Pegasys advertisement.

[s.l.]: [s.n.], 2003

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 Therapy should be withdrawn in patients with persistently severe or worsening signs or symptoms of these conditions.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 CONTRAINDICATIONS, WARNINGS, PRECAUTIONS and ADVERSE REACTIONS in complete product information).

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 CONTRAINDICATIONS, WARNINGS, PRECAUTIONS and ADVERSE REACTIONS in complete product information).

PEGASYS, 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).

PEGASYS is contraindicated in patients with hypersensitivity to PEGASYS or any of its components, autoimmune hepatitis, and decompensated hepatic disease (Child-Pugh class B and C) before or during treatment with PEGASYS. PEGASYS is also contraindicated in neonates and infants because it contains benzyl alcohol. Benzyl alcohol is associated with an increased incidence of neurological and other complications in neonates and infants, which are sometimes fatal. PEGASYS and COPEGUS therapy is additionally contraindicated in patients with a hypersensitivity to COPEGUS or any of its components, in women who are pregnant, men whose female partners are pregnant, and patients with hemoglobinopathies (eg, thalassemia major, sickle-cell anemia).

IN THE TREATMENT OF HEPATITIS C

Experience the PEGASYS perspective

Consider the weight of the evidence.
Proven in clinical trials...proven in clinical practice.

PEGASYS® (Peginterferon alfa-2a) FOR INJECTION

COPEGUS® (Ribavirin, USP) 200 MG TABLETS

Designed to make a difference

Please see brief summary of complete product information for PEGASYS and COPEGUS on adjacent pages.

For more information, please call toll-free 1-877-PEGASYS (1-877-734-2797)
or visit our Web sites, www.pegasys.com and www.pegassist.com.

THE MOST FREQUENTLY PRESCRIBED PEGYLATED INTERFERON*

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 during the 6 months after treatment has concluded. For male patients, one of the two forms of contraception must be a condom with spermicide. Routine monthly pregnancy tests must be performed during this time. If pregnancy should 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. Physicians and patients are also strongly encouraged to report any pregnancies that do occur to Roche by calling 1-800-526-6367.

The most common adverse events reported for PEGASYS and COPEGUS combination therapy observed in clinical trials (N=451) were fatigue/asthenia (65%), headache (43%), pyrexia (41%), myalgia (40%), irritability/anxiety/nervousness (33%), insomnia (30%), alopecia (28%), neutropenia (27%), nausea/vomiting (25%), rigors (25%), anorexia (24%), injection site reaction (23%), arthralgia (22%), depression (20%), pruritus (19%) and dermatitis (16%).

Serious adverse events included neuropsychiatric disorders (suicidal ideation and suicide attempt), serious and severe bacterial infections (sepsis), bone marrow toxicity (cytopenia and, rarely, aplastic anemia), cardiovascular disorders (hypertension, arrhythmias and myocardial infarction), hypersensitivity (including anaphylaxis), endocrine disorders (including thyroid disorders and diabetes mellitus), autoimmune disorders (including psoriasis and lupus), pulmonary disorders (dyspnea, pneumonia, bronchiolitis obliterans, interstitial pneumonitis and sarcoidosis), colitis (ulcerative and hemorrhagic/ischemic colitis), pancreatitis, and ophthalmologic disorders (decrease or loss of vision, retinopathy including macular edema and retinal thrombosis/hemorrhages, optic neuritis and papilledema).

*IMS, NPA Weekly, November 21, 2003—February 27, 2004.

Roche Pharmaceuticals

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

PEGASYS®
(peginterferon alfa-2a)

Before prescribing, please consult complete product information, a summary of which follows:

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).

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 ≥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) ≥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 µg/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 17ß-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 µg/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.

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
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
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 <0.5x10^9/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 (<0.5x10^9/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 below).

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.

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.
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.

HOW SUPPLIED

Single Dose Vial

Each PEGASYS (peginterferon alfa-2a) 180 µg single use, clear glass vial provides 1.0 mL containing 180 µg peginterferon alfa-2a for sc injection. Each package contains 1 vial (NDC 0004-0350-09).

Vials Monthly Convenience Pack

Four vials of PEGASYS (peginterferon alfa-2a), 180 µg single use, clear glass vials, in a box with 4 syringes and 8 alcohol swabs (NDC 0004-0350-39). Each syringe is a 1 mL (1 cc) volume syringe supplied with a 27 gauge, 1/2 inch needle with needle-stick protection device.

