CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-511

APPROVED LABELING

COPEGUS™

(ribavirin, USP)

TABLETS

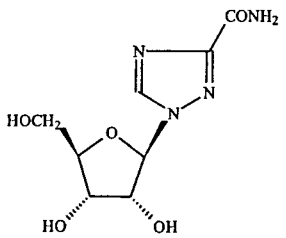
COPEGUS (ribavirin) monotherapy is not effective for the treatment of chronic hepatitis C virus infection and should not be used alone for this indication (see WARNINGS).

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

Significant teratogenic and/or embryocidal effects have been demonstrated in all animal species exposed to ribavirin. In addition, ribavirin has a multiple dose half-life of 12 days, and it may persist in non-plasma compartments for as long as 6 months. Ribavirin therapy is contraindicated in women who are pregnant and in the male partners of women who are pregnant. Extreme care must be taken to avoid pregnancy during therapy and for 6 months after completion of treatment in both female patients and in female partners of male patients who are taking ribavirin therapy. At least two reliable forms of effective contraception must be utilized during treatment and during the 6-month posttreatment follow-up period (see CONTRAINDICATIONS, WARNINGS, and PRECAUTIONS: Information for Patients, and Pregnancy: Category X).

DESCRIPTION

COPEGUS, the Hoffmann-La Roche brand name for 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, corn starch, 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.

Mechanism of Action

Ribavirin is a synthetic nucleoside analogue. The mechanism by which the combination of ribavirin and an interferon product exerts its effects against the hepatitis C virus has not been fully established.

CLINICAL PHARMACOLOGY

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) $AUC_{0\text{-}12hr}$ 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 >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 **PRECAUTIONS** and **DOSAGE AND ADMINISTRATION**).

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.

Special Populations

Race

There were insufficient numbers of non-Caucasian subjects studied to adequately determine potential pharmacokinetic differences between populations.

Renal Dysfunction

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

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.

Pediatric Patients

Pharmacokinetic evaluations in pediatric patients have not been performed.

Elderly Patients

Pharmacokinetic evaluations in elderly patients have not been performed.

Gender

Ribavirin pharmacokinetics, when corrected for weight, are similar in male and female patients.

Drug Interactions

In vitro studies indicate that ribavirin does not inhibit CYP450 enzymes.

Nucleoside Analogues

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

Clinical Studies

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).

In study NV15801 (described as study 4 in the PEGASYS Package Insert), patients were randomized to receive either PEGASYS 180 µg sc once weekly (qw) with an oral placebo, PEGASYS 180 µg qw with COPEGUS 1000 mg po (body weight <75 kg) or 1200 mg po (body weight ≥75 kg) or REBETRON™ (interferon alfa-2b 3 MIU sc tiw plus ribavirin 1000 mg or 1200 mg po). All patients received 48 weeks of therapy followed by 24 weeks of treatment-free follow-up. COPEGUS or placebo treatment assignment was blinded. PEGASYS in combination with COPEGUS resulted in a higher SVR (defined as undetectable HCV RNA at the end of the 24-week treatment-free follow-up period) compared to PEGASYS alone or interferon alfa-2b and ribavirin (Table 1). 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 1 Sustained Virologic Response 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).
* Described as study 4 in the PEGASYS Package Insert.

In study NV15942 (described as study 5 in the PEGASYS Package Insert), all patients received PEGASYS 180 µg sc qw 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 <75 kg / ≥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 >2 x 10^6 HCV RNA copies/mL serum) were preferentially assigned to treatment for 48 weeks.

Genotype 1

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.

Genotype non-1

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 2).

Table 2 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%)
Genotype 2-3	79/96 (82%)	116/144 (81%)	75/ 99 (76%)	117/153 (76%)

* Described as study 5 in the PEGASYS Package Insert.
**1000 mg for body weight <75 kg; 1200 mg for body weight ≥75 kg.

Among the 36 patients with genotype 4, response rates were similar to those observed in patients with genotype 1 (data not shown). The numbers of patients with genotype 5 and 6 were too few to allow for meaningful assessment.

Treatment Response in Patient Subgroups

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.

Paired liver biopsies were performed on approximately 20% of patients in studies NV15801 and NV15942. Modest reductions in inflammation compared to baseline were seen in all treatment groups.

