CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

125083Orig1s000

LABELING

Roche

COPEGUS®

(ribavirin, USP)

TABLETS

R_x only

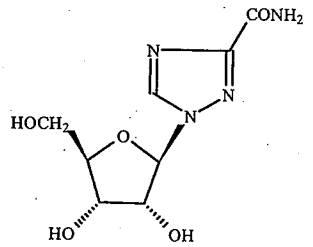
COPEGUS (ribavirin) monotherapy is not effective for the treatment of chronic hepatitis C virus infection and should not be used alone for this indication (see WARNINGS).

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 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 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 (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).
* 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%)
Genotypes 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 PEGASYS 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 6 months after treatment has been stopped. Pregnancy testing should occur monthly during COPEGUS therapy and for 6 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 Dosage 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 healthcare provider immediately in the event of a pregnancy (see **CONTRAINDICATIONS** and **WARNINGS**).

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 the 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.

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 six months following cessation of treatment. Physicians and patients are encouraged to report such cases by calling 1-800-593-2214.

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 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 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		
Fatigue/Asthenia	65	68
Pyrexia	41	55
Rigors	25	37
Pain	10	9
Gastrointestinal		

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
	%	%
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
Skin and Subcutaneous Tissue		
Alopecia	28	33
Pruritus	19	18
Dermatitis	16	13
Dry Skin	10	13
Rash	8	5

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
	%	%
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	48 weeks
		≥75 kg = 1200 mg	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).

PEGASYS® COPEGUS® Combination Pack

Copegus is also available as a combination pack with PEGASYS (peginterferon alfa-2a) and is available in the following three monthly combination packs for patients with a daily dose requirement of 800 mg, 1000 mg or 1200 mg of COPEGUS:

800 mg COPEGUS® Daily Dose

Each combination pack contains a bottle of 112 COPEGUS (ribavirin), 200 mg, tablets and a box containing four PEGASYS (peginterferon alfa-2a), 180 µg, single use, graduated, clear glass, prefilled syringes, 4 needles, and 4 alcohol swabs. Each syringe contains 0.6 mL of solution to deliver 0.5 mL (½ cc) of drug product and supplied with a 27 gauge, ½ inch needle with needle-stick protection device. (NDC 0004-0353-17)

PEGASYS® COPEGUS® Combination Pack

1000 mg COPEGUS® Daily Dose

Each combination pack contains a bottle of 140 COPEGUS (ribavirin), 200 mg, tablets and a box containing four PEGASYS (peginterferon alfa-2a), 180 µg, single use, graduated, clear glass, prefilled syringes, 4 needles, and 4 alcohol swabs. Each syringe contains 0.6 mL of solution to deliver 0.5 mL (½ cc) of drug product and supplied with a 27 gauge, ½ inch needle with needle-stick protection device. (NDC 0004-0353-18).

PEGASYS® COPEGUS® Combination Pack

1200 mg COPEGUS® Daily Dose

Each combination pack contains a bottle of 168 COPEGUS (ribavirin), 200 mg, tablets and a box containing four PEGASYS (peginterferon alfa-2a), 180 µg, single use, graduated, clear glass, prefilled syringes, 4 needles, and 4 alcohol swabs. Each syringe contains 0.6 mL of solution to deliver 0.5 mL (½ cc) of drug product and supplied with a 27 gauge, ½ inch needle with needle-stick protection device. (NDC 0004-0353-39).

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] or under refrigeration between 2° and 8°C (36°and 46°F). Keep bottle tightly closed.

PEGASYS® COPEGUS® Combination Packs

The combination packs should be stored under refrigeration at 2° to 8°C (36° to 46°F). Do not freeze or shake. Protect from light. Prefilled syringes are for single use only. Discard any unused portion.

When separated, the individual prefilled syringes of PEGASYS should be stored refrigerated between 2° and 8°C (36° and 46°F).

When separated, the individual bottle of COPEGUS Tablets should be stored at 25°C (77°F); excursions are permitted between 15° and 30°C (59° and 86°F) [see USP Controlled Room Temperature] or under refrigeration between 2° and 8°C (36° and 46°F). Keep bottle tightly closed.

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Revised: June 2004

MEDICATION GUIDE

COPEGUS® (Co-PEG-UHS)

(ribavirin, USP)

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, a form of ribavirin, may cause birth defects or death of an unborn child. Therefore, if you are pregnant or your partner is pregnant or plans to become pregnant, do not take COPEGUS.** Female patients and female partners of male patients being treated with COPEGUS must not become pregnant during treatment and for 6 months after treatment has stopped.

   During this time you must have pregnancy tests that show you are not pregnant. You must also use 2 effective forms of birth control during therapy and for 6 months after stopping therapy. Male patients should use a condom with spermicide as one of the two forms.

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

   If you or a female sexual partner becomes pregnant, you should tell your healthcare provider. There is a Ribavirin Pregnancy Registry that collects information about pregnancy outcomes of female patients and female partners of male patients exposed to ribavirin. You or your healthcare provider are encouraged to contact the Registry at 1-800-593-2214.

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 than 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 or 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 and for 6 months after treatment in female and male patients.

- **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 or 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?

COPEGUS tablets may be stored at 25°C (77°F) or under refrigeration between 2° and 8°C (36° to 46°F). Keep bottle tightly closed.

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.

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340 Kingsland Street
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Please submit final printed labeling at the time of use and include implementation information on Form 356h. Please provide a PDF-format electronic copy and original paper copies (10 for circulars and 5 for other labels).

PEGASYS®

(peginterferon alfa-2a)

Rx only

Alpha interferons, including PEGASYS (peginterferon alfa-2a), may cause or aggravate fatal or life-threatening neuropsychiatric, autoimmune, ischemic, and infectious disorders. Patients should be monitored closely with periodic clinical and laboratory evaluations. Therapy should be withdrawn in patients with persistently severe or worsening signs or symptoms of these conditions. In many, but not all cases, these disorders resolve after stopping PEGASYS therapy (see WARNINGS and ADVERSE REACTIONS).

Use with Ribavirin. Ribavirin, including COPEGUS®, may cause birth defects and/or death of the fetus. Extreme care must be taken to avoid pregnancy in female patients and in female partners of male patients. Ribavirin causes hemolytic anemia. The anemia associated with ribavirin therapy may result in a worsening of cardiac disease. Ribavirin is genotoxic and mutagenic and should be considered a potential carcinogen (see COPEGUS Package Insert for additional information and other WARNINGS).

DESCRIPTION

PEGASYS, peginterferon alfa-2a, is a covalent conjugate of recombinant alfa-2a interferon (approximate molecular weight [MW] 20,000 daltons) with a single branched bis-monomethoxy polyethylene glycol (PEG) chain (approximate MW 40,000 daltons). The PEG moiety is linked at a single site to the interferon alfa moiety via a stable amide bond to lysine. Peginterferon alfa-2a has an approximate molecular weight of 60,000 daltons. Interferon alfa-2a is produced using recombinant DNA technology in which a cloned human leukocyte interferon gene is inserted into and expressed in *Escherichia coli*.

PEGASYS is supplied as an injectable solution in vials and prefilled syringes.

180 µg/1.0 mL Vial: A vial contains approximately 1.2 mL of solution to deliver 1.0 mL of drug product. Subcutaneous (sc) administration of 1.0 mL delivers 180 µg of drug product (expressed as the amount of interferon alfa-2a), 8.0 mg sodium chloride, 0.05 mg polysorbate 80, 10.0 mg benzyl alcohol, 2.62 mg sodium acetate trihydrate, and 0.05 mg acetic acid. The solution is colorless to light yellow and the pH is 6.0 ± 0.5.

180 µg/0.5 mL Prefilled Syringe: Each syringe contains 0.6 mL of solution to deliver 0.5 mL of drug product. Subcutaneous (sc) administration of 0.5 mL delivers 180 µg of drug product (expressed as the amount of interferon alfa-2a), 4.0 mg sodium chloride, 0.025 mg polysorbate 80, 5.0 mg benzyl alcohol, 1.3085 mg sodium acetate trihydrate, and 0.0231 mg acetic acid. The solution is colorless to light yellow and the pH is 6.0 ± 0.5.

CLINICAL PHARMACOLOGY

Pharmacodynamics

Interferons bind to specific receptors on the cell surface initiating intracellular signaling via a complex cascade of protein-protein interactions leading to rapid activation of gene transcription. Interferon-stimulated genes modulate many biological effects including the inhibition of viral replication in infected cells, inhibition of cell proliferation and immunomodulation. The clinical relevance of these in vitro activities is not known.

PEGASYS stimulates the production of effector proteins such as serum neopterin and 2', 5'-oligoadenylate synthetase.

Pharmacokinetics

Maximal serum concentrations (C_{max}) occur between 72 to 96 hours post-dose. The C_{max} and AUC measurements of PEGASYS increase in a dose-related manner. Week 48 mean trough concentrations (16 ng/mL; range 4 to 28) at 168 hours post-dose are approximately 2-fold higher than week 1 mean trough concentrations (8 ng/mL; range 0 to 15). Steady-state serum levels are reached within 5 to 8 weeks of once weekly dosing. The peak to trough ratio at week 48 is approximately 2.0.

The mean systemic clearance in healthy subjects given PEGASYS was 94 mL/h, which is approximately 100-fold lower than that for interferon alfa-2a (ROFERON®-A). The mean terminal half-life after sc dosing in patients with chronic hepatitis C was 80 hours (range 50 to 140 hours) compared to 5.1 hours (range 3.7 to 8.5 hours) for ROFERON®-A.

Special Populations

Gender and Age

PEGASYS administration yielded similar pharmacokinetics in male and female healthy subjects. The AUC was increased from 1295 to 1663 ng·h/mL in subjects older than 62 years taking 180 µg PEGASYS, but peak concentrations were similar (9 vs 10 ng/mL) in those older and younger than 62 years.

Pediatric Patients

The pharmacokinetics of PEGASYS have not been adequately studied in pediatric patients.

Renal Dysfunction

In patients with end stage renal disease undergoing hemodialysis, there is a 25% to 45% reduction in PEGASYS clearance (see **PRECAUTIONS: Renal Impairment**).

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**).

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**).

Drug Interactions

Nucleoside Analogues

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

Methadone

The pharmacokinetics of concomitant administration of methadone and PEGASYS were evaluated in 24 PEGASYS naïve chronic hepatitis C patients (15 male, 9 female) who received 180 µg PEGASYS subcutaneously weekly. All patients were on stable methadone maintenance therapy (median dose 95 mg, range 30 mg to 150 mg) prior to receiving PEGASYS. Mean methadone PK parameters were 10% to 15% higher after 4 weeks of PEGASYS treatment as compared to baseline (see **PRECAUTIONS: Drug Interactions**). Methadone did not significantly alter the PK of PEGASYS as compared to a PK study of 6 chronic hepatitis C patients not receiving methadone.

