo arm who did not achieve undetectable viral load at week 24 switched to combination treatment thereafter. Therefore, only the first 24 weeks are presented for the comparison of combination therapy with monotherapy.

In patients randomized to combination therapy, the incidence of abnormalities during the entire treatment phase (up to 48 weeks plus 24 weeks follow-up) in comparison to the first 24 weeks increased slightly for neutrophils between 500 and 1,000 cells/mm³ and hemoglobin values between 8.5 and 10 g/dL. The majority of hematologic abnormalities occurred in the first 24 weeks of treatment.

6.2 Postmarketing Experience

The following adverse reactions have been identified and reported during post-approval use of PEGASYS/COPEGUS 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 PEGASYS (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 coinfected patients.

In Study NR15961 among the CHC/HIV coinfected cirrhotic patients receiving NRTIs, cases of hepatic decompensation (some fatal) were observed *[see Warnings and Precautions (5.3)]*.

Patients receiving PEGASYS/COPEGUS 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 PEGASYS, COPEGUS or both should

also be considered if worsening toxicities are observed, including hepatic decompensation (e.g., Child-Pugh greater than or equal to 6) *[see Warnings and Precautions (5.3) and Dosage and Administration (2.3)]*.

Didanosine

Co-administration of COPEGUS 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 hyperlactatemia/lactic acidosis have been reported in clinical trials *[see Contraindications (4)]*.

Zidovudine

In Study NR15961, patients who were administered zidovudine in combination with PEGASYS/COPEGUS developed severe neutropenia (ANC less than 500) and severe anemia (hemoglobin less than 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 CYP 2C9, CYP 2C19, CYP 2D6 or CYP 3A4.

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-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 (5.6)]*.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy: Category X *[see Contraindications (4)]*.

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

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 daily human 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 (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 intracellular 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.

COPEGUS 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 COPEGUS 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 COPEGUS, 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 COPEGUS have not been established in patients below the age of 5 years.

8.5 Geriatric Use

Clinical studies of COPEGUS and PEGASYS 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. The dose of COPEGUS should be reduced in patients with creatinine clearance less than or equal to 50 mL/min; and the dose of PEGASYS should be reduced in patients with creatinine clearance less than 30 mL/min *[see Dosage and Administration (2.4); Use in Specific Populations (8.7)]*.

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

Renal function should be evaluated in all patients prior to initiation of COPEGUS by estimating the patient's creatinine clearance.

A clinical trial evaluated treatment with COPEGUS and PEGASYS in 50 CHC subjects with moderate (creatinine clearance 30 – 50 mL/min) or severe (creatinine clearance less than 30 mL/min) renal impairment or end stage renal disease (ESRD) requiring chronic hemodialysis (HD). In 18 subjects with ESRD receiving chronic HD, COPEGUS was administered at a dose of 200 mg daily with no apparent difference in the adverse event profile in comparison to subjects with normal renal function. Dose reductions and temporary interruptions of COPEGUS (due to COPEGUS-related adverse reactions, mainly anemia) were observed in up to one-third ESRD/HD subjects during treatment; and only one-third of these subjects received COPEGUS for 48 weeks. Ribavirin plasma exposures were approximately 20% lower in subjects with ESRD on HD compared to subjects with normal renal function receiving the standard 1000/1200 mg COPEGUS daily dose.

Subjects with moderate (n=17) or severe (n=14) renal impairment did not tolerate 600 mg or 400 mg daily doses of COPEGUS, respectively, due to COPEGUS-related adverse reactions, mainly anemia, and exhibited 20% to 30% higher ribavirin plasma exposures (despite frequent dose modifications) compared to subjects with normal renal function (creatinine clearance greater than 80 mL/min) receiving the standard dose of COPEGUS. Discontinuation rates were higher in subjects with severe renal impairment compared to that observed in subjects with moderate renal impairment or normal renal function. Pharmacokinetic modeling and simulation

indicate that a dose of 200 mg daily in patients with severe renal impairment and a dose of 200 mg daily alternating with 400 mg the following day in patients with moderate renal impairment will provide plasma ribavirin exposure similar to patients with normal renal function receiving the approved regimen of COPEGUS. These doses have not been studied in patients *[see Dosage and Administration (2.4), and Clinical Pharmacology (12.3)]*.