Prefilled Syringes Monthly Convenience Pack

Four prefilled syringes of PEGASYS (peginterferon alfa-2a), 180 µg single use, graduated, clear glass prefilled syringes, in a box with 4 needles and 4 alcohol swabs (NDC 0004-0352-39). Each syringe is a 0.5 mL (1/2 cc) volume syringe supplied with a 27 gauge, 1/2 inch needle with needle-stick protection device.

Storage

Store in the refrigerator at 2°C 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.

REBETRON™ is a trademark of Schering Corporation.

Rx only

Roche Pharmaceuticals

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

U.S. Govt. Lic. No. 0136

Revised: December 2003

Precision.

NEW PEGASYS PREFILLED SYRINGE

PEGASYS®
(Peginterferon alfa-2a) FOR INJECTION

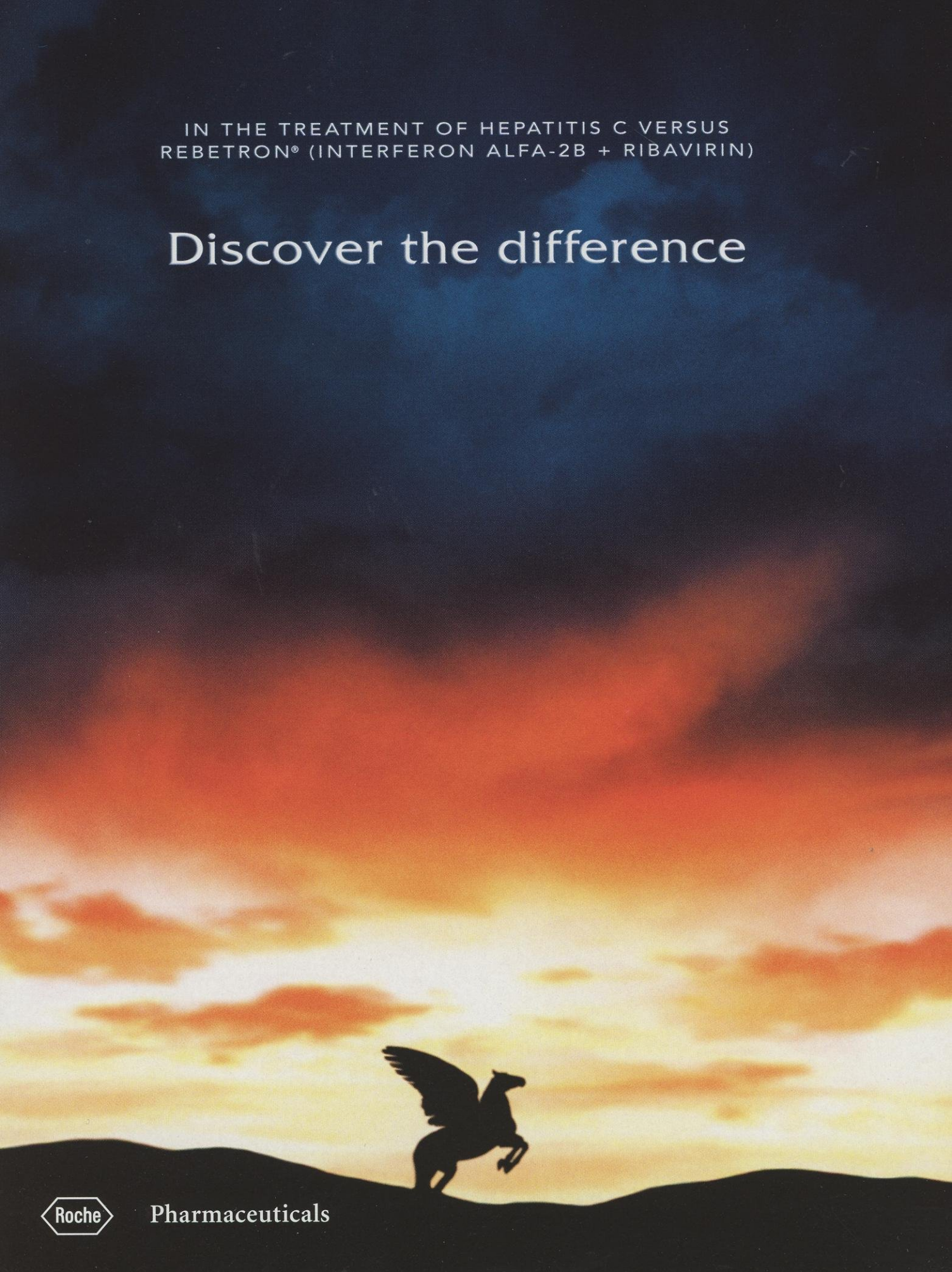
Please see brief summary of complete product information for PEGASYS and COPEGUS on adjacent pages.