In studies NV15801 and NV15942, lack of early virologic response at 12 weeks (defined as HCV RNA undetectable or >2log10 lower than baseline)

was grounds for discontinuation of treatment. Of patients who lacked an early viral response at 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 at 24 weeks, nineteen completed a full course of therapy and none achieved an SVR.

INDICATIONS AND USAGE

COPEGUS in combination with PEGASYS (peginterferon alfa-2a) is indicated for the treatment of adults with chronic hepatitis C virus infection who have compensated liver disease and have not been previously treated with interferon alpha. Patients in whom efficacy was demonstrated included patients with compensated liver disease and histological evidence of cirrhosis (Child-Pugh class A).

CONTRAINDICATIONS

COPEGUS (ribavirin) is contraindicated in:

- Patients with known hypersensitivity to COPEGUS or to any component of the tablet.
- Women who are pregnant.
- Men whose female partners are pregnant.
- Patients with hemoglobinopathies (eg, thalassemia major or sickle-cell anemia).

COPEGUS and PEGASYS combination therapy is contraindicated in patients with:

- Autoimmune hepatitis.
- Hepatic decompensation (Child-Pugh class B and C) before or during treatment.

WARNINGS

COPEGUS must not be used alone because ribavirin monotherapy is not effective for the treatment of chronic hepatitis C virus infection. The safety and efficacy of COPEGUS have only been established when used together with PEGASYS (pegylated interferon alfa-2a, recombinant).

COPEGUS and PEGASUS should be discontinued in patients who develop evidence of hepatic decompensation during treatment.

There are significant adverse events caused by COPEGUS/PEGASYS therapy, including severe depression and suicidal ideation, hemolytic anemia, suppression of bone marrow function, autoimmune and infectious disorders, pulmonary dysfunction, pancreatitis, and diabetes. The PEGASYS package insert and MEDICATION GUIDE should be

reviewed in their entirety prior to initiation of combination treatment for additional safety information.

General

Treatment with COPEGUS and PEGASYS should be administered under the guidance of a qualified physician and may lead to moderate to severe adverse experiences requiring dose reduction, temporary dose cessation or discontinuation of therapy.

Pregnancy

Ribavirin may cause birth defects and/or death of the exposed fetus. Extreme care must be taken to avoid pregnancy in female patients and in female partners of male patients. 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. Patients should be instructed to use at least two forms of effective contraception during treatment and for at least six-months after treatment has been stopped. Pregnancy testing should occur monthly during COPEGUS therapy and for six months after therapy has stopped (see CONTRAINDICATIONS and PRECAUTIONS: Information for Patients and Pregnancy: Category X).

Anemia

The primary toxicity of ribavirin is hemolytic anemia (hemoglobin <10 g/dL), which was observed in approximately 13% of COPEGUS and PEGASYS treated patients in clinical trials (see PRECAUTIONS: Laboratory Tests). The 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.

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: COPEGUS Dose Modification Guidelines). 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 ADVERSE REACTIONS).

Pulmonary

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

Other

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

COPEGUS should not be used in patients with creatinine clearance <50 mL/min (see **CLINICAL PHARMACOLOGY: Special Populations**).

COPEGUS must be discontinued immediately and appropriate medical therapy instituted if an acute hypersensitivity reaction (eg, urticaria, angioedema, bronchoconstriction, anaphylaxis) develops. Transient rashes do not necessitate interruption of treatment.

PRECAUTIONS

The safety and efficacy of COPEGUS and PEGASYS therapy for the treatment of HIV infection, 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.

The safety and efficacy of COPEGUS and PEGASYS therapy have not been established in liver or other organ transplant patients, patients with decompensated liver disease due to hepatitis C virus infection, patients who are non-responders to interferon therapy or patients co-infected with HBV or HIV.

Information for Patients

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 posttherapy. 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 posttherapy.

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 posttherapy. Patients should be advised to notify the physician immediately in the event of a pregnancy (see **CONTRAINDICATIONS** and **WARNINGS**).

To monitor maternal-fetal outcomes of pregnant women exposed to COPEGUS, the COPEGUS Pregnancy Registry has been established. Physicians and patients are strongly encouraged to register by calling 1-800-526-6367.