Based on the pharmacokinetic and safety results from this trial, patients with creatinine clearance less than or equal to 50 mL/min should receive a reduced dose of COPEGUS; and patients with creatinine clearance less than 30 mL/min should receive a reduced dose of PEGASYS. The clinical and hematologic status of patients with creatinine clearance less than or equal to 50 mL/min receiving COPEGUS should be carefully monitored. Patients with clinically significant laboratory abnormalities or adverse reactions which are persistently severe or worsening should have therapy withdrawn *[see Dosage and Administration (2.4), Clinical Pharmacology (12.3), and PEGASYS Package Insert]*.

8.8 Hepatic Impairment

The effect of hepatic impairment on the pharmacokinetics of ribavirin following administration of COPEGUS has not been evaluated. The clinical trials of COPEGUS 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

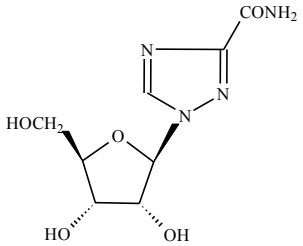
The safety and efficacy of PEGASYS and COPEGUS treatment have not been established in patients with liver and other transplantations. As with other alpha interferons, liver and renal graft rejections have been reported on PEGASYS, alone or in combination with COPEGUS *[see Adverse Reactions (6.2)]*.

10 OVERDOSAGE

No cases of overdose with COPEGUS 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

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



The empirical formula of ribavirin is $C_8H_{12}N_4O_5$ 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.

COPEGUS (ribavirin) is available as a light pink to pink colored, flat, oval-shaped, film-coated tablet for oral administration. Each tablet contains 200 mg of ribavirin and the following inactive ingredients: pregelatinized starch, microcrystalline cellulose, sodium starch glycolate, cornstarch, and magnesium stearate. The coating of

the tablet contains Chromatone-P® or Opadry® Pink (made by using hydroxypropyl methyl cellulose, talc, titanium dioxide, synthetic yellow iron oxide, and synthetic red iron oxide), ethyl cellulose (ECD-30), and triacetin.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Ribavirin is an antiviral drug *[see Microbiology (12.4)]*.

12.3 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 greater than 75 kg) $AUC_{0\text{-}12hr}$ 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 greater than 75 kg).

The terminal half-life of ribavirin following administration of a single oral dose of COPEGUS is about 120 to 170 hours. The total apparent clearance following administration of a single oral dose of COPEGUS 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 $AUC_{0\text{-}192h}$ and C_{max} increased by 42% and 66%, respectively, when COPEGUS was taken with a high-fat meal compared with fasting conditions *[see Dosage and Administration (2) and Patient Counseling Information (17)]*.

Elimination and Metabolism

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

Renal Impairment

A clinical trial evaluated 50 CHC subjects with either moderate (creatinine clearance 30 to 50 mL/min) or severe (creatinine clearance less than 30 mL/min) renal impairment or end stage renal disease (ESRD) requiring chronic hemodialysis (HD). The apparent clearance of ribavirin was reduced in subjects with creatinine clearance less than or equal to 50 mL/min, including subjects with ESRD on HD, exhibiting approximately 30% of the value found in subjects with normal renal function. Pharmacokinetic modeling and simulation indicates that a dose of 200 mg daily in patients with severe renal impairment and a dose of 200 mg daily alternating with 400 mg the following day in patients with moderate renal impairment will provide plasma ribavirin exposures similar to that observed in patients with normal renal function receiving the standard 1000/1200 mg COPEGUS daily dose. These doses have not been studied in patients.

In 18 subjects with ESRD receiving chronic HD, COPEGUS was administered at a dose of 200 mg daily. Ribavirin plasma exposures in these subjects were approximately 20% lower compared to subjects with normal renal function receiving the standard 1000/1200 mg COPEGUS daily dose *[see Dosage and Administration (2.4), Use in Specific Populations (8.7)]*.

Plasma ribavirin is removed by hemodialysis with an extraction ratio of approximately 50%; however, due to the large volume of distribution of ribavirin, plasma exposure is not expected to change with hemodialysis.