Roche Pharmaceuticals

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

IN THE TREATMENT OF HEPATITIS C VERSUS
REBETRON® (INTERFERON ALFA-2B + RIBAVIRIN)

Discover the difference



Roche Pharmaceuticals

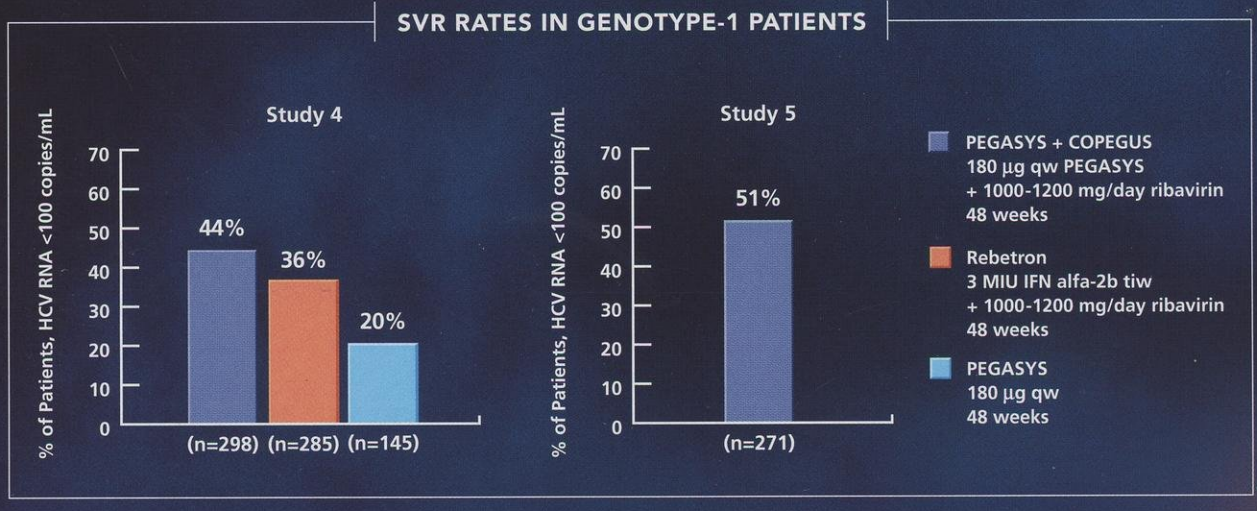
IN THE TREATMENT OF HEPATITIS C

Your needs haven't changed, your options have

Powerful efficacy...regardless of patient type

- In **two clinical trials,** more than half of all patients—53% of all patients in study 4 and 61% of all patients in study 5—achieved a sustained virologic response (SVR) on PEGASYS + COPEGUS combination therapy
- In genotype 2 and 3 patients, similar efficacy in less time with less ribavirin; 82% achieved an SVR following 24 weeks of PEGASYS + a low dose of COPEGUS (800 mg/day), compared with 76% of patients taking 48 weeks of PEGASYS + COPEGUS, regardless of COPEGUS dose (800,1000, or 1200 mg/day)

Genotype 1: Significant SVR rates in patients you treat most



Roche

Please see brief summary of complete product information for PEGASYS and COPEGUS on adjacent pages.

A treatment strategy tailored by genotype

DOSAGE RECOMMENDATIONS: COMBINATION THERAPY

Genotype	PEGASYS Dose	COPEGUS Dose	Duration
Genotype 1 or 4	180 µg qw	Patient weight: ≥75 kg=1200 mg; <75 kg=1000 mg	48 weeks
Genotype 2 or 3	180 µg qw	800 mg	24 weeks

- As monotherapy, the recommended dose of PEGASYS is 180 µg qw for 48 weeks
- No dose adjustments with PEGASYS for patient weight

Sustained virologic response is defined as an undetectable HCV RNA value at the end of the treatment-free follow-up period (week 48 or 72, depending on viral genotype).