The most common adverse event associated with ribavirin is anemia, which may be severe (see **ADVERSE REACTIONS**). Patients should be advised that laboratory evaluations are required prior to starting COPEGUS therapy and periodically thereafter (see **Laboratory Tests**). 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 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.

Patients should be advised to take COPEGUS with food.

Laboratory Tests

Before beginning COPEGUS therapy, standard hematological and biochemical laboratory tests must be conducted for all patients. Pregnancy screening for women of childbearing potential must be done.

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. Monthly pregnancy testing should be done during combination therapy and for 6 months after discontinuing therapy.

The entrance criteria used for the clinical studies of COPEGUS and PEGASYS combination therapy may be considered as a guideline to acceptable baseline values for initiation of treatment:

- Platelet count ≥90,000 cells/mm^3
- Absolute neutrophil count (ANC) ≥1500 cells/mm^3
- TSH and T_4 within normal limits or adequately controlled thyroid function
- ECG (see **WARNINGS**)

The maximum drop in hemoglobin usually occurred during the first 8 weeks of initiation of COPEGUS therapy. Because of this initial acute drop in hemoglobin, it is advised that a complete blood count should be obtained pretreatment and at week 2 and week 4 of therapy or more frequently if clinically indicated. Additional testing should be performed periodically during therapy. Patients should then be followed as clinically appropriate.

Drug Interactions

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

Nucleoside Analogues

Didanosine

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

Stavudine and Zidovudine

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

Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis

The carcinogenic potential of ribavirin has not been fully determined. In a p53 (+/-) mouse carcinogenicity study at doses up to the maximum tolerated dose of 100 mg/kg/day, ribavirin was not oncogenic. However, on a body surface area basis, this dose was 0.5 times maximum recommended human 24-hour dose of ribavirin. A study to assess the carcinogenic potential of ribavirin in rats is ongoing.

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 0.1-0.8 times the maximum recommended human 24-hour 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 posttherapy (ie, 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.

Pregnancy

Pregnancy: Category X (see **CONTRAINDICATIONS)**

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

In conventional embryotoxicity/teratogenicity studies in rats and rabbits, observed no effect dose levels were well below those for proposed clinical use (0.3 mg/kg/day for both the rat and rabbit; approximately 0.06 times the recommended human 24-hour dose of ribavirin). No maternal toxicity or effects on offspring were observed in a peri/postnatal toxicity study in rats dosed orally at up to 1 mg/kg/day (approximately 0.01 times the maximum recommended human 24-hour dose of ribavirin).

Treatment and Posttreatment: 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. 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). 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 posttherapy.

To monitor maternal-fetal outcomes of pregnant women exposed to COPEGUS, the COPEGUS Pregnancy Registry has been established. Physicians and patients are strongly encouraged to register by calling 1-800-526-6367.

Animal Toxicology

Long-term study in the mouse and rat (18-24 months; dose 20-75 and 10-40 mg/kg/day, respectively (approximately 0.1-0.4 times the maximum human daily 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.

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.

Pediatric Use

Safety and effectiveness of COPEGUS have not been established in patients below the age of 18.

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. COPEGUS should not be administered to patients with creatinine clearance <50 mL/min. (see **CLINICAL PHARMACOLOGY: Special Populations).**

Effect of Gender

No clinically significant differences in the pharmacokinetics of ribavirin were observed between male and female subjects.

ADVERSE REACTIONS

PEGASYS in combination with COPEGUS causes a broad variety of serious adverse reactions (see **BOXED WARNING** and **WARNINGS**). In all studies, one or more serious adverse reactions occurred in 10% of patients receiving PEGASYS in combination with COPEGUS.

The most common life-threatening or fatal events induced or aggravated by PEGASYS and COPEGUS were depression, suicide, relapse of drug abuse/overdose, and bacterial infections; each occurred at a frequency of <1%.

Nearly all patients in clinical trials experienced one or more adverse events. The most commonly reported adverse reactions were psychiatric reactions, including depression, irritability, anxiety, and flu-like symptoms such as fatigue, pyrexia, myalgia, headache and rigors.