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 (EC_{50}) value of 11-21 mcM. In the same model, PEG-IFN α-2a also inhibited HCV RNA replication, with an EC_{50} value of 0.1-3 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

Carcinogenesis

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.

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 COPEGUS 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 PEGASYS in combination with COPEGUS. 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

Adult Patients

The safety and effectiveness of PEGASYS in combination with COPEGUS 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 coinfected with HIV were excluded from these studies.

In Study NV15801, patients were randomized to receive either PEGASYS 180 mcg subcutaneous once weekly with an oral placebo, PEGASYS 180 mcg once weekly with COPEGUS 1000 mg by mouth (body weight less than 75 kg) or 1200 mg by mouth (body weight greater than or equal to 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. COPEGUS or placebo treatment assignment was blinded. Sustained virological response was defined as undetectable (less than 50 IU/mL) HCV RNA on or after study week 68. PEGASYS in combination with COPEGUS resulted in a higher SVR compared to PEGASYS alone or interferon alfa-2b and ribavirin (**Table 9**). In all treatment arms, patients with viral genotype 1, regardless of viral load, had a lower response rate to PEGASYS in combination with COPEGUS compared to patients with other viral genotypes.

Table 9 Sustained Virologic Response (SVR) to Combination Therapy (Study NV15801)

	Interferon alfa-2b + Ribavirin 1000 mg or 1200 mg	**PEGASYS + placebo**	**PEGASYS + COPEGUS 1000 mg or 1200 mg**
All patients	197/444 (44%)	65/224 (29%)	241/453 (53%)
Genotype 1	103/285 (36%)	29/145 (20%)	132/298 (44%)
Genotypes 2-6	94/159 (59%)	36/79 (46%)	109/155 (70%)

Difference in overall treatment response (PEGASYS/COPEGUS – Interferon alfa-2b/ribavirin) was 9% (95% CI 2.3, 15.3).

In Study NV15942, all patients received PEGASYS 180 mcg subcutaneous once weekly and were randomized to treatment for either 24 or 48 weeks and to a COPEGUS dose of either 800 mg or 1000 mg/1200 mg (for body weight less than 75 kg/greater than or equal to 75 kg). Assignment to the four treatment arms was stratified by viral genotype and baseline HCV viral titer. Patients with genotype 1 and high viral titer (defined as greater than 2×10^6 HCV RNA copies/mL serum) were preferentially assigned to treatment for 48 weeks.

Sustained Virologic Response (SVR) and HCV Genotype

HCV 1 and 4 — Irrespective of baseline viral titer, treatment for 48 weeks with PEGASYS and 1000 mg or 1200 mg of COPEGUS resulted in higher SVR (defined as undetectable HCV RNA at the end of the 24-week treatment-free follow-up period) compared to shorter treatment (24 weeks) and/or 800 mg COPEGUS.

HCV 2 and 3 — Irrespective of baseline viral titer, treatment for 24 weeks with PEGASYS and 800 mg of COPEGUS resulted in a similar SVR compared to longer treatment (48 weeks) and/or 1000 mg or 1200 mg of COPEGUS (see **Table 10**).

The numbers of patients with genotype 5 and 6 were too few to allow for meaningful assessment.

Table 10 Sustained Virologic Response as a Function of Genotype (Study NV15942)

	24 Weeks Treatment		48 Weeks Treatment	
	PEGASYS + COPEGUS 800 mg (N=207)	**PEGASYS + COPEGUS 1000 mg or 1200 mg* (N=280)**	**PEGASYS + COPEGUS 800 mg (N=361)**	**PEGASYS + COPEGUS 1000 mg or 1200 mg* (N=436)**
Genotype 1	29/101 (29%)	48/118 (41%)	99/250 (40%)	138/271 (51%)
Genotypes 2, 3	79/96 (82%)	116/144 (81%)	75/99 (76%)	117/153 (76%)
Genotype 4	0/5 (0%)	7/12 (58%)	5/8 (63%)	9/11 (82%)

*1000 mg for body weight less than 75 kg; 1200 mg for body weight greater than or equal to 75 kg.