Study design: In study 4, patients were randomized to receive either PEGASYS 180 µg qw with placebo, PEGASYS 180 µg qw with COPEGUS 1000 mg (body weight <75 kg) or 1200 mg (body weight ≥75 kg), or Rebetron® (interferon alfa-2b 3 MIU tiw plus 1000 mg or 1200 mg ribavirin) for 48 weeks of therapy followed by 24 weeks of treatment-free follow-up.

Study design: In study 5, all patients received PEGASYS 180 µg qw and were randomized to treatment for either 24 or 48 weeks and to a COPEGUS dose of 800 mg/day or either 1000 mg or 1200 mg/day (for body weight <75 kg/≥75 kg).

PEGASYS® (Peginterferon alfa-2a) FOR INJECTION

COPEGUS® (Ribavirin, USP) 200 MG TABLETS

Unleash the power of pegylation

For more information, call **1-877-PEGASYS (1-877-734-2797)** or log onto **www.pegasys.com.**

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 CONTRAINDICATIONS, WARNINGS, PRECAUTIONS and ADVERSE REACTIONS in complete product information).

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 CONTRAINDICATIONS, WARNINGS, PRECAUTIONS and ADVERSE REACTIONS in complete product information).

PEGASYS, 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).

PEGASYS is contraindicated in patients with hypersensitivity to PEGASYS or any of its components, autoimmune hepatitis, and decompensated hepatic disease (Child-Pugh class B and C) before or during treatment with PEGASYS. PEGASYS is also contraindicated in neonates and infants because it contains benzyl alcohol. Benzyl alcohol is associated with an increased incidence of neurological and other complications in neonates and infants, which are sometimes fatal. PEGASYS and COPEGUS therapy is additionally contraindicated in patients with a hypersensitivity to COPEGUS or any of its components, in women who are pregnant, men whose female partners are pregnant, and patients with hemoglobinopathies (eg, thalassemia major, sickle-cell anemia).

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 during the 6 months after treatment has concluded. Routine monthly pregnancy tests must be performed during this time. If pregnancy should 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. Physicians and patients are also strongly encouraged to report any pregnancies that do occur to Roche by calling 1-800-526-6367.

The most common adverse events reported for PEGASYS and COPEGUS combination therapy observed in clinical trials (N=451) were fatigue/asthenia (65%), headache (43%), pyrexia (41%), myalgia (40%), irritability/anxiety/nervousness (33%), insomnia (30%), alopecia (28%), neutropenia (27%), nausea/vomiting (25%), rigors (25%), anorexia (24%), injection site reaction (23%), arthralgia (22%), depression (20%), pruritus (19%) and dermatitis (16%).

Serious adverse events included neuropsychiatric disorders (suicidal ideation and suicide attempt), serious and severe bacterial infections (sepsis), bone marrow toxicity (cytopenia and, rarely, aplastic anemia), cardiovascular disorders (hypertension, arrhythmias and myocardial infarction), hypersensitivity (including anaphylaxis), endocrine disorders (including thyroid disorders and diabetes mellitus), autoimmune disorders (including psoriasis and lupus), pulmonary disorders (dyspnea, pneumonia, bronchiolitis obliterans, interstitial pneumonitis and sarcoidosis), colitis (ulcerative and hemorrhagic/ischemic colitis), pancreatitis, and ophthalmologic disorders (decrease or loss of vision, retinopathy including macular edema and retinal thrombosis/hemorrhages, optic neuritis and papilledema).

PEGASYS® (Peginterferon alfa-2a) FOR INJECTION

COPEGUS® (Ribavirin, USP) 200 MG TABLETS

Unleash the power of pegylation

Please see brief summary of complete product information for PEGASYS and COPEGUS on adjacent pages.

Roche Pharmaceuticals

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

PEGASYS®
(peginterferon alfa-2a)

Before prescribing, please consult complete product information, a summary of which follows:

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).

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 ≥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) ≥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 µg/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 µg/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.

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
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
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.

PEGASYS® (peginterferon alfa-2a)

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 <0.5x10^9/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 (<0.5x10^9/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 below).

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.

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.
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.

HOW SUPPLIED

Single Dose Vial

Each PEGASYS (peginterferon alfa-2a) 180 µg single use, clear glass vial provides 1.0 mL containing 180 µg peginterferon alfa-2a for sc injection. Each package contains 1 vial (NDC 0004-0350-09).