CLINICAL STUDIES

PEGASYS Monotherapy (Studies 1, 2, and 3)

The safety and effectiveness of PEGASYS for the treatment of hepatitis C virus infection were assessed in three randomized, open-label, active-controlled clinical studies. All patients were adults, had compensated liver disease, detectable hepatitis C virus (HCV), liver biopsy diagnosis of chronic hepatitis, and were previously untreated with interferon. All patients received therapy by sc injection for 48 weeks, and were followed for an additional 24 weeks to assess the durability of response. In studies 1 and 2, approximately

20% of subjects had cirrhosis or bridging fibrosis. Study 3 enrolled patients with a histological diagnosis of cirrhosis (78%) or bridging fibrosis (22%).

In study 1 (n=630), patients received either ROFERON-A (interferon alfa-2a) 3 MIU three times/week (tiw), PEGASYS 135 µg once each week (qw) or PEGASYS 180 µg qw. In study 2 (n=526), patients received either ROFERON-A 6 MIU tiw for 12 weeks followed by 3 MIU tiw for 36 weeks or PEGASYS 180 µg qw. In study 3 (n=269), patients received ROFERON-A 3 MIU tiw, PEGASYS 90 µg qw or PEGASYS 180 µg once each week.

In all three studies, treatment with PEGASYS 180 µg resulted in significantly more patients who experienced a sustained response (defined as undetectable HCV RNA and normalization of ALT on or after study week 68) compared to treatment with ROFERON-A. In study 1, response to PEGASYS 135 µg was not different from response to 180 µg. In study 3, response to PEGASYS 90 µg was intermediate between PEGASYS 180 µg and ROFERON-A.

Table 1 Sustained Response to Monotherapy Treatment

	Study 1			Study 2			Study 3		
	ROFERON-A 3 MIU (N=207)	PEGASYS 180 µg (N=208)	DIFF* (95% CI)	ROFERON-A 6/3 MIU (N=261)	PEGASYS 180 µg (N=265)	DIFF* (95% CI)	ROFERON-A 3 MIU (N=86)	PEGASYS 180 µg (N=87)	DIFF* (95% CI)
Combined Virologic and Biologic Sustained Response	11%	24%	13 (6, 20)	17%	35%	18 (11, 25)	7%	23%	16 (6, 26)
Sustained Virologic Response**	11%	26%	15 (8, 23)	19%	38%	19 (11, 26)	8%	30%	22 (11, 33)

*Percent difference between PEGASYS and ROFERON-A treatment

**COBAS AMPLICOR® HCV Test, version 2.0

Matched pre- and post-treatment liver biopsies were obtained in approximately 70% of patients. Similar modest reductions in inflammation compared to baseline were observed in all treatment groups.

Of the patients who did not demonstrate either undetectable HCV RNA or at least a 2log10 drop in HCV RNA titer from baseline by 12 weeks of PEGASYS 180 µg therapy, 2% (3/156) achieved a sustained virologic response (see **DOSAGE AND ADMINISTRATION**).

Averaged over study 1, study 2, and study 3, response rates to PEGASYS were 23% among patients with viral genotype 1 and 48% in patients with other viral genotypes. The treatment response rates were similar in men and women.

PEGASYS/COPEGUS Combination Therapy (Studies 4 and 5)

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 4, 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 2). In all treatment arms, patients with viral genotype 1, regardless of viral load, had a lower response rate.

Table 2 Sustained Virologic Response to Combination Therapy (Study 4)

	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 5, 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 3).

Table 3 Sustained Virologic Response as a Function of Genotype (Study 5)

	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%)

*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 4 and 5, 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 4 and 5. Modest reductions in inflammation compared to baseline were seen in all treatment groups.

In studies 4 and 5, 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.

PEGASYS® (peginterferon alfa-2a)

INDICATIONS AND USAGE

PEGASYS, peginterferon alfa-2a, alone or in combination with COPEGUS, 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

PEGASYS is contraindicated in patients with:

- Hypersensitivity to PEGASYS or any of its components
- Autoimmune hepatitis
- Hepatic decompensation (Child-Pugh class B and C) before or during treatment

PEGASYS is contraindicated in neonates and infants because it contains benzyl alcohol. Benzyl alcohol is associated with an increased incidence of neurologic and other complications in neonates and infants, which are sometimes fatal.

PEGASYS and COPEGUS combination therapy is additionally 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, sickle-cell anemia)

WARNINGS

General

Patients should be monitored for the following serious conditions, some of which may become life threatening. Patients with persistently severe or worsening signs or symptoms should have their therapy withdrawn (see **BOXED WARNING**).

Neuropsychiatric

Life-threatening or fatal neuropsychiatric reactions may manifest in patients receiving therapy with PEGASYS and include suicide, suicidal ideation, depression, relapse of drug addiction, and drug overdose. These reactions may occur in patients with and without previous psychiatric illness.

PEGASYS should be used with extreme caution in patients who report a history of depression. Neuropsychiatric adverse events observed with alpha interferon treatment include aggressive behavior, psychoses, hallucinations, bipolar disorders, and mania.

Physicians should monitor all patients for evidence of depression and other psychiatric symptoms. Patients should be advised to report any sign or symptom of depression or suicidal ideation to their prescribing physicians. In severe cases, therapy should be stopped immediately and psychiatric intervention instituted (see **ADVERSE REACTIONS** and **DOSAGE AND ADMINISTRATION**).

Infections

Serious and severe bacterial infections, some fatal, have been observed in patients treated with alpha interferons including PEGASYS. Some of the infections have been associated with neutropenia. PEGASYS should be discontinued in patients who develop severe infections and appropriate antibiotic therapy instituted.

Bone Marrow Toxicity

PEGASYS suppresses bone marrow function and may result in severe cytopenias. Ribavirin may potentiate the neutropenia and lymphopenia induced by alpha interferons including PEGASYS. Very rarely alpha interferons may be associated with aplastic anemia. It is advised that complete blood counts (CBC) be obtained pre-treatment and monitored routinely during therapy (see **PRECAUTIONS: Laboratory Tests**).

PEGASYS and COPEGUS should be used with caution in patients with baseline neutrophil counts <1500 cells/mm^3, with baseline platelet counts <90,000 cells/mm^3 or baseline hemoglobin <10 g/dL. PEGASYS therapy should be discontinued, at least temporarily, in patients who develop severe decreases in neutrophil and/or platelet counts (see **DOSAGE AND ADMINISTRATION: Dose Modifications**).

Cardiovascular Disorders

Hypertension, supraventricular arrhythmias, chest pain, and myocardial infarction have been observed in patients treated with PEGASYS.

PEGASYS should be administered with caution to patients with pre-existing cardiac disease. Because cardiac disease may be worsened by ribavirin-induced anemia, patients with a history of significant or unstable cardiac disease should not use COPEGUS (see **WARNINGS: Anemia** and **COPEGUS Package Insert**).

Hypersensitivity

Severe acute hypersensitivity reactions (eg, urticaria, angioedema, bronchoconstriction, anaphylaxis) have been rarely observed during alpha interferon and ribavirin therapy. If such reaction occurs, therapy with PEGASYS and COPEGUS should be discontinued and appropriate medical therapy immediately instituted.

Endocrine Disorders

PEGASYS causes or aggravates hypothyroidism and hyperthyroidism. Hyperglycemia, hypoglycemia, and diabetes mellitus have been observed to develop in patients treated

with PEGASYS. Patients with these conditions at baseline who cannot be effectively treated by medication should not begin PEGASYS therapy. Patients who develop these conditions during treatment and cannot be controlled with medication may require discontinuation of PEGASYS therapy.

Autoimmune Disorders

Development or exacerbation of autoimmune disorders including myositis, hepatitis, ITP, psoriasis, rheumatoid arthritis, interstitial nephritis, thyroiditis, and systemic lupus erythematosus have been reported in patients receiving alpha interferon. PEGASYS should be used with caution in patients with autoimmune disorders.

Pulmonary Disorders

Dyspnea, pulmonary infiltrates, pneumonia, bronchiolitis obliterans, interstitial pneumonitis and sarcoidosis, some resulting in respiratory failure and/or patient deaths, may be induced or aggravated by PEGASYS or alpha interferon therapy. Patients who develop persistent or unexplained pulmonary infiltrates or pulmonary function impairment should discontinue treatment with PEGASYS.

Colitis

Ulcerative, and hemorrhagic/ischemic colitis, sometimes fatal, have been observed within 12 weeks of starting alpha interferon treatment. Abdominal pain, bloody diarrhea, and fever are the typical manifestations of colitis. PEGASYS should be discontinued immediately if these symptoms develop. The colitis usually resolves within 1 to 3 weeks of discontinuation of alpha interferon.

Pancreatitis

Pancreatitis, sometimes fatal, has occurred during alpha interferon and ribavirin treatment. PEGASYS and COPEGUS should be suspended if symptoms or signs suggestive of pancreatitis are observed. PEGASYS and COPEGUS should be discontinued in patients diagnosed with pancreatitis.

Ophthalmologic Disorders

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

Pregnancy: Use with Ribavirin (also, see COPEGUS Package Insert.)

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 taking PEGASYS and COPEGUS combination therapy. COPEGUS THERAPY SHOULD NOT BE STARTED UNLESS A REPORT OF A NEGATIVE PREGNANCY TEST HAS BEEN OBTAINED IMMEDIATELY PRIOR TO INITIATION OF THERAPY. Women of childbearing potential and men must use two forms of effective contraception during treatment and for at least six months after treatment has concluded. Routine monthly pregnancy tests must be performed during this time (see BOXED WARNING, CONTRAINDICATIONS, PRECAUTIONS: Information for Patients, and COPEGUS Package Insert).

Anemia

The primary toxicity of ribavirin is hemolytic anemia. Hemoglobin <10 g/dL 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 with maximum drop in hemoglobin observed during the first eight weeks. BECAUSE THE INITIAL DROP IN HEMOGLOBIN MAY BE SIGNIFICANT, IT IS ADVISED THAT HEMOGLOBIN OR HEMATOCRIT BE OBTAINED PRE-TREATMENT 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 Dosage 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 **COPEGUS Package Insert**).

Renal

It is recommended that renal function be evaluated in all patients started on COPEGUS. COPEGUS should not be administered to patients with creatinine clearance <50 mL/min (see **CLINICAL PHARMACOLOGY: Special Populations**).

PRECAUTIONS

General

The safety and efficacy of PEGASYS alone or in combination with COPEGUS for the treatment of hepatitis C have not been established in:

- Patients who have failed other alpha interferon treatments

- Liver or other organ transplant recipients
- Patients co-infected with human immunodeficiency virus (HIV) or hepatitis B virus (HBV)

Renal Impairment

A 25% to 45% higher exposure to PEGASYS is seen in subjects undergoing hemodialysis. In patients with impaired renal function, signs and symptoms of interferon toxicity should be closely monitored. Doses of PEGASYS should be adjusted accordingly. PEGASYS should be used with caution in patients with creatinine clearance <50 mL/min (see **DOSAGE AND ADMINISTRATION: Dose Modifications**).

Information for Patients

Patients receiving PEGASYS alone or in combination with COPEGUS should be directed in its appropriate use, informed of the benefits and risks associated with treatment, and referred to the PEGASYS and, if applicable, COPEGUS (ribavirin) MEDICATION GUIDES.

PEGASYS and COPEGUS combination therapy must not be used by women who are pregnant or by men whose female partners are pregnant. COPEGUS therapy should not be initiated until a report of a negative pregnancy test has been obtained immediately before starting 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 physician immediately in the event of a pregnancy (see **CONTRAINDICATIONS** and **WARNINGS**).

