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

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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.

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