Vials Monthly Convenience Pack

Four vials of PEGASYS (peginterferon alfa-2a), 180 µg single use, clear glass vials, in a box with 4 syringes and 8 alcohol swabs (NDC 0004-0350-39). Each syringe is a 1 mL (1 cc) volume syringe supplied with a 27 gauge, 1/2 inch needle with needle-stick protection device.

Prefilled Syringes Monthly Convenience Pack

Four prefilled syringes of PEGASYS (peginterferon alfa-2a), 180 µg single use, graduated, clear glass prefilled syringes, in a box with 4 needles and 4 alcohol swabs (NDC 0004-0352-39). Each syringe is a 0.5 mL (1/2 cc) volume syringe supplied with a 27 gauge, 1/2 inch needle with needle-stick protection device.

Storage

Store in the refrigerator at 2°C 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.

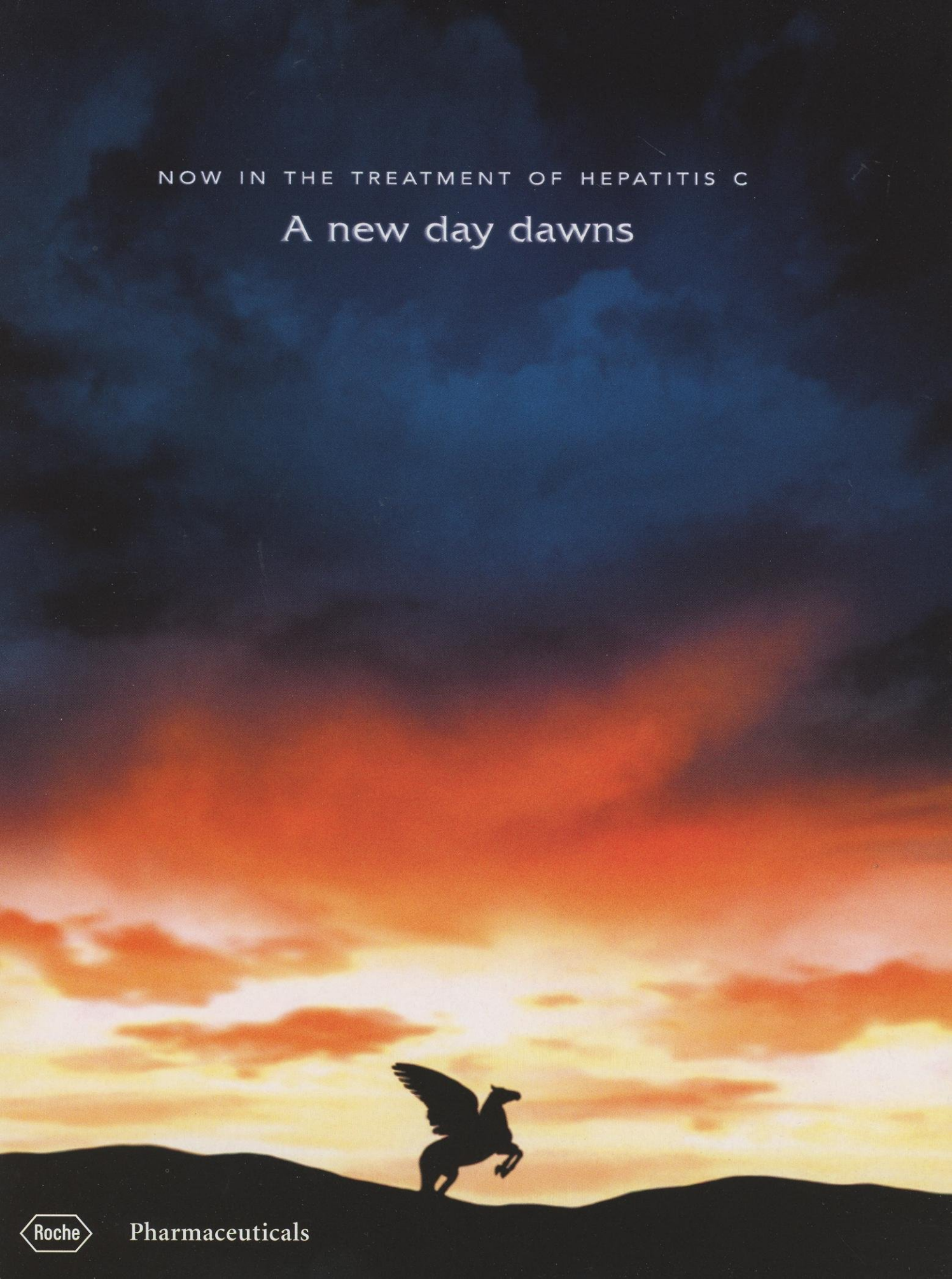
Rx only

Roche Pharmaceuticals

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

U.S. Govt. Lic. No. 0136

Revised: December 2003


NOW IN THE TREATMENT OF HEPATITIS C
A new day dawns
Roche
Pharmaceuticals

IN THE TREATMENT OF HEPATITIS C

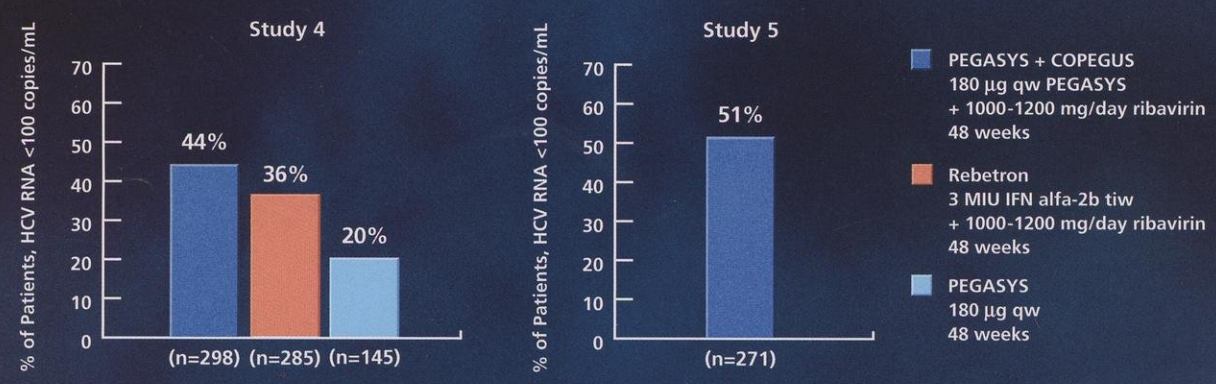
Your needs haven't changed, your options have

Powerful efficacy...regardless of patient type

- In **two clinical trials,** more than half of all patients—53% of all patients in study 4 and 61% of all patients in study 5—achieved a sustained virologic response (SVR) on PEGASYS + COPEGUS combination therapy
- In genotype 2 and 3 patients, similar efficacy in less time with less ribavirin; 82% achieved an SVR following 24 weeks of PEGASYS + a low dose of COPEGUS (800 mg/day), compared with 76% of patients taking 48 weeks of PEGASYS + COPEGUS, regardless of COPEGUS dose (800,1000, or 1200 mg/day)