Women of childbearing potential and men must use two forms of effective contraception during treatment and during the 6 months after treatment has concluded; routine monthly pregnancy tests must be performed during this time (see **CONTRAINDICATIONS** and **COPEGUS Package Insert**).

If pregnancy does occur during treatment or during 6 months post-therapy, the patient must be advised of the significant teratogenic risk of COPEGUS therapy to the fetus. 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.

Patients should be advised that laboratory evaluations are required before starting therapy and periodically thereafter (see **Laboratory Tests**). Patients should be instructed to remain well hydrated, especially during the initial stages of treatment. Patients should be advised to take COPEGUS with food.

Patients should be informed that it is not known if therapy with PEGASYS alone or in combination with COPEGUS will prevent transmission of HCV infection to others or

prevent cirrhosis, liver failure or liver cancer that might result from HCV infection. Patients who develop dizziness, confusion, somnolence, and fatigue should be cautioned to avoid driving or operating machinery.

If home use is prescribed, a puncture-resistant container for the disposal of used needles and syringes should be supplied to the patients. Patients should be thoroughly instructed in the importance of proper disposal and cautioned against any reuse of any needles and syringes. The full container should be disposed of according to the directions provided by the physician (see **MEDICATION GUIDE**).

Laboratory Tests

Before beginning PEGASYS or PEGASYS and COPEGUS combination therapy, standard hematological and biochemical laboratory tests are recommended for all patients. Pregnancy screening for women of childbearing potential must be performed.

After initiation of therapy, hematological tests should be performed at 2 weeks and 4 weeks and biochemical tests should be performed at 4 weeks. Additional testing should be performed periodically during therapy. In the clinical studies, the CBC (including hemoglobin level and white blood cell and platelet counts) and chemistries (including liver function tests and uric acid) were measured at 1, 2, 4, 6, and 8, and then every 4 weeks or more frequently if abnormalities were found. Thyroid stimulating hormone (TSH) was measured every 12 weeks. Monthly pregnancy testing should be performed during combination therapy and for 6 months after discontinuing therapy.

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

- Platelet count $\geq$90,000 cells/mm^3 (as low as 75,000 cells/mm^3 in patients with cirrhosis)
- Caution should be exercised in initiating treatment in any patient with baseline risk of severe anemia (eg, spherocytosis, history of GI bleeding).
- Absolute neutrophil count (ANC) $\geq$1500 cells/mm^3
- Serum creatinine concentration <1.5 x upper limit of normal
- TSH and T_4 within normal limits or adequately controlled thyroid function

PEGASYS treatment was associated with decreases in WBC, ANC, lymphocytes, and platelet counts often starting within the first 2 weeks of treatment (see **ADVERSE REACTIONS**). Dose reduction is recommended in patients with hematologic abnormalities (see **DOSAGE AND ADMINISTRATION: Dose Modifications**).

While fever is commonly caused by PEGASYS therapy, other causes of persistent fever must be ruled out, particularly in patients with neutropenia (see **WARNINGS: Infections**).

Transient elevations in ALT (2-fold to 5-fold above baseline) were observed in some patients receiving PEGASYS, and were not associated with deterioration of other liver function tests. When the increase in ALT levels is progressive despite dose reduction or is accompanied by increased bilirubin, PEGASYS therapy should be discontinued (see **DOSAGE AND ADMINISTRATION: Dose Modifications**).

Drug Interactions

Treatment with PEGASYS once weekly for 4 weeks in healthy subjects was associated with an inhibition of P450 1A2 and a 25% increase in theophylline AUC. Theophylline serum levels should be monitored and appropriate dose adjustments considered for patients given both theophylline and PEGASYS (see **PRECAUTIONS**). There was no effect on the pharmacokinetics of representative drugs metabolized by CYP 2C9, CYP 2C19, CYP 2D6 or CYP 3A4.

In a PK study of HCV patients concomitantly receiving methadone, treatment with PEGASYS once weekly for 4 weeks was associated with methadone levels that were 10% to 15% higher than at baseline (see **CLINICAL PHARMACOLOGY: Drug Interactions**). The clinical significance of this finding is unknown; however, patients should be monitored for the signs and symptoms of methadone toxicity.

In patients with chronic hepatitis C treated with PEGASYS in combination with COPEGUS, PEGASYS treatment did not affect ribavirin distribution or clearance.

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.

Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis

PEGASYS has not been tested for its carcinogenic potential.

Mutagenesis

PEGASYS did not cause DNA damage when tested in the Ames bacterial mutagenicity assay and in the in vitro chromosomal aberration assay in human lymphocytes, either in the presence or absence of metabolic activation.

Use with Ribavirin

Ribavirin is genotoxic and mutagenic. 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 in rats to assess the carcinogenic potential of ribavirin is ongoing (see COPEGUS Package Insert).

Impairment of Fertility

PEGASYS may impair fertility in women. Prolonged menstrual cycles and/or amenorrhea were observed in female cynomolgus monkeys given sc injections of 600 μg/kg/dose (7200 $\mu g/m^2$/dose) of PEGASYS every other day for one month, at approximately 180 times the recommended weekly human dose for a 60 kg person (based on body surface area). Menstrual cycle irregularities were accompanied by both a decrease and delay in the peak 17β-estradiol and progesterone levels following administration of PEGASYS to female monkeys. A return to normal menstrual rhythm followed cessation of treatment. Every other day dosing with 100 μg/kg (1200 $\mu g/m^2$) PEGASYS (equivalent to approximately 30 times the recommended human dose) had no effects on cycle duration or reproductive hormone status.

The effects of PEGASYS on male fertility have not been studied. However, no adverse effects on fertility were observed in male Rhesus monkeys treated with non-pegylated interferon alfa-2a for 5 months at doses up to 25 x 10^6 IU/kg/day.

Use with Ribavirin

Ribavirin has shown reversible toxicity in animal studies of male fertility (see **COPEGUS Package Insert**).

Pregnancy

Pregnancy: Category C

PEGASYS has not been studied for its teratogenic effect. Non-pegylated interferon alfa-2a treatment of pregnant Rhesus monkeys at approximately 20 to 500 times the human weekly dose resulted in a statistically significant increase in abortions. No teratogenic effects were seen in the offspring delivered at term. PEGASYS should be assumed to have abortifacient potential. There are no adequate and well-controlled studies of PEGASYS in pregnant women. PEGASYS is to be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. PEGASYS is recommended for use in women of childbearing potential only when they are using effective contraception during therapy.

Pregnancy: Category X: Use With Ribavirin (see CONTRAINDICATIONS)

Significant teratogenic and/or embryocidal effects have been demonstrated in all animal species exposed to ribavirin. COPEGUS therapy is contraindicated in

women who are pregnant and in the male partners of women who are pregnant (see CONTRAINDICATIONS, WARNINGS, and COPEGUS Package Insert).

If pregnancy occurs in a patient or partner of a patient during treatment or during the 6 months after treatment cessation, such cases should be reported to the COPEGUS Pregnancy Registry at 1-800-526-6367.

Nursing Mothers

It is not known whether peginterferon or ribavirin or its components are excreted in human milk. The effect of orally ingested peginterferon or ribavirin from breast milk on the nursing infant has not been evaluated. Because of the potential for adverse reactions from the drugs in nursing infants, a decision must be made whether to discontinue nursing or discontinue PEGASYS and COPEGUS treatment.

Pediatric Use

The safety and effectiveness of PEGASYS, alone or in combination with COPEGUS in patients below the age of 18 years have not been established.

PEGASYS contains benzyl alcohol. Benzyl alcohol has been reported to be associated with an increased incidence of neurological and other complications in neonates and infants, which are sometimes fatal (see **CONTRAINDICATIONS**).

Geriatric Use

Younger patients have higher virologic response rates than older patients. Clinical studies of PEGASYS alone or in combination with COPEGUS did not include sufficient numbers of subjects aged 65 or over to determine whether they respond differently from younger subjects. Adverse reactions related to alpha interferons, such as CNS, cardiac, and systemic (eg, flu-like) effects may be more severe in the elderly and caution should be exercised in the use of PEGASYS in this population. PEGASYS and COPEGUS are excreted by the kidney, and the risk of toxic reactions to this therapy may be greater in patients with impaired renal function. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection and it may be useful to monitor renal function. PEGASYS should be used with caution in patients with creatinine clearance <50 mL/min and COPEGUS should not be administered to patients with creatinine clearance <50 mL/min.

ADVERSE REACTIONS

PEGASYS alone or 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 alone or 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.

Overall 11% of patients receiving 48 weeks of therapy with PEGASYS either alone (7%) or in combination with COPEGUS (10%) 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 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 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 4 Adverse Reactions Occurring in ≥5% of Patients in Hepatitis C Clinical Trials (Pooled Studies 1, 2, 3, and Study 4)

Body System	PEGASYS 180 µg 48 week†	ROFERON-A*†	PEGASYS 180 µg + 1000 mg or 1200 mg COPEGUS 48 week**	Intron A + 1000 mg or 1200 mg REBETOL® 48 week**
	N=559	N=554	N=451	N=443
	%	%	%	%
Application Site Disorders				
Injection site reaction	22	18	23	16
Endocrine Disorders				
Hypothyroidism	3	2	4	5

PEGASYS® (peginterferon alfa-2a)

Body System	PEGASYS 180 µg 48 week†	ROFERON-A*†	PEGASYS 180 µg + 1000 mg or 1200 mg COPEGUS 48 week**	Intron A + 1000 mg or 1200 mg REBETOL® 48 week**
	N=559	N=554	N=451	N=443
	%	%	%	%
Flu-like Symptoms and Signs				
Fatigue/Asthenia	56	57	65	68
Pyrexia	37	41	41	55
Rigors	35	44	25	37
Pain	11	12	10	9
Gastrointestinal				
Nausea/Vomiting	24	33	25	29
Diarrhea	16	16	11	10
Abdominal pain	15	15	8	9
Dry mouth	6	3	4	7
Dyspepsia	<1	1	6	5
Hematologic‡				
Lymphopenia	3	5	14	12
Anemia	2	1	11	11
Neutropenia	21	8	27	8
Thrombocytopenia	5	2	5	<1
Metabolic and Nutritional				
Anorexia	17	17	24	26
Weight decrease	4	3	10	10
Musculoskeletal, Connective Tissue and Bone				
Myalgia	37	38	40	49
Arthralgia	28	29	22	23
Back pain	9	10	5	5
Neurological				
Headache	54	58	43	49
Dizziness (excluding vertigo)	16	12	14	14

PEGASYS® (peginterferon alfa-2a)

Body System	PEGASYS 180 µg 48 week†	ROFERON-A*†	PEGASYS 180 µg + 1000 mg or 1200 mg COPEGUS 48 week**	Intron A + 1000 mg or 1200 mg REBETOL® 48 week**
	N=559	N=554	N=451	N=443
	%	%	%	%
Memory impairment	5	4	6	5
Psychiatric				
Irritability/Anxiety/ Nervousness	19	22	33	38
Insomnia	19	23	30	37
Depression	18	19	20	28
Concentration impairment	8	10	10	13
Mood alteration	3	2	5	6
Resistance Mechanism Disorders				
Overall	10	6	12	10
Respiratory, Thoracic and Mediastinal				
Dyspnea	4	2	13	14
Cough	4	3	10	7
Dyspnea exertional	<1	<1	4	7
Skin and Subcutaneous Tissue				
Alopecia	23	30	28	33
Pruritus	12	8	19	18
Dermatitis	8	3	16	13
Dry skin	4	3	10	13
Rash	5	4	8	5
Sweating increased	6	7	6	5
Eczema	1	1	5	4
Visual Disorders				
Vision blurred	4	2	5	2

† Pooled studies 1, 2, and 3
* Either 3 MIU or 6/3 MIU of ROFERON-A
**Study 4

‡ 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%), Hgb <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.