Ten percent of patients receiving 48 weeks of therapy with PEGASYS in combination with COPEGUS discontinued therapy. The most common reasons for discontinuation of therapy were psychiatric, flu-like syndrome (eg, lethargy, fatigue, headache), dermatologic and gastrointestinal disorders.

The most common reason for dose modification in patients receiving combination therapy was for laboratory abnormalities; neutropenia (20%) and thrombocytopenia (4%) for PEGASYS and anemia (22%) for COPEGUS.

PEGASYS dose was reduced in 12% of patients receiving1000 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 12% in patients receiving 800 mg COPEGUS for 24 weeks.

Because clinical trials are conducted under widely varying and controlled conditions, adverse reaction rates observed in clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug. Also, the adverse event rates listed here may not predict the rates observed in a broader patient population in clinical practice.

Table 3 Adverse Reactions Occurring in ≥5% of Patients in Hepatitis C Clinical Trials (Study NV15801*)

Body System	**PEGASYS 180 µg + 1000 mg or 1200 mg COPEGUS 48 wk**	**Intron A + 1000 mg or 1200 mg REBETOL® 48 wk**
	N=451	**N=443**
	%	**%**
Application Site Disorders Injection site reaction	23	16
Endocrine Disorders Hypothyroidism	4	5
Flu-like Symptoms and Signs		

Body System	PEGASYS 180 µg + 1000 mg or 1200 mg COPEGUS 48 wk	Intron A + 1000 mg or 1200 mg REBETOL® 48 wk
	N=451	N=443
	%	%
Fatigue/Asthenia	65	68
Pyrexia	41	55
Rigors	25	37
Pain	10	9
Gastrointestinal		
Nausea/vomiting	25	29
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
Cough	10	7
Dyspnea exertional	4	7

Body System	PEGASYS 180 µg + 1000 mg or 1200 mg COPEGUS 48 wk	Intron A + 1000 mg or 1200 mg REBETOL® 48 wk
	N=451	N=443
	%	%
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

* Described as study 4 in the PEGASYS Package Insert.
** Severe hematologic abnormalities

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 <10g/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.

The most common serious adverse event (3%) was bacterial infection (eg, sepsis, osteomyelitis, endocarditis, pyelonephritis, pneumonia). Other SAEs 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 (eg, hyperthyroidism, hypothyroidism, sarcoidosis, systemic lupus erythematosis, rheumatoid arthritis) peripheral neuropathy, aplastic anemia, peptic ulcer, gastrointestinal bleeding, pancreatitis, colitis, corneal ulcer, pulmonary embolism, coma, myositis, and cerebral hemorrhage.

Laboratory Test Values

Anemia due to hemolysis is the most significant toxicity of ribavirin therapy. Anemia (hemoglobin <10 g/dL) was observed in 13% of 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: Dose Modifications**).

OVERDOSAGE

No cases of overdose with COPEGUS have been reported in clinical trials.

DOSAGE AND ADMINISTRATION

The recommended dose of COPEGUS tablets is provided in Table 4. 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 (eg, genotype), response to therapy, and tolerability of the regimen (see Table 4).

In the pivotal clinical trials, patients were instructed to take COPEGUS with food; therefore, patients are advised to take COPEGUS with food.

Table 4 PEGASYS and COPEGUS Dosing Recommendations

Genotype	PEGASYS Dose	COPEGUS Dose	Duration
Genotype 1, 4	180 μg	<75 kg = 1000 mg ≥75 kg = 1200 mg	48 weeks 48 weeks
Genotype 2, 3	180 μg	800 mg	24 weeks

Genotypes non-1 showed no increased response to treatment beyond 24 weeks (see Table 2).
Data on genotypes 5 and 6 are insufficient for dosing recommendations.

Dose Modifications

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. If intolerance persists after dose adjustment, COPEGUS/PEGASYS therapy should be discontinued.

COPEGUS should be administered with caution to patients with pre-existing cardiac disease (see Table 5). 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**).

Table 5 COPEGUS Dosage Modification Guidelines

Laboratory Values	Reduce Only COPEGUS Dose to 600 mg/day* if:	Discontinue COPEGUS 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 COPEGUS has been withheld due to either a laboratory abnormality or clinical manifestation, an attempt may be made to restart COPEGUS at 600 mg daily and further increase the dose to 800 mg daily depending upon the physician's judgment. However, it is not recommended that COPEGUS be increased to its original assigned dose (1000 mg to 1200 mg).