Genotype 1: Significant SVR rates in patients you treat most

SVR RATES IN GENOTYPE-1 PATIENTS



Roche

Please see brief summary of complete product information for PEGASYS and COPEGUS on adjacent pages.

A treatment strategy tailored by genotype

DOSAGE RECOMMENDATIONS: COMBINATION THERAPY

Genotype	PEGASYS Dose	COPEGUS Dose	Duration
Genotype 1 or 4	180 µg qw	Patient weight: ≥75 kg=1200 mg; <75 kg=1000 mg	48 weeks
Genotype 2 or 3	180 µg qw	800 mg	24 weeks

- As monotherapy, the recommended dose of PEGASYS is 180 µg qw for 48 weeks
- No dose adjustments with PEGASYS for patient weight

Sustained virologic response is defined as an undetectable HCV RNA value at the end of the treatment-free follow-up period (week 72).

Study design: In study 4, patients were randomized to receive either PEGASYS 180 µg qw with placebo, PEGASYS 180 µg qw with COPEGUS 1000 mg (body weight <75 kg) or 1200 mg (body weight ≥75 kg), or Rebetron® (interferon alfa-2b 3 MIU tiw plus 1000 mg or 1200 mg ribavirin) for 48 weeks of therapy followed by 24 weeks of treatment-free follow-up.

Study design: In study 5, all patients received PEGASYS 180 µg 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).

NEW

PEGASYS® (Peginterferon alfa-2a) FOR INJECTION

COPEGUS™ (Ribavirin, USP) 200 MG TABLETS

Unleash the power of pegylation

For more information, call **1-877-PEGASYS (1-877-734-2797)** or log onto **www.pegasys.com.**

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 CONTRAINDICATIONS, WARNINGS, PRECAUTIONS and ADVERSE EVENTS in complete product information).