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 erythematosus, rheumatoid arthritis), peripheral neuropathy, aplastic anemia, peptic ulcer, gastrointestinal bleeding, pancreatitis, colitis, corneal ulcer, pulmonary embolism, coma, myositis, and cerebral hemorrhage.

Laboratory Test Values

Hemoglobin

The hemoglobin concentration decreased below 12 g/dL in 17% (median Hgb drop = 2.2 g/dL) of monotherapy and 52% (median Hgb drop = 3.7 g/dL) of combination therapy patients. Severe anemia (Hgb <10 g/dL) was encountered in 13% of patients receiving combination therapy and 2% of monotherapy recipients. Dose modification for anemia was required in 22% of ribavirin recipients treated for 48 weeks. Hemoglobin decreases in PEGASYS monotherapy were generally mild and did not require dose modification (see **DOSAGE AND ADMINISTRATION: Dose Modifications**).

Neutrophils

Decreases in neutrophil count below normal were observed in 95% of patients treated with PEGASYS either alone or in combination with COPEGUS. Severe potentially life-threatening neutropenia (ANC <0.5 x 10^9/L) occurred in approximately 5% of patients receiving PEGASYS either alone or in combination with COPEGUS. Seventeen percent of patients receiving PEGASYS monotherapy and 20% to 24% of patients receiving PEGASYS/COPEGUS combination therapy required modification of interferon dosage for neutropenia. Two percent of patients required permanent reductions of PEGASYS dosage and <1% required permanent discontinuation. Median neutrophil counts return to pre-treatment levels 4 weeks after cessation of therapy (see **DOSAGE AND ADMINISTRATION: Dose Modifications**).

Lymphocytes

Decreases in lymphocyte count are induced by interferon alpha therapy. Lymphopenia was observed during both monotherapy (86%) and combination therapy with PEGASYS and COPEGUS (94%). Severe lymphopenia (<0.5 x 10^9/L) occurred in approximately

5% of monotherapy patients and 14% of combination PEGASYS and COPEGUS therapy recipients. Dose adjustments were not required by protocol. Median lymphocyte counts return to pre-treatment levels after 4 to 12 weeks of the cessation of therapy. The clinical significance of the lymphopenia is not known.

Platelets

Platelet counts decreased in 52% of patients treated with PEGASYS alone (median drop 45% from baseline), 33% of patients receiving combination with COPEGUS (median drop 30% from baseline). Median platelet counts return to pre-treatment levels 4 weeks after the cessation of therapy.

Triglycerides

Triglyceride levels are elevated in patients receiving alfa interferon therapy and were elevated in the majority of patients participating in clinical studies receiving either PEGASYS alone or in combination with COPEGUS. Random levels higher ≥400 mg/dL were observed in about 20% of patients.

ALT Elevations

Less than 1% of patients experienced marked elevations (5- to 10-fold above baseline) in ALT levels during treatment. These transaminase elevations were on occasion associated with hyperbilirubinemia and were managed by dose reduction or discontinuation of study treatment. Liver function test abnormalities were generally transient. One case was attributed to autoimmune hepatitis, which persisted beyond study medication discontinuation (see **DOSAGE AND ADMINISTRATION: Dose Modifications**).

Thyroid Function

PEGASYS alone or in combination with COPEGUS was associated with the development of abnormalities in thyroid laboratory values, some with associated clinical manifestations. Hypothyroidism or hyperthyroidism requiring treatment, dose modification or discontinuation occurred in 4% and 1% of PEGASYS treated patients and 4% and 2% of PEGASYS and COPEGUS treated patients, respectively. Approximately half of the patients, who developed thyroid abnormalities during PEGASYS treatment, still had abnormalities during the follow-up period (see **PRECAUTIONS: Laboratory Tests**).

Immunogenicity

Nine percent (71/834) of patients treated with PEGASYS with or without COPEGUS developed binding antibodies to interferon alfa-2a, as assessed by an ELISA assay. Three percent of patients (25/835) receiving PEGASYS with or without COPEGUS, developed low-titer neutralizing antibodies (using an assay of a sensitivity of 100 INU/mL).

The clinical and pathological significance of the appearance of serum neutralizing antibodies is unknown. No apparent correlation of antibody development to clinical response or adverse events was observed. The percentage of patients whose test results

were considered positive for antibodies is highly dependent on the sensitivity and specificity of the assays.

Additionally, the observed incidence of antibody positivity in these assays may be influenced by several factors including sample timing and handling, concomitant medications, and underlying disease. For these reasons, comparison of the incidence of antibodies to PEGASYS with the incidence of antibodies to these products may be misleading.

OVERDOSAGE

There is limited experience with overdosage. The maximum dose received by any patient was 7 times the intended dose of PEGASYS (180 µg/day for 7 days). There were no serious reactions attributed to overdosages. Weekly doses of up to 630 µg have been administered to patients with cancer. Dose-limiting toxicities were fatigue, elevated liver enzymes, neutropenia, and thrombocytopenia. There is no specific antidote for PEGASYS. Hemodialysis and peritoneal dialysis are not effective.

DOSAGE AND ADMINISTRATION

There are no safety and efficacy data on treatment for longer than 48 weeks. Consideration should be given to discontinuing therapy after 12 to 24 weeks of therapy if the patient has failed to demonstrate an early virologic response (see **CLINICAL STUDIES**).

PEGASYS

The recommended dose of PEGASYS monotherapy is 180 µg (1.0 mL vial or 0.5 mL prefilled syringe) once weekly for 48 weeks by subcutaneous administration in the abdomen or thigh.

PEGASYS and COPEGUS Combination

The recommended dose of PEGASYS when used in combination with ribavirin is 180 µg (1.0 mL vial or 0.5 mL prefilled syringe) once weekly. The recommended dose of COPEGUS and duration for PEGASYS/COPEGUS therapy is based on viral genotype (see Table 5).

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.

Since COPEGUS absorption increases when administered with a meal, patients are advised to take COPEGUS with food.

Table 5 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 2 & 3 showed no increased response to treatment beyond 24 weeks (see Table 3).
Data on genotypes 5 and 6 are insufficient for dosing recommendations.

A patient should self-inject PEGASYS only if the physician determines that it is appropriate and the patient agrees to medical follow-up as necessary and training in proper injection technique has been provided to him/her (see illustrated PEGASYS **MEDICATION GUIDE** for directions on injection site preparation and injection instructions).

PEGASYS should be inspected visually for particulate matter and discoloration before administration, and not used if particulate matter is visible or product is discolored. Vials and prefilled syringes with particulate matter or discoloration should be returned to the pharmacist.

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.

PEGASYS

General

When dose modification is required for moderate to severe adverse reactions (clinical and/or laboratory), initial dose reduction to 135 µg (which is 0.75 mL for the vials or adjustment to the corresponding graduation mark for the syringes) is generally adequate. However, in some cases, dose reduction to 90 µg (which is 0.5 mL for the vials or adjustment to the corresponding graduation mark for the syringes) may be needed. Following improvement of the adverse reaction, re-escalation of the dose may be considered (see **WARNINGS, PRECAUTIONS**, and **ADVERSE REACTIONS**).

Hematological

Table 6 PEGASYS Hematological Dose Modification Guidelines

Laboratory Values	PEGASYS Dose Reduction	Discontinue PEGASYS if:
ANC <750/mm^3	135 µg	ANC <500/mm^3, treatment should be suspended until ANC values return to more than 1000/mm^3.

		Reinstitute at 90 µg and monitor ANC
Platelet <50,000/mm^3	90 µg	Platelet count <25,000/mm^3

Psychiatric: Depression

Table 7 Guidelines for Modification or Discontinuation of PEGASYS and for Scheduling Visits for Patients with Depression

Depression Severity	Initial Management (4-8 weeks)		Depression		
	Dose modification	Visit schedule	Remains stable	Improves	Worsens
Mild	No change	Evaluate once weekly by visit and/or phone	Continue weekly visit schedule	Resume normal visit schedule	(See moderate or severe depression)
Moderate	Decrease PEGASYS dose to 135 µg (in some cases dose reduction to 90 µg may be needed)	Evaluate once weekly (office visit at least every other week)	Consider psychiatric consultation. Continue reduced dosing	If symptoms improve and are stable for 4 weeks, may resume normal visit schedule. Continue reduced dosing or return to normal dose	(See severe depression)
Severe	Discontinue PEGASYS permanently	Obtain immediate psychiatric consultation	Psychiatric therapy necessary		

Renal Function

In patients with end-stage renal disease requiring hemodialysis, dose reduction to 135 µg PEGASYS is recommended. Signs and symptoms of interferon toxicity should be closely monitored.

Liver Function

In patients with progressive ALT increases above baseline values, the dose of PEGASYS should be reduced to 135 µg. If ALT increases are progressive despite dose reduction or accompanied by increased bilirubin or evidence of hepatic decompensation, therapy should be immediately discontinued.

COPEGUS

Table 8 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 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 the original dose (1000 mg or 1200 mg).

Renal Impairment

COPEGUS should not be used in patients with creatinine clearance <50 mL/min (see **WARNINGS** and **COPEGUS Package Insert**).

HOW SUPPLIED

PEGASYS is available in vials, in prefilled syringes and as part of a combination package containing both PEGASYS prefilled syringes and a bottle of COPEGUS (ribavirin, USP) tablets. Peginterferon alfa-2a is for subcutaneous injection.

PEGASYS® Single Vial

One single use, clear, glass vial containing 180µg of PEGASYS (peginterferon alfa-2a) in 1.0 mL of solution (NDC 0004-0350-09)

PEGASYS® Vials Monthly Convenience Pack

Four, single use, clear, glass vials containing 180µg of PEGASYS (peginterferon alfa-2a) in 1.0 mL of solution, four 1 mL (1cc) volume syringes, four-27 gauge, ½ inch needles with needle stick protection device and eight alcohol swabs (NDC 0004-0350-39).

PEGASYS® Prefilled Syringes Monthly Convenience Pack

Four single use, graduated, clear, glass prefilled syringes containing 180 µg of PEGASYS (peginterferon alfa-2a) in 0.5 mL of solution, four 27 gauge, ½ inch needles with needle stick protection device and four alcohol swabs (NDC 0004-0352-39).