Renal Impairment

COPEGUS should not be used in patients with creatinine clearance <50 mL/min (see **WARNINGS** and **CLINICAL PHARMACOLOGY: Special Populations**).

HOW SUPPLIED

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 Conditions

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

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Rx only

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MEDICATION GUIDE

COPEGUS™ (Co-PEG-UHS)

(ribavirin)

Tablets

Read this Medication Guide carefully before you start taking COPEGUS and read the Medication Guide each time you get more COPEGUS. There may be new information. This information does not take the place of talking to your healthcare provider about your medical condition or your treatment.

What is the most important information I should know about COPEGUS?

1. **COPEGUS may cause birth defects or death of an unborn child. Therefore, if you are pregnant or your sexual partner is pregnant or plans to become pregnant, do not take COPEGUS.** If you could become pregnant, you must not become pregnant while taking COPEGUS and for 6 months after you have stopped treatment with COPEGUS. **During this time you must use 2 forms of birth control, and you must have pregnancy tests that show you are not pregnant.**

   Female sexual partners of male patients being treated with COPEGUS must not become pregnant during treatment and for 6 months after treatment has stopped. You must use 2 forms of birth control during this time.

   If pregnancy occurs, report the pregnancy to your healthcare provider right away. (See **"What should I avoid while taking COPEGUS?")**

2. **COPEGUS can cause a dangerous drop in your red blood cell count.** COPEGUS can cause anemia, which is a decrease in the number of red blood cells. This can be dangerous, especially if you have heart or breathing problems. This may cause a worsening of heart (cardiovascular) or circulatory problems. Some patients may get chest pain and rarely, a heart attack. Patients with a history of heart disease have the highest chance of this. Tell your healthcare provider, before taking COPEGUS if you have or have ever had any heart or breathing problems. Your healthcare provider should check your red blood cell count before you start treatment with COPEGUS and often during the first 4 weeks of treatment. Your red blood cell count may be done more often if you have any heart or breathing problems.

3. **Do not take COPEGUS alone to treat hepatitis C virus infection.** COPEGUS does not treat hepatitis C virus infections by itself. COPEGUS should be used in combination with PEGASYS® (peginterferon alfa-2a) to treat continuing (chronic) hepatitis C virus infections. You should read the Medication Guide for PEGASYS because it has additional important

information about treatment that is not covered in this Medication Guide. Your healthcare provider or pharmacist should give you a copy of the PEGASYS Medication Guide.

What is COPEGUS?

COPEGUS is the antiviral medicine ribavirin. It is used in combination with a medicine called PEGASYS (peginterferon alfa-2a) to treat some adults with chronic hepatitis C whose liver still works normally, and who have not been treated before with a medicine called an interferon alpha. It is not known how COPEGUS and PEGASYS work together to fight hepatitis C virus infections.

It is not known if treatment with COPEGUS and PEGASYS combination therapy can cure hepatitis C or if it can prevent liver damage (cirrhosis), liver failure or liver cancer that is caused by hepatitis C virus infections. It is not known if treatment with COPEGUS and PEGASYS combination therapy will prevent an infected person from spreading the hepatitis C virus to another person.
Treatment with COPEGUS has not been studied in children under 18 years of age.

Who should not take COPEGUS?

Do not use COPEGUS if:

- **You are a female and you are pregnant or plan to become pregnant** during treatment or during the 6 months after your treatment has ended. (See **"What is the most important information I should know about COPEGUS?"** and **"What should I avoid while taking COPEGUS?")**
- **You are a male patient with a female sexual partner who is pregnant or plans to become pregnant** at any time while you are being treated with COPEGUS or during the 6 months after your treatment has ended. (See **"What is the most important information I should know about COPEGUS?"** and **"What should I avoid while taking COPEGUS?")**
- **You are breast feeding. We do not know if COPEGUS can pass through your milk and if it can harm your baby. You will need to choose either to breast feed or take COPEGUS, but not both.**
- **You have a liver disease called autoimmune hepatitis** (hepatitis caused by your immune system attacking your liver).
- **You have unstable or advanced liver disease.**
- **You are allergic to any of the ingredients in COPEGUS.** The active ingredient in COPEGUS is ribavirin. See the end of this Medication Guide for a list of all the ingredients in COPEGUS.