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 CONTRAINDICATIONS, WARNINGS, PRECAUTIONS and ADVERSE EVENTS in complete product information).

PEGASYS, 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).

PEGASYS is contraindicated in patients with hypersensitivity to PEGASYS or any of its components, autoimmune hepatitis, and decompensated hepatic disease (Child-Pugh class B and C) before or during treatment with PEGASYS. PEGASYS is also contraindicated in neonates and infants because it contains benzyl alcohol. Benzyl alcohol is associated with an increased incidence of neurological and other complications in neonates and infants, which are sometimes fatal. PEGASYS and COPEGUS therapy is additionally contraindicated in patients with a hypersensitivity to COPEGUS or any of its components, in women who are pregnant, men whose female partners are pregnant, and patients with hemoglobinopathies (eg, thalassemia major, sickle-cell anemia).

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 during the 6 months after treatment has concluded. Routine monthly pregnancy tests must be performed during this time. If pregnancy should 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.

The most common adverse events reported for PEGASYS and COPEGUS combination therapy observed in clinical trials (N=451) were fatigue/asthenia (65%), headache (43%), pyrexia (41%), myalgia (40%), irritability/anxiety/nervousness (33%), insomnia (30%), alopecia (28%), neutropenia (27%), nausea/vomiting (25%), rigors (25%), anorexia (24%), injection site reaction (23%), arthralgia (22%), depression (20%), pruritus (19%) and dermatitis (16%).

Serious adverse events included neuropsychiatric disorders (suicidal ideation and suicide attempt), serious and severe bacterial infections (sepsis), bone marrow toxicity (cytopenia and rarely, aplastic anemia), cardiovascular disorders (hypertension, arrhythmias and myocardial infarction), hypersensitivity (including anaphylaxis), endocrine disorders (including thyroid disorders and diabetes mellitus), autoimmune disorders (including psoriasis and lupus), pulmonary disorders (dyspnea, pneumonia, bronchiolitis obliterans, interstitial pneumonitis and sarcoidosis), colitis (ulcerative and hemorrhagic/ischemic colitis), pancreatitis, and ophthalmologic disorders (decrease or loss of vision, retinopathy including macular edema and retinal thrombosis/hemorrhages, optic neuritis and papilledema).

NEW

PEGASYS® (Peginterferon alfa-2a) FOR INJECTION

COPEGUS™ (Ribavirin, USP) 200 MG TABLETS

Unleash the power of pegylation

Please see brief summary of complete product information for PEGASYS and COPEGUS on adjacent pages.

Roche Pharmaceuticals

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

PEGASYS®
(peginterferon alfa-2a)

Before prescribing, please consult the complete product information, a summary of which follows:

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).

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 **WARNING: 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.

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 Dose Modification Guidelines**). Because cardiac disease may be worsened by drug-induced anemia, patients with a history of significant or unstable cardiac disease should not use COPEGUS (see **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/minute (see **CLINICAL PHARMACOLOGY: Special Populations** in complete product information).

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 ≥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) ≥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 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** in complete product information).

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.

Mutagenesis (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 µg/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 µg/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 (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.

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
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
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.

PEGASYS® (peginterferon alfa-2a)

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 <0.5x10^9/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 (<0.5x10^9/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** in complete product information).

PEGASYS

The recommended dose of PEGASYS monotherapy is 180 µg (1.0 mL) 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) once weekly. The recommended dose of COPEGUS and duration for PEGASYS/COPEGUS therapy is based on viral genotype (see table below).

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.

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.
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 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.

HOW SUPPLIED

Single Dose Vial

Each PEGASYS (peginterferon alfa-2a) 180 µg single use, clear glass vial provides 1.0 mL containing 180 µg peginterferon alfa-2a for sc injection. Each package contains 1 vial (NDC 0004-0350-09).

Monthly Convenience Pack

Four vials of PEGASYS (peginterferon alfa-2a), 180 µg single use, in a box with 4 syringes and 8 alcohol swabs (NDC 0004-0350-39). Each syringe is a 1 mL (1 cc) volume syringe supplied with a 27 gauge, 1/2 inch needle with needle-stick protection device.

Storage

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

Rx only

Roche Pharmaceuticals

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

U.S. Govt. Lic. No. 0136

Issued: January 2003