PEGASYS® COPEGUS® Combination Packs

These Combination Packs contain COPEGUS (ribavirin, USP) tablets and PEGASYS prefilled syringes to provide for four weeks of dosing. Each pack contains four single use, graduated, clear, glass prefilled syringes containing 180 µg of PEGASYS (peginterferon alfa-2a) in 0.5 mL of solution, four 27 gauge, ½ inch needles with needle stick protection device, four alcohol swabs and one bottle of COPEGUS 200 mg tablets for oral administration. Each ribavirin tablet 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. The Combination Packs are available in the following configurations (identified by the prescribed daily dose of COPEGUS):

800 mg COPEGUS® Daily Dose. This Combination Pack includes a bottle of 112 COPEGUS (200 mg) tablets, four PEGASYS prefilled syringes, and other components as listed above (NDC 0004-0353-17)

1000 mg COPEGUS® Daily Dose. This Combination Pack includes a bottle of 140 COPEGUS (200 mg) tablets, four PEGASYS prefilled syringes, and other components as listed above (NDC 0004-0353-18).

1200 mg COPEGUS® Daily Dose. This Combination Pack includes a bottle of 168 COPEGUS (200 mg) tablets, four PEGASYS prefilled syringes, and other components as listed above (NDC 0004-0353-39).

Storage Conditions

PEGASYS® Vials and Prefilled Syringes

Store in the refrigerator between 2° to 8°C (36° to 46°F). Do not freeze or shake. Protect from light. Vials and prefilled syringes are for single use only. Discard any unused portion.

PEGASYS® COPEGUS® Combination Packs

The combination packs should be stored in the refrigerator between 2° to 8°C (36° to 46°F). Do not freeze or shake. Protect from light. Prefilled syringes are for single use only. Discard any unused portion.

When separated, the individual syringes of PEGASYS should be stored refrigerated between 2° and 8°C (36° and 46°F).

When separated, the individual bottle of COPEGUS tablets should be stored at 25°C (77°F); excursions are permitted between 15° and 30°C (59° and 86°F) [see USP Controlled Room Temperature] or under refrigeration between 2° and 8°C (36° and 46°F). Keep bottle tightly closed.

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Revised: June 2004

MEDICATION GUIDE

PEGASYS®

(peginterferon alfa-2a)

Before you start taking PEGASYS (PEG-ah-sis), alone or in combination with COPEGUS® (Co-PEG-UHS), please read this Medication Guide carefully. Read this Medication Guide each time you refill your prescription in case new information has been added and make sure the pharmacist has given you the medicine your healthcare provider prescribed for you. Reading the information in this Medication Guide does not take the place of talking with your healthcare provider.

If you are taking PEGASYS in combination with COPEGUS, you should also read the Medication Guide for COPEGUS (ribavirin, USP) Tablets.

What is the most important information I should know about PEGASYS therapy?

PEGASYS, taken alone or in combination with COPEGUS, is a treatment for some people who are infected with hepatitis C virus. However, PEGASYS and COPEGUS can have serious side effects that may cause death in rare cases. Before starting PEGASYS therapy, you should talk with your healthcare provider about the possible benefits and the possible side effects of treatment, to decide if either of these treatments is right for you. If you begin treatment you will need to see your healthcare provider regularly for examinations and blood tests to make sure your treatment is working and to check for side effects.

The most serious possible side effects of PEGASYS taken alone or in combination with COPEGUS include:

Risks to Pregnancy:

Taking PEGASYS in combination with COPEGUS tablets can cause death, serious birth defects or other harm to your unborn child. If you are a woman of childbearing age, you must have negative pregnancy tests just before beginning treatment, during treatment, and for 6 months after you have stopped treatment. You must not become pregnant while either you or your partner are being treated with the PEGASYS/COPEGUS combination therapy or for 6 months after stopping therapy. Men and women should use two forms of birth control while taking the combination therapy and for the 6 months after treatment is completed. If you are a man, one of the two forms of birth control should be a condom. You must use birth control even if you believe that you are not fertile or that your fertility is low. You should talk to your healthcare provider about birth control for you and your partner.

If you are pregnant, you or your male partner must not take PEGASYS/COPEGUS combination therapy. If you or your partner are being treated and you become pregnant either during treatment or within 6 months of stopping treatment, call your healthcare provider right away.

Mental health problems:

PEGASYS may cause some patients to develop mood or behavioral problems. Signs of these problems include irritability (getting easily upset), depression (feeling low, feeling bad about yourself or feeling hopeless), and anxiety. Some patients may have aggressive behavior. Some patients may develop thoughts about ending their lives (suicidal thoughts) and may attempt to do so. A few patients have even ended their lives. Former drug addicts may fall back into drug addiction or overdose. You must tell your healthcare provider if you are being treated for a mental illness or have a history of mental illness or if you are or have ever been addicted to drugs or alcohol. Call your healthcare provider immediately if you develop any of these problems while on PEGASYS treatment.

Blood problems:

Many patients taking PEGASYS have had a drop in the number of their white blood cells and their platelets. If the numbers of these blood cells are too low, you could be at risk for serious infections or bleeding.

COPEGUS causes a decrease in the number of your red blood cells (anemia). This can be dangerous, especially for patients who already have heart or circulatory (cardiovascular) problems. If you have or have ever had any cardiovascular problems, talk with your healthcare provider before taking the combination of PEGASYS and COPEGUS.

Infections:

Some patients taking interferon have had serious infections. Sometimes these infections have been fatal. If you develop a fever that does not go away or gets higher, call your

healthcare provider right away. Your healthcare provider will need to examine you to rule out your having a serious infection.

Body organ problems:

Some patients may experience lung problems (such as difficulty breathing or pneumonia) and eye problems that can cause blurred vision or loss of your vision.

Call your healthcare provider immediately if you develop any of these conditions:

- **You become very depressed or think about suicide**
- **You have severe chest pain**
- **You have trouble breathing**
- **You have a change in your vision**
- **You become pregnant**
- **You notice unusual bleeding or bruising**
- **You have psoriasis (a skin disease) and it gets worse while taking PEGASYS**
- **High fever or a fever that does not go away**
- **You have severe stomach pain or lower back pain**
- **Bloody diarrhea**

For more information on possible side effects with PEGASYS therapy, alone or in combination with COPEGUS, please read the section on ***"What are the possible side effects of PEGASYS, and PEGASYS taken with COPEGUS?"*** *in this Medication Guide. You should also read the Medication Guide for COPEGUS tablets if you are taking that medicine with PEGASYS.*

What is PEGASYS?

PEGASYS is a drug used to treat adults who have a lasting (chronic) infection with hepatitis C virus and who show signs that the virus is damaging the liver. Patients with hepatitis C have the virus in their blood and in their liver. PEGASYS reduces the amount of virus in the body and helps the body's immune system fight the virus. The drug COPEGUS are tablets that may be taken with PEGASYS to help fight the virus infection. Do not take COPEGUS by itself.

In some patients that have received PEGASYS treatment for approximately one year, the amount of the hepatitis C virus in the body was decreased to a level so low that it could not be measured by blood tests. After 3 months of therapy, your healthcare provider may ask you to have a blood test to help determine how you are responding to your treatment.

It is not known if PEGASYS, used alone or in combination with COPEGUS, can cure hepatitis C (permanently eliminate the virus) or if it can prevent liver failure or liver cancer that is caused by hepatitis C infection.

It is also not known if PEGASYS, alone or in combination with COPEGUS, will prevent one infected person from infecting another person with hepatitis C.

Who should not take PEGASYS, or PEGASYS with COPEGUS?

Do not take PEGASYS or PEGASYS/COPEGUS therapy if you:

- are pregnant, planning to get pregnant during treatment or during the 6 months after treatment or breast-feeding

- 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

- have hepatitis caused by your immune system attacking your liver (autoimmune hepatitis) or unstable liver disease

- had an allergic reaction to another alpha interferon or are allergic to any of the ingredients in PEGASYS or COPEGUS tablets

- Do not take PEGASYS, alone or in combination with COPEGUS, if you have abnormal red blood cells such as sickle-cell anemia or thalassemia major.

If you have ever had any of the following conditions or serious medical problems, tell your healthcare provider before you start taking PEGASYS:

- History of or current severe mental illness (such as depression or anxiety)
- History of drug or alcohol addiction or abuse
- History of heart disease or previous heart attack
- History of cancer
- Autoimmune disease (where the body's immune system attacks the body's own cells), such as psoriasis (a skin disease), systemic lupus erythematosus, rheumatoid arthritis
- Kidney problems
- Blood disorders
- You take a medicine called theophylline
- Diabetes (high blood sugar)
- Problems with the thyroid gland
- Liver problems, other than hepatitis C
- Hepatitis B infection
- HIV infection
- Colitis (an inflammation of the bowels)

You should tell your healthcare provider if you are taking or planning to take other prescription or nonprescription medicines or vitamin and mineral supplements or herbal medicines.

If you have any questions about your health condition or about taking PEGASYS alone or in combination with COPEGUS, you should talk to your healthcare provider.

How should I take PEGASYS, or PEGASYS with COPEGUS?

PEGASYS is given by injection under the skin (subcutaneous injection). PEGASYS comes in two different forms (a liquid in a single use vial and a liquid in a prefilled syringe). Your healthcare provider will determine which is best for you. Your healthcare provider will also decide whether you will take PEGASYS alone or with COPEGUS. Your dose of PEGASYS is given as a single injection once per week. At some point, your healthcare provider may change your dose of PEGASYS or COPEGUS. Do not change your dose unless your healthcare provider tells you to change it. It is important that you take PEGASYS and COPEGUS exactly as your healthcare provider tells you. Once you start treatment with PEGASYS, do not switch to another brand of interferon without talking to your healthcare provider. Other interferons may not have the same effect on the treatment of your disease. Switching brands will also require a change in your dose.

Take your prescribed dose of PEGASYS once a week, on the same day of each week and at approximately the same time. Your total dose of COPEGUS tablets should be divided so you take it twice a day with food (breakfast and dinner). Taking half your dose of COPEGUS in the morning and the other half at night will keep the medicine in your body at a steady level. Do not take more than your prescribed dose of PEGASYS or COPEGUS. **Be sure to read the Medication Guide for COPEGUS (ribavirin, USP) for complete instructions on how to take the COPEGUS tablets.**

Your healthcare provider will train you and/or the person that will be giving you the PEGASYS injections on the proper way to give injections. Whether you give yourself the injection or another person gives the injection to you, it is important that you are comfortable with preparing and injecting a dose of PEGASYS, and you understand the instructions in "How do I inject PEGASYS?" **At the end of this guide (see Appendix) there are detailed instructions on how to prepare and give yourself an injection of PEGASYS using the form your healthcare provider has prescribed for you.**

If you miss a dose and you remember **within 2 days** of when you should have taken PEGASYS, give yourself an injection of PEGASYS as soon as you remember. Take your next dose on the day you would usually take it. If **more than 2 days** have passed, ask your healthcare provider what you should do. If you miss a dose of COPEGUS, take the missed dose as soon as you remember during the same day. Do not take 2 doses too close together in time. If it is late in the day, wait until the next day and go back on schedule. **Do not double the next dose.**

If you take more than the prescribed amount of PEGASYS, call your healthcare provider right away. Your healthcare provider may want to examine you and take blood for testing.

You must get regular blood tests to help your healthcare provider check how the treatment is working and to check for side effects.