Pediatric Patients

Previously untreated pediatric subjects 5 through 17 years of age (55% less than 12 years old) with chronic hepatitis C, compensated liver disease and detectable HCV RNA were treated with COPEGUS approximately 15 mg/kg/day plus PEGASYS 180 mcg/1.73 m^2 x body surface area once weekly for 48 weeks. All subjects were followed for 24 weeks post-treatment. Sustained virological response (SVR) was defined as undetectable (less than 50 IU/mL) HCV RNA on or after study week 68. A total of 114 subjects were randomized to receive either combination treatment of COPEGUS plus PEGASYS or PEGASYS monotherapy; subjects failing PEGASYS monotherapy at 24 weeks or later could receive open-label COPEGUS plus PEGASYS. The initial randomized arms were balanced for demographic factors; 55 subjects received initial combination treatment of COPEGUS plus PEGASYS and 59 received PEGASYS plus placebo; in the overall intent-to-treat population, 45% were female, 80% were Caucasian, and 81% were infected with HCV genotype 1. The SVR results are summarized in **Table 11**.

Table 11 Sustained Virologic Response (Study NV17424)

	PEGASYS 180 mcg/1.73 m² x BSA + COPEGUS 15 mg/kg* (N=55)	**PEGASYS 180 mcg/1.73 m² x BSA + Placebo* (N=59)**
All HCV genotypes**	29 (53%)	12 (20%)
HCV genotype 1	21/45 (47%)	8/47 (17%)
HCV non-genotype 1***	8/10 (80%)	4/12 (33%)

*Results indicate undetectable HCV RNA defined as HCV RNA less than 50 IU/mL at 24 weeks post-treatment using the AMPLICOR HCV test v2

**Scheduled treatment duration was 48 weeks regardless of the genotype

***Includes HCV genotypes 2,3 and others

14.2 Other Treatment Response Predictors

Treatment response rates are lower in patients with poor prognostic factors receiving pegylated interferon alpha therapy. In studies NV15801 and NV15942, treatment response rates were lower in patients older than 40 years (50% vs. 66%), in patients with cirrhosis (47% vs. 59%), in patients weighing over 85 kg (49% vs. 60%), and in patients with genotype 1 with high vs. low viral load (43% vs. 56%). African-American patients had lower response rates compared to Caucasians.

In studies NV15801 and NV15942, lack of early virologic response by 12 weeks (defined as HCV RNA undetectable or greater than 2 $\log_{10}$ lower than baseline) was grounds for discontinuation of treatment. Of patients who lacked an early viral response by 12 weeks and completed a recommended course of therapy despite a protocol-defined option to discontinue therapy, 5/39 (13%) achieved an SVR. Of patients who lacked an early viral response by 24 weeks, 19 completed a full course of therapy and none achieved an SVR.

14.3 Chronic Hepatitis C/HIV Coinfected Patients

In Study NR15961, patients with CHC/HIV were randomized to receive either PEGASYS 180 mcg subcutaneous once weekly plus an oral placebo, PEGASYS 180 mcg once weekly plus COPEGUS 800 mg by mouth daily or interferon alfa-2a, 3 MIU subcutaneous three times a week plus COPEGUS 800 mg by mouth daily. All patients received 48 weeks of therapy and sustained virologic response (SVR) was assessed at 24 weeks of treatment-free follow-up. COPEGUS or placebo treatment assignment was blinded in the PEGASYS treatment arms. All patients were adults, had compensated liver disease, detectable hepatitis C virus, liver biopsy diagnosis of chronic hepatitis C, and were previously untreated with interferon. Patients also had CD4+ cell count greater than or equal to 200 cells/mm^3 or CD4+ cell count greater than or equal to 100 cells/mm^3 but less than 200 cells/mm^3 and HIV-1 RNA less than 5000 copies/mL, and stable status of HIV. Approximately 15% of patients in the study had cirrhosis. Results are shown in **Table 12.**

Table 12 Sustained Virologic Response in Patients with Chronic Hepatitis C Coinfected With HIV (Study NR15961)

	Interferon alfa-2a + COPEGUS 800 mg (N=289)	**PEGASYS + Placebo (N=289)**	**PEGASYS + COPEGUS 800 mg (N=290)**
All patients	33 (11%)	58 (20%)	116 (40%)
Genotype 1	12/171 (7%)	24/175 (14%)	51/176 (29%)
Genotypes 2, 3	18/89 (20%)	32/90 (36%)	59/95 (62%)

Treatment response rates were lower in CHC/HIV patients with poor prognostic factors (including HCV genotype 1, HCV RNA greater than 800,000 IU/mL, and cirrhosis) receiving pegylated interferon alpha therapy.