Tell your healthcare provider before starting treatment with COPEGUS in combination with PEGASYS (see also the PEGASYS Medication Guide) if you have any of the following medical conditions:

- **mental health problems, such as depression or anxiety:** COPEGUS and PEGASYS combination therapy may make them worse. Tell your healthcare provider if you are being treated or had treatment in the past for any mental problems, including depression, thoughts of ending your life (suicidal thoughts) or a feeling of loss of contact with reality, such as hearing voices or seeing things that are not there (psychosis). Tell your healthcare provider if you take any medicines for these problems.
- **high blood pressure, heart problems or have had a heart attack.** COPEGUS may worsen heart problems such as high blood pressure, increased heart rate, and chest pain. Tell your healthcare provider if you have or had a heart problem. Patients who have had certain heart problems should not take COPEGUS.
- **blood disorders,** including anemia (low red blood cell count), thalassemia (Mediterranean anemia) and sickle-cell anemia. COPEGUS can reduce the number of red blood cells you have. This may make you feel dizzy or weak and could worsen any heart problems you might have.
- **kidney problems.** If your kidneys do not work properly, you may have worse side effects from COPEGUS treatment and require a lower dose.
- **liver problems** (other then hepatitis C virus infection).
- **organ transplant,** and you are taking medicine that keeps your body from rejecting your transplant (suppresses your immune system).
- **thyroid disease.** COPEGUS and PEGASYS combination therapy may make your thyroid disease worse or harder to treat. COPEGUS and PEGASYS treatment may be stopped if you develop thyroid problems that cannot be controlled by medicine.
- **have or had drug or alcohol addiction or abuse.**
- **cancer.**
- **infection with hepatitis B virus and/or human immunodeficiency virus** (HIV, the virus that causes AIDS).
- **diabetes.** COPEGUS and PEGASYS combination therapy may make your diabetes worse or harder to treat.
- **past interferon treatment for hepatitis C virus infection that did not work for you.**

Tell your healthcare provider about all the medicines you take, including prescription and non-prescription medicines, vitamins, and herbal supplements. Some medicines can cause

serious side effects if taken while you also take COPEGUS. Some medicines may affect how COPEGUS works or COPEGUS may affect how your other medicines work. Be especially sure to tell your healthcare provider if you take any medicines to treat HIV.

For more information see the PEGASYS Medication Guide.

How should I take COPEGUS?

- Your healthcare provider will determine the right dose of COPEGUS based on your weight.
- Take COPEGUS 1 time in the morning and 1 time at night (2 times a day). Take COPEGUS the same 2 times each day.
- Take COPEGUS with food.
- It is very important to follow your dosing schedule and your healthcare provider's instructions on how to take your medicines.
- Take COPEGUS for as long as it is prescribed, and do not take more than your healthcare provider prescribes.
- If you miss a dose of COPEGUS and remember **the same day**, take the missed dose as soon as you remember. If **the whole day has passed**, ask your healthcare provider what to do. Do not take 2 doses at the same time.
- Your healthcare provider may adjust your dose of COPEGUS based on blood tests that show your response to treatment and side effects you may have.
- **Females taking COPEGUS or female sexual partners of male patients taking COPEGUS must have a pregnancy test:**
- before treatment begins
- every month during treatment
- for 6 months after treatment ends to make sure there is no pregnancy

It is also important not to use other ribavirin medicines without talking to your healthcare provider. Please see the PEGASYS Medication Guide for the proper use of PEGASYS injection.

What should I avoid while taking COPEGUS?

Avoid the following during COPEGUS treatment:

- **Do not get pregnant.** If you or your sexual partner get pregnant during treatment with COPEGUS or in the 6 months after treatment ends, tell your healthcare provider right away. (See **"What is the most important information I should know about treatment with COPEGUS?")**

Talk with your healthcare provider about birth control methods and how to avoid pregnancy. You must use extreme care to avoid pregnancy during COPEGUS treatment and for 6 months after treatment in female and male patients.