What should I avoid while taking PEGASYS, or PEGASYS with COPEGUS?

- If you are pregnant do not start taking or continue taking COPEGUS in combination with PEGASYS.
- Avoid becoming pregnant while taking PEGASYS, alone or in combination with COPEGUS. PEGASYS, alone or in combination with COPEGUS, may harm your unborn child (death or serious birth defects) or cause you to lose your baby (miscarry). **If you or your partner become pregnant during or within 6 months after treatment with COPEGUS, immediately report the pregnancy to your healthcare provider. You or your healthcare provider should call 1-800-526-6367.** When you call this number, you will be asked for information about you and/or your partner that will be added to a pregnancy registry. This information will be used to help you and your healthcare provider make decisions about your treatment for hepatitis in the future. You, your partner and/or your healthcare provider may also be asked follow-up information on the outcome of the pregnancy.
- Do not breast-feed your baby while on PEGASYS, alone or in combination with COPEGUS.

What are the possible side effects of PEGASYS, and PEGASYS taken with COPEGUS?

Possible, serious side effects include:

- **Risk to pregnancy, mental health problems including suicidal thoughts, blood problems, infections, and body organ problems:** *See "What is the most important information I should know about PEGASYS therapy?" in this Medication Guide.*
- **Autoimmune problems:** Some patients may develop a disease where the body's own immune system begins to attack itself (autoimmune disease) while on PEGASYS therapy. These diseases can include psoriasis or thyroid problems. In some patients who already have an autoimmune disease, the disease may worsen while on PEGASYS therapy.
- **Heart problems:** PEGASYS may cause some patients to experience chest pain, and very rarely a heart attack. Patients who already have heart disease could be at greatest risk. Tell your healthcare provider if you have or have had a heart problem in the past.

Common, but less serious, side effects include:

- **Flu-like symptoms:** Most patients who take PEGASYS have flu-like symptoms that usually lessen after the first few weeks of treatment. Flu-like symptoms may include fever, chills, muscle aches, joint pain, and headaches. Taking pain and fever reducers such as acetaminophen or ibuprofen before you take PEGASYS can help with these symptoms. You can also try taking PEGASYS at night. You may be able to sleep through the symptoms.

- **Extreme fatigue (tiredness):** Many patients may become extremely tired while on PEGASYS therapy.
- **Upset stomach:** Nausea, taste changes, diarrhea, and loss of appetite occur commonly.
- **Blood sugar problems:** Some patients may develop a problem with the way their body controls their blood sugar and may develop diabetes.
- **Skin reactions:** Some patients may develop rash, dry or itchy skin, and redness and swelling at the site of injection.
- **Hair thinning:** Temporary hair loss is not uncommon during treatment with PEGASYS.
- **Trouble sleeping**

These are not all of the side effects of PEGASYS, and PEGASYS taken with COPEGUS. Your healthcare provider or pharmacist can give you a more complete list.

Talk to your healthcare provider if you are worried about side effects or find them very bothersome.

General advice about prescription medicines

Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. If you have any concerns or questions about PEGASYS, contact your healthcare provider. Do not use PEGASYS for a condition or person other than that for which it is prescribed. If you want to know more about PEGASYS, your healthcare provider or pharmacist will be able to provide you with detailed information that is written for health-care providers.

If you are taking COPEGUS (ribavirin, USP) in combination with PEGASYS, also read the Medication Guide supplied with that medicine.

Keep this and all drugs out of the reach of children.

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

Revised: Month/2004

Medication Guide Appendix: Instructions for Preparing and Giving a Dose with a PEGASYS® Prefilled Syringe

How should I store PEGASYS Prefilled Syringes?

PEGASYS must be stored in the refrigerator at a temperature of 2°C to 8°C (36°F to 46°F). Do not leave PEGASYS outside of the refrigerator for more than 24 hours. Do not freeze PEGASYS. Keeping PEGASYS at temperatures outside the recommended range can destroy the medicine.

Each PEGASYS prefilled syringe can only be used once. Discard after use.

Do not shake the prefilled syringe of PEGASYS. If PEGASYS is shaken too hard, it will not work properly.

Protect PEGASYS from light during storage.

Keep this and all other medicines out of the reach of children.

How do I prepare and inject PEGASYS?

You should read through all of these directions and ask your healthcare provider for help if you have any questions before trying to give yourself an injection. It is important to follow these directions carefully. Talk to your healthcare provider if you have any questions about PEGASYS.

Your healthcare provider may not want you to take all the medicine that comes in the prefilled syringe. To appropriately administer the dose that your healthcare provider tells you to take, you may have to get rid of some of the medicine before injecting the medicine.

If you ever switch between using prefilled syringes and vials, talk to your healthcare provider about how much PEGASYS to use. Equal volumes of liquid from the prefilled syringes and the vials DO NOT contain the same amount of PEGASYS. If you switch between prefilled syringes and vials, you will have to adjust the volume of liquid that you use to give your injection. If you do not adjust this, you could accidentally take too much or too little of your medicine.

If you are giving this injection to someone else, a healthcare provider must teach you how to avoid needle sticks. Being stuck by a used needle can pass diseases on to you.

The prefilled syringes are used for injecting PEGASYS under the surface of the skin (subcutaneous).

1. Collect all the materials you will need before you start to give the injection:

    - One PEGASYS prefilled syringe Monthly Convenience Pack containing an inner carton holding the PEGASYS prefilled syringe

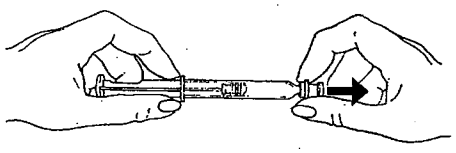
- A puncture-resistant container for cleaning up when you are finished

2. Open the convenience pack and look at the contents.
   - Each convenience pack has everything you need for the PEGASYS injection.
     - 4 single use syringes filled with medicine (should be colorless to light yellow)
     - four 27 gauge, 1/2 inch needles with needle stick protection device
     - 4 alcohol swabs
   - Do not use PEGASYS if:
     - the medicine is cloudy
     - the medicine has particles floating in it
     - the medicine is any color besides colorless to light yellow
     - the expiration date has passed

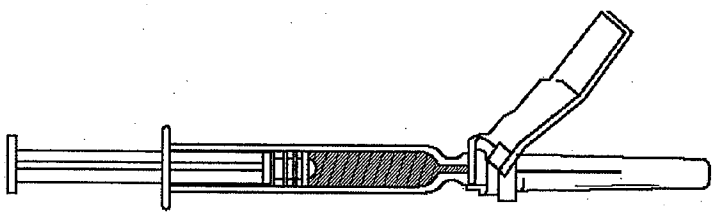
3. Warm the refrigerated medicine by gently rolling it in the palms of your hands for about one minute. Do not shake.

4. Wash your hands with soap and warm water to prevent infection.

5. Attachment of the needle to the PEGASYS prefilled syringe:
   - Remove the needle from its package. Do not remove the needle shield yet. Keep the needle covered until just before you give the injection.
   - Remove and discard the rubber cap from the tip of the syringe barrel.



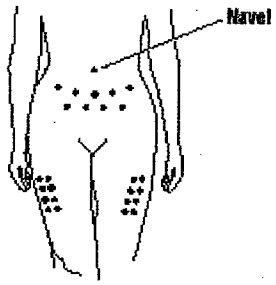
   - Put the needle onto the end of the syringe barrel so it fits tightly.
   - Here is a picture of the assembled syringe:



   - Keep the syringe in a horizontal position until ready for use.

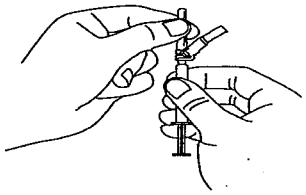
- If you need to set the syringe down, make sure the plastic shield covers the needle. Never let the needle touch any surface.

6. Decide where you will give the injection.
   - Pick a place on your stomach or thigh (see the picture below). Avoid your navel and waistline. You should use a different place each time you give yourself an injection.

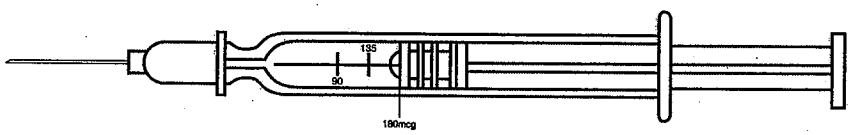


7. Prepare your skin for the injection.
   - To minimize the discomfort from injections, you may want to gently tap the area where you plan to give yourself an injection.
   - Clean the area using the alcohol pad. Let the skin dry for 10 seconds.

8. Uncover the needle.
   - Remove the plastic safety shield covering the needle. Do not remove the orange cap that is attached to the end of the syringe and above the needle that is the needle-stick protection device.

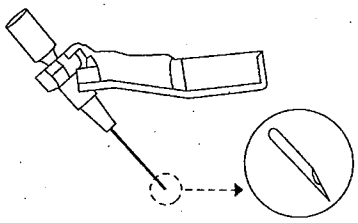


9. Remove air bubbles from the syringe.
   - Hold the syringe with the needle pointing up to the ceiling.
   - Using your thumb and finger, tap the syringe to bring air bubbles to the top.
   - Press the plunger in slightly to push air bubbles out of the syringe.
   - Your healthcare provider may not want you to take all the medicine that comes in the prefilled syringe.
   - To appropriately administer the dose that your healthcare provider tells you to take, you may have to get rid of some of the medicine before injecting the medicine.
   - The syringe has markings for 180 mcg, 135 mcg, and 90 mcg. Your healthcare provider will tell you which mark to use.

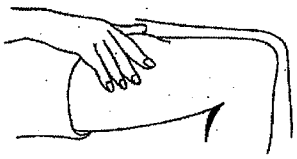


- Once you know which mark to use, slowly and carefully press on the plunger rod of the syringe to push out medicine from the syringe. Keep pressing until the edge of the plunger stopper reaches the right mark on the side of the syringe.
- Do not decrease or increase your dose of PEGASYS unless your healthcare provider tells you to.

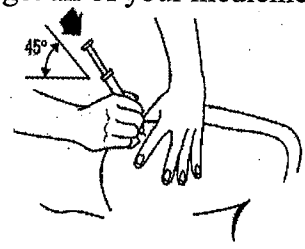
10. Give the injection of PEGASYS.
    - Position the point of the needle (the bevel) so it is facing up.



- Pinch a fold of skin on your stomach or thigh firmly with your thumb and forefinger.



- Hold the syringe like a pencil at a 45° to 90° angle to your skin. In one quick motion, insert the needle as far as it will go into the pinched area of skin. Pull the plunger of the syringe back very slightly. If blood comes into the syringe, the needle has entered a blood vessel. **Do not inject. Withdraw the needle and discard the syringe as outlined in step 11. Repeat the above steps with a new prefilled syringe and prepare a new site.**
- If no blood appears, release your skin and slowly push the plunger all the way down so that you get all of your medicine.



- Pull out the needle at same angle you put it in.

- Wipe the area with an alcohol swab.

11. For safety reasons, before you dispose of the syringe and needle, place the free end of the orange cap on a flat surface and push down on it until it clicks and covers over the needle. Always place used syringes and needles in a puncture-resistant container immediately after use and never reuse them. Keep your disposal container out of the reach of children.