Of the patients who did not demonstrate either undetectable HCV RNA or at least a 2 $\log_{10}$ reduction from baseline in HCV RNA titer by 12 weeks of PEGASYS and COPEGUS combination therapy, 2% (2/85) achieved an SVR.

In CHC patients with HIV coinfection who received 48 weeks of PEGASYS alone or in combination with COPEGUS treatment, mean and median HIV RNA titers did not increase above baseline during treatment or 24 weeks post-treatment.

16 HOW SUPPLIED/STORAGE AND HANDLING

COPEGUS® (ribavirin) is available as tablets for oral administration. Each tablet contains 200 mg of ribavirin and is light pink to pink colored, flat, oval-shaped, film-coated, and engraved with RIB 200 on one side and ROCHE on the other side. They are packaged as bottle of 168 tablets (NDC 0004-0086-94).

Storage and Handling

Store the COPEGUS® Tablets bottle at 25ºC (77ºF); excursions are permitted between 15ºC and 30ºC (59ºF and 86ºF) [see USP Controlled Room Temperature]. Keep bottle tightly closed.

17 PATIENT COUNSELING INFORMATION

- See FDA-approved patient labeling (Medication Guide)

Pregnancy

Patients must be informed that ribavirin may cause birth defects and/or death of the exposed fetus. COPEGUS therapy must not be used by women who are pregnant or by men whose female partners are pregnant. Extreme care must be taken to avoid pregnancy in female patients and in female partners of male patients taking COPEGUS therapy and for 6 months post therapy. Patients should use two reliable methods of birth control while taking COPEGUS therapy and for 6 months post therapy. COPEGUS therapy should not be initiated until a report of a negative pregnancy test has been obtained immediately prior to initiation of therapy. Patients must perform a pregnancy test monthly during therapy and for 6 months post therapy.

Female patients of childbearing potential and male patients with female partners of childbearing potential must be advised of the teratogenic/embryocidal risks and must be instructed to practice effective contraception during COPEGUS therapy and for 6 months post therapy. Patients should be advised to notify the healthcare provider immediately in the event of a pregnancy *[see Contraindications (4) and Warnings and Precautions (5.1)]*.

Anemia

The most common adverse event associated with ribavirin is anemia, which may be severe *[see Boxed Warning, Warnings and Precautions (5.2) and Adverse Reactions (6.1)]*. Patients should be advised that laboratory evaluations are required prior to starting COPEGUS therapy and periodically thereafter *[see Warnings and Precautions (5.9)]*. It is advised that patients be well hydrated, especially during the initial stages of treatment.

Patients who develop dizziness, confusion, somnolence, and fatigue should be cautioned to avoid driving or operating machinery.

Patients should be advised to take COPEGUS with food.

Patients should be questioned about prior history of drug abuse before initiating COPEGUS/PEGASYS, as relapse of drug addiction and drug overdoses have been reported in patients treated with interferons.

Patients should be advised not to drink alcohol, as alcohol may exacerbate chronic hepatitis C infection.

Patients should be informed about what to do in the event they miss a dose of COPEGUS. The missed doses should be taken as soon as possible during the same day. Patients should not double the next dose. Patients should be advised to call their healthcare provider if they have questions.

Patients should be informed that the effect of PEGASYS/COPEGUS treatment of hepatitis C infection on transmission is not known, and that appropriate precautions to prevent transmission of hepatitis C virus during treatment or in the event of treatment failure should be taken.

Patients should be informed regarding the potential benefits and risks attendant to the use of COPEGUS. Instructions on appropriate use should be given, including review of the contents of the enclosed MEDICATION GUIDE, which is not a disclosure of all or possible adverse effects.

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