If you or your sexual partner get pregnant while on COPEGUS or during the 6 months after your treatment ends, you must report the pregnancy to your healthcare provider right away. Your healthcare provider should call Roche, the company that makes COPEGUS, at 1-800-526-6367. Your healthcare provider will be asked to give follow-up information about the pregnancy. Any information about your pregnancy that is reported about you will be kept private (confidential).

- **Do not take COPEGUS alone to treat your hepatitis C virus infection.** COPEGUS should be used in combination with PEGASYS (peginterferon alfa-2a) to treat chronic hepatitis C virus infections. (See **"What is the most important information I should know about treatment with COPEGUS?")**
- **Do not breast-feed.** COPEGUS may pass through your milk and may harm your baby.
- **Do not drink alcohol**, including beer, wine, and liquor. This may make your liver disease worse.
- **Do not drive or operate machinery** if COPEGUS makes you feel tired, dizzy or confused.
- **Do not take other medicines unless your healthcare provider knows about them.** Take only medicines prescribed or approved by your healthcare provider. These include prescription and non-prescription medicines, vitamins, and herbal supplements. Talk to your healthcare provider before starting any new medicine.

What are the possible side effects of COPEGUS?

The most serious possible side effects of COPEGUS are:

- **Harm to unborn children.** COPEGUS may cause birth defects or death of an unborn child. (For more details, see **"What is the most important information I should know about COPEGUS?")**
- **Anemia.** Anemia is a reduction in the number of red blood cells you have. Anemia can be dangerous, especially if you have heart or breathing problems. Tell your healthcare provider right away if you feel tired, have chest pain or shortness of breath. These may be signs of low red blood cell counts.

Call your healthcare provider right away if you have any of the following symptoms. They may be signs of a serious side effect of COPEGUS and PEGASYS treatment.

- trouble breathing

- hives or swelling
- chest pain
- severe stomach pain or low back pain
- bloody diarrhea or bloody stools (bowel movements). These may look like black tar.
- bruising or unusual bleeding
- change in your vision
- high fever (temperature greater than 100.5°F)
- you have psoriasis (a skin disease) and it gets worse
- you become very depressed or think about suicide (ending your life)

The most common side effects of COPEGUS are likely to be the same as for other ribavirin products. These are:

- *feeling tired*
- *nausea and appetite loss*
- *rash and itching*
- *cough*

These are not all the possible side effects of COPEGUS treatment. For more information, ask your doctor or pharmacist and see the PEGASYS Medication Guide.

What should I know about hepatitis C infection?

Hepatitis C infection is a disease caused by a virus that infects the liver. Hepatitis C is more serious for some people than others. Most people who get hepatitis C carry the virus in their blood for the rest of their lives. Most of these people will have some liver damage, but many do not feel sick from the disease. In some people, the liver becomes badly damaged and scarred. This is called cirrhosis. Cirrhosis can cause the liver to stop working. Some people may get liver cancer or liver failure from the hepatitis C virus.

Hepatitis C virus is spread from one person to another by contact with an infected person's blood. You should talk to your healthcare provider about ways to prevent you from infecting others.

How should I store COPEGUS?

Store COPEGUS tablets at room temperature (77°F).

Please refer to the PEGASYS Medication Guide for storage information about PEGASYS injection.

General information about the safe and effective use of COPEGUS

Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. Do not use COPEGUS for a condition for which it was not prescribed. Do not give COPEGUS to other people, even if they have the same symptoms that you have.

This Medication Guide summarizes the most important information about COPEGUS. If you would like more information, talk with your healthcare provider. You can ask your healthcare provider or pharmacist for information about COPEGUS that is written for healthcare professionals.

What are the ingredients in COPEGUS?

Active Ingredient: ribavirin

Inactive Ingredients: pregelatinized starch, sodium starch glycolate, cornstarch, microcrystalline cellulose, and magnesium stearate. The tablet is coated with aquacoat ECD-30, triacetin, and colored with a coating system composed of hydroxypropyl methyl cellulose, talc, titanium dioxide, synthetic yellow iron oxide, and synthetic red iron oxide.

This Medication Guide has been approved by the U.S. Food and Drug Administration.

R_X only

Roche Pharmaceuticals

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