How should I dispose of materials used to inject PEGASYS?

There may be special state and local laws for disposal of used needles and syringes. Your healthcare provider or pharmacist should provide you with instructions on how to properly dispose of your used syringes and needles. Always follow these instructions.

The instructions below should be used as a general guide for proper disposal:

- The needles and syringes should never be reused.
- Place all used needles and syringes in a puncture-proof disposable container that is available through your pharmacy or healthcare provider (Sharp's container).
- DO NOT use glass or clear plastic containers for disposal of needles and syringes.
- Dispose of the full container as instructed by your healthcare provider or pharmacist.

DO NOT throw the container in your household trash. DO NOT recycle. Keep the container out of the reach of children.

Appendix revision date: January 2004

Medication Guide Appendix: Instructions for Preparing and Giving a Dose with a PEGASYS® Vial

How should I store PEGASYS vials?

PEGASYS must be stored in the refrigerator at a temperature of 2°C to 8°C (36°F to 46°F). Do not leave PEGASYS outside of the refrigerator for more than 24 hours. Do not freeze PEGASYS. Keeping PEGASYS at temperatures outside the recommended range can destroy the medicine.

Each PEGASYS vial can only be used once. Discard after use.

Do not shake the vial of PEGASYS. If PEGASYS is shaken too hard, it will not work properly.

Protect PEGASYS from light during storage.

Keep this and all other medicines out of the reach of children.

How do I inject PEGASYS?

The following instructions will help you learn how to measure your dose and give yourself an injection of PEGASYS. You should read through all of these directions and ask your healthcare provider for help if you have any questions before trying to give yourself an injection. It is important to follow these directions carefully. Talk to your healthcare provider if you have any questions about PEGASYS.

If you are giving an injection to someone else, a healthcare provider must teach you how to avoid needle sticks. Being stuck by a used needle can pass diseases on to you.

1. Collect all the materials you will need before you start to give the injection:
   - One vial of PEGASYS
   - One syringe and needle
   - Several alcohol pads
   - A puncture-resistant container to dispose of the needle and syringe when you are finished

If you have received the PEGASYS Convenience Pack, it includes PEGASYS, safety syringes and needles with a needle-stick protection device attached, and alcohol swabs.

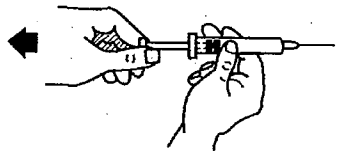
2. Check the date on the carton the PEGASYS comes in and make sure the expiration date has not passed, then remove a vial from the package and look at the medicine.
   - Do not use PEGASYS if:
     - the medicine is cloudy
     - the medicine has particles floating in it
     - the medicine is any color besides colorless to light yellow
     - the expiration date has passed

3. Warm the refrigerated medicine by gently rolling it in the palms of your hands for about one minute. Do not shake.
4. Wash your hands with soap and warm water to prevent infection.
5. Take the vial of PEGASYS and flip off the plastic top covering the vial opening, and clean the rubber stopper on the top of the vial with a different alcohol pad.

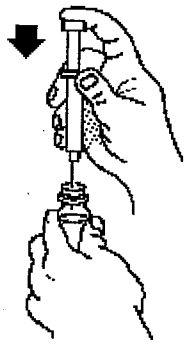
If you are not sure how much medicine to use or which mark to use, STOP and call your healthcare provider right away.

6. Remove the needle and syringe from their packaging and attach the needle to the end of the syringe.
   - If you are using a syringe and needle supplied with the PEGASYS Convenience Pack, the needle is already attached to the syringe and it will have a needle-stick protection device attached. Remove the clear protective cap from the end of the needle. Do not remove the orange cap that is attached to the end of the syringe and above the needle that is the needle-stick protection device.

   - Pull the plunger back so the end of it is to the mark on the syringe barrel that matches the dose prescribed for you by your healthcare provider. This will pull air into the syringe barrel.



   - Push the needle through the center of the stopper on the vial.
   - Slowly inject all the air from the syringe into the air space above the solution. Do not inject air into the fluid.



   - Keep the needle inside the vial and turn both upside down. Hold the vial and syringe straight up. Slowly pull back on the plunger until the medicine is in the syringe up to the mark that matches your dose. Make sure the needle tip always stays in the medicine (not in the air space above it).

   - When the medicine is up to the right mark on the syringe barrel, take the syringe and needle out of the rubber stopper on the vial.
   - Keep the syringe pointing up until you are ready to use it.

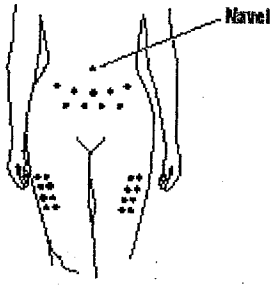
- If you need to set the syringe down, make sure that you never let the needle touch any surface.

7. Remove air bubbles from the syringe.

- Hold the syringe with the needle pointing up to the ceiling.
- Using your thumb and finger, tap the syringe to bring air bubbles to top.
- Press the plunger in slightly to push air bubbles out of the syringe.

8. Decide where you will give the injection.

- Pick a place on your stomach or thigh (see the picture below). Avoid your navel and waistline. You should use a different place each time you give yourself an injection.

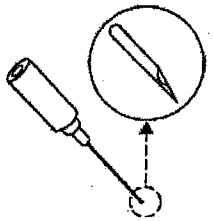


9. Prepare your skin for the injection.

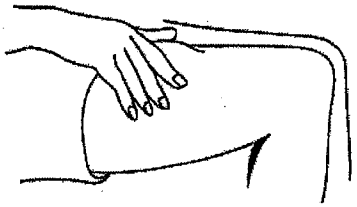
- To minimize the discomfort from injections, you may want to gently tap the area where you plan to give yourself an injection.
- Clean the area using an alcohol pad. Let the skin dry for 10 seconds.

10. Give the injection of PEGASYS.

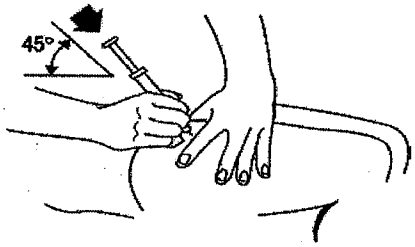
- Position the point of the needle (the bevel) so it is facing up.



- Pinch a fold of skin on your stomach or thigh firmly between your thumb and forefinger.



- Hold the syringe like a pencil at a 45° to 90° angle to your skin. In one quick motion, insert the needle as far as it will go into the pinched area of skin. Pull the plunger of the syringe back very slightly. If blood comes into the syringe, the needle has entered a blood vessel. **Do not inject. Withdraw the needle and discard the syringe as outlined in step 11. Repeat the above steps with a new vial and syringe and prepare a new site.**
- If no blood appears, release your skin and slowly push the plunger all the way down so that you get all of your medicine.



- Pull out the needle at same angle you put it in. Wipe the area with an alcohol pad.

11. For safety reasons, always place used syringes and needles in a puncture-resistant container immediately after use and never reuse them.
    - If you are using a syringe with a needle-stick protection device, before you dispose of the syringe and needle, place the free end of the orange cap on a flat surface and push down on it until it clicks and covers over the needle.

How should I dispose of materials used to inject PEGASYS?

There may be special state and local laws for disposal of used needles and syringes. Your healthcare provider or pharmacist should provide you with instructions on how to properly dispose of your used syringes and needles. Always follow these instructions.

The instructions below should be used as a general guide for proper disposal:

- The needles and syringes should never be reused.
- Place all used needles and syringes in a puncture-proof disposable container that is available through your pharmacy or healthcare provider (Sharp's container).
- DO NOT use glass or clear plastic containers for disposal of needles and syringes.
- Dispose of the full container as instructed by your healthcare provider or pharmacist.

DO NOT throw the container in your household trash. DO NOT recycle. Keep the container out of the reach of children.

Appendix revision date: January 2004

Roche Pharmaceuticals

Hoffmann-La Roche Inc.
340 Kingsland Street
Nutley, New Jersey 07110-1199

U.S. Govt. Lic. No. 0136

XXXXXXXX

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Please submit final printed labeling at the time of use and include implementation information on Form 356h. Please provide a PDF-format electronic copy and original paper copies (10 for circulars and 5 for other labels).

Roche

PEGASYS® COPEGUS® Combination Pack
(peginterferon alfa-2a) (ribavirin, USP)
180 µg/0.5 mL 200 mg

Each PEGASYS® Prefilled Syringe Contains:
180 µg/0.5 mL

Each COPEGUS® Tablet Contains:
200 mg ribavirin

℞only

Medication Guides for patient enclosed.

XXXXXXXX

Built at 100%

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Please submit final printed labeling at the time of use and include implementation information on Form 356h. Please provide a PDF-format electronic copy and original paper copies (10 for circulars and 5 for other labels).

800 mg COPEGUS® Daily Dose

Each 0.5 mL Prefilled Syringe contains:
180 µg of peginterferon alfa-2a (expressed as the amount of interferon alfa-2a), 4.0 mg sodium chloride, 0.025 mg polysorbate 80, 5.0 mg benzyl alcohol, 1.3085 mg sodium acetate trihydrate and 0.0231 mg acetic acid.

No US standard of potency.

Each Tablet contains: 200 mg ribavirin.

Storage: Refrigerate at 2°– 8°C (36°– 46°F).
Protect From Light.
Do NOT Freeze. **Do NOT Shake.**

Refrigerate Immediately

*Hoffmann-La Roche Inc.
Nutley, New Jersey 07110
(US Govt. Lic. No. 0136)

†Roche Laboratories Inc.
Nutley, New Jersey 07110

Package Contains:
4 Single-Use Prefilled Syringes, PEGASYS® 180 µg/0.5 mL*, NDC 0004-0352-30
4 Needles (27 gauge, 1/2 inch)
4 Alcohol Swabs
1 Bottle, 112 COPEGUS® 200 mg Tablets†, NDC 0004-0086-17

800 mg COPEGUS®
Daily Dose

NDC 0004-0353-17

Roche

PEGASYS® COPEGUS® Combination Pack
(peginterferon alfa-2a) (ribavirin, USP)
180 µg/0.5 mL 200 mg

Monthly Combination Pack:
PEGASYS® 180 µg/0.5 mL
4 Single-Use Prefilled Syringes


Not Actual Size

For Subcutaneous Injection Only

COPEGUS® 200 mg
112 Tablets

AVOID PREGNANCY WHILE TAKING THIS MEDICATION. READ THE MEDICATION GUIDE FOR IMPORTANT INFORMATION.

℞only

800 mg COPEGUS® Daily Dose

2789XXXX

ATTENTION PHARMACIST: Each patient is required to receive the enclosed Medication Guides.
For additional dosage information and other important prescribing information, see enclosed inserts.

3 0004-0353-17 4

800 mg COPEGUS®
Daily Dose

NOT ACTUAL SIZE

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1000 mg COPEGUS® Daily Dose

Each 0.5 mL Prefilled Syringe contains:
180 µg of peginterferon alfa-2a (expressed as the amount of interferon alfa-2a), 4.0 mg sodium chloride, 0.025 mg polysorbate 80, 5.0 mg benzyl alcohol, 1.3085 mg sodium acetate trihydrate and 0.0231 mg acetic acid.

No US standard of potency.

Each Tablet contains: 200 mg ribavirin.

Storage: Refrigerate at 2°–8°C (36°–46°F).
Protect From Light.
Do NOT Freeze. **Do NOT Shake.**

Refrigerate Immediately

*Hoffmann-La Roche Inc.
Nutley, New Jersey 07110
(US Govt. Lic. No. 0136)

†Roche Laboratories Inc.
Nutley, New Jersey 07110

Package Contains:
4 Single-Use Prefilled Syringes, PEGASYS® 180 µg/0.5 mL*, NDC 0004-0352-30
4 Needles (27 gauge, 1/2 inch)
4 Alcohol Swabs
1 Bottle, 140 COPEGUS® 200 mg Tablets†, NDC 0004-0086-18

1000 mg COPEGUS® Daily Dose

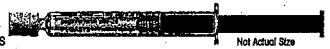
NDC 0004-0353-18

Roche

PEGASYS® COPEGUS® Combination Pack
(peginterferon alfa-2a) (ribavirin, USP)
180 µg/0.5 mL 200 mg

Monthly Combination Pack:

PEGASYS® 180 µg/0.5 mL
4 Single-Use Prefilled Syringes



For Subcutaneous Injection Only

COPEGUS® 200 mg
140 Tablets

AVOID PREGNANCY WHILE TAKING THIS MEDICATION. READ THE MEDICATION GUIDE FOR IMPORTANT INFORMATION.

℞only

1000 mg COPEGUS® Daily Dose

2769XXXX

ATTENTION PHARMACIST: Each patient is required to receive the enclosed Medication Guides.
For additional dosage information and other important prescribing information, see enclosed inserts.

N 3 0004-0353-18 1

1000 mg COPEGUS® Daily Dose

NOT ACTUAL SIZE

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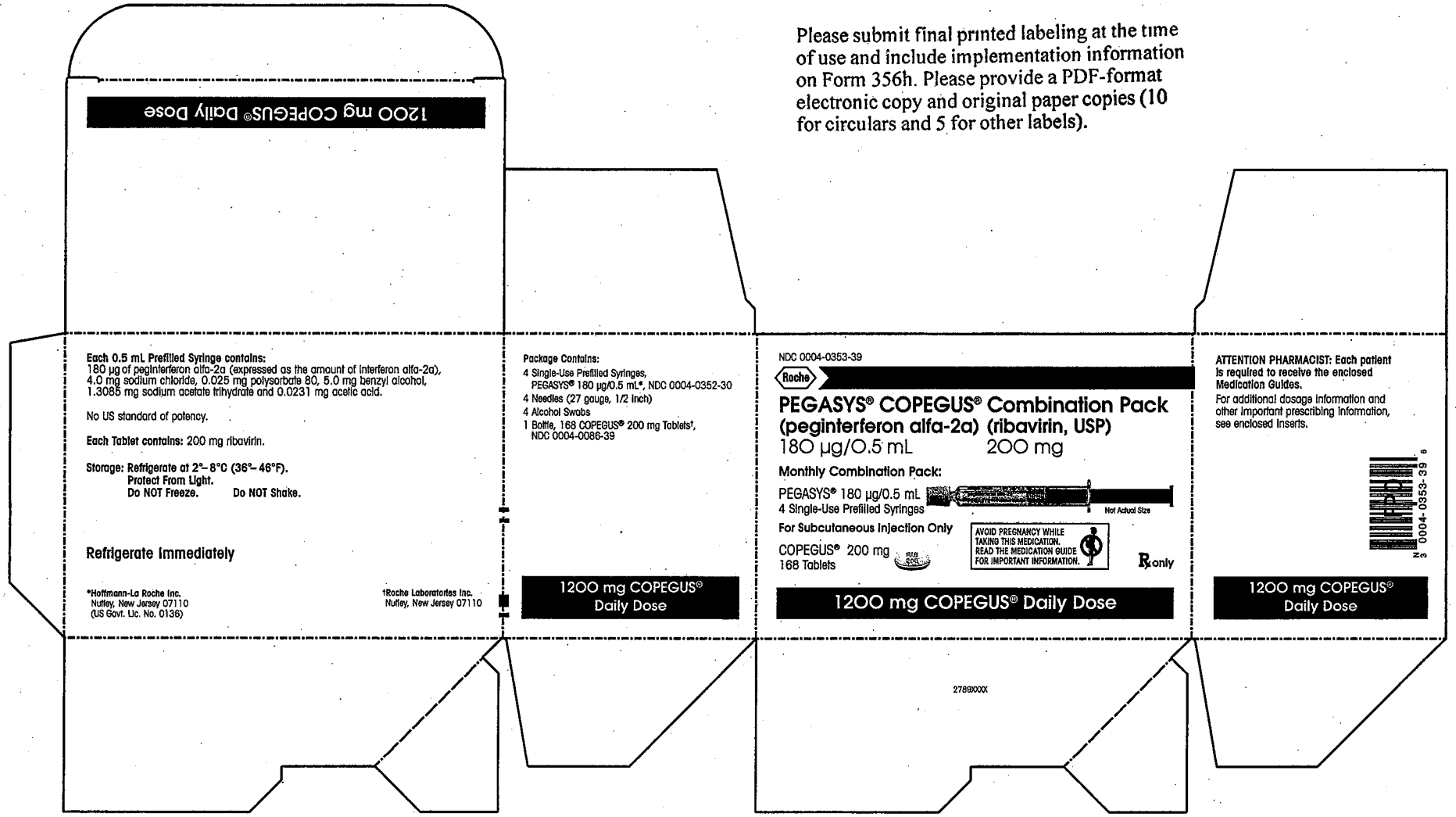

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FS-Zuschnitt Neotop 150 x 89 x 21 mm
NP 1523
Register Nr. 00.4.3749/0
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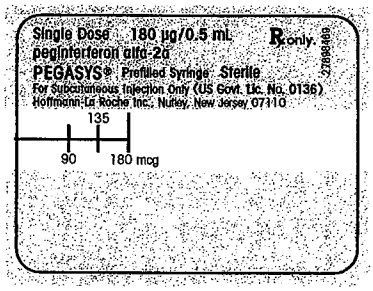

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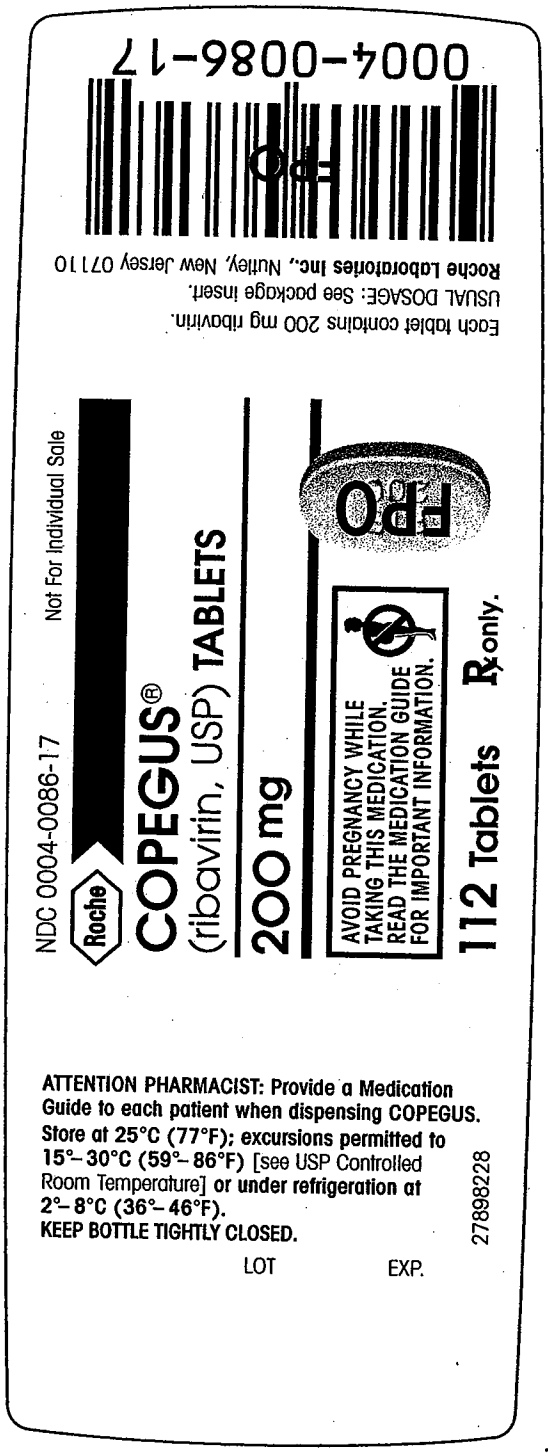

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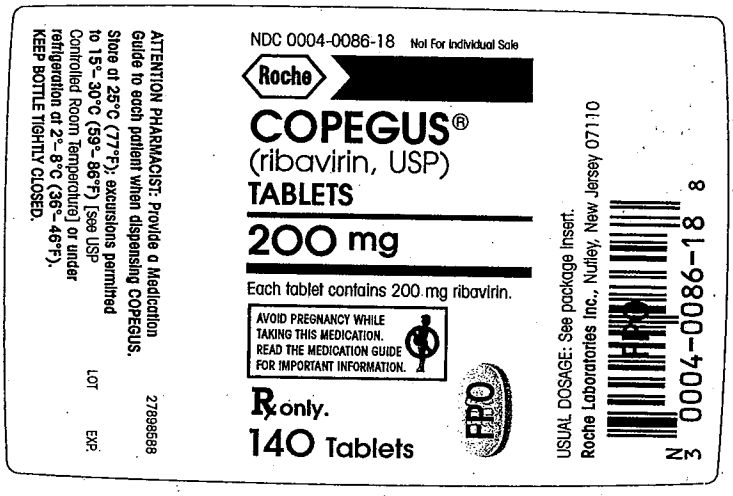

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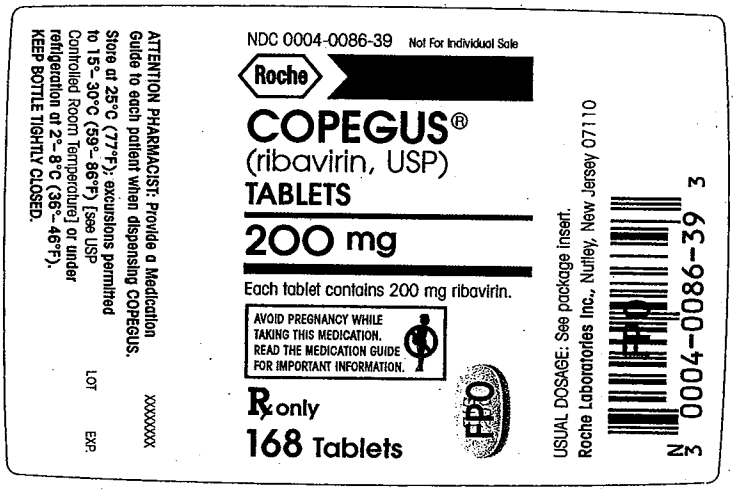

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