

HIGHLIGHTS OF PRESCRIBING INFORMATION

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

COPEGUS® (ribavirin) Tablets
Initial U.S. Approval: 2002

WARNING: RISK OF SERIOUS DISORDERS AND RIBAVIRIN-ASSOCIATED EFFECTS

See full prescribing information for complete boxed warning.

- Ribavirin monotherapy, including COPEGUS, is not effective for the treatment of chronic hepatitis C virus infection (Boxed Warning).
- The hemolytic anemia associated with ribavirin therapy may result in worsening of cardiac disease and lead to fatal and nonfatal myocardial infarctions. Patients with a history of significant or unstable cardiac disease should not be treated with COPEGUS (2.3, 5.2, 6.1).
- Significant teratogenic and embryocidal effects have been demonstrated in all animal species exposed to ribavirin. Therefore, COPEGUS is contraindicated in women who are pregnant and in the male partners of women who are pregnant. Extreme care must be taken to avoid pregnancy during therapy and for 6 months after completion of treatment in both female patients and in female partners of male patients who are taking COPEGUS therapy (4, 5.1, 8.1).

RECENT MAJOR CHANGES

Boxed Warning	10/2010
Indications and Usage (1)	08/2011
Dosage and Administration	
Discontinuation of Dosing (2.5)	10/2010
Renal Impairment (2.4)	08/2011
Dosage and Administration (2)	08/2011
Chronic Hepatitis C Monoinfection (2.1)	08/2011
Dose Modifications (2.3)	08/2011
Contraindications (4)	12/2010
Warnings and Precautions	
Warnings and Precautions (5)	10/2010
Anemia (5.2)	10/2010
Pulmonary Disorders (5.5)	10/2010
Hepatic Failure (5.3)	12/2010
Impact on Growth in Pediatric Patients (5.8)	08/2011
Laboratory Tests (5.9)	08/2011

INDICATIONS AND USAGE

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

DOSAGE AND ADMINISTRATION

- CHC: COPEGUS is administered according to body weight and genotype (2.1)
- CHC with HIV coinfection: 800 mg by mouth daily for a total of 48 weeks, regardless of genotype (2.2)
- Dose reduction or discontinuation is recommended in patients experiencing certain adverse reactions or renal impairment (2.3, 2.4)

DOSAGE FORMS AND STRENGTHS

- COPEGUS tablets 200 mg (3)

CONTRAINDICATIONS

- Pregnant women and men whose female partners are pregnant (4, 5.1, 8.1)
- Hemoglobinopathies (4)
- Coadministration with didanosine (4, 7.1)

COPEGUS in combination with PEGASYS is contraindicated in patients with:

- Autoimmune hepatitis (4)
- Hepatic decompensation in cirrhotic patients (4, 5.3)

WARNINGS AND PRECAUTIONS

- Birth defects and fetal death with ribavirin: Do not use in pregnancy and for 6 months after treatment. Patients must have a negative pregnancy test prior to therapy, use at least 2 forms of contraception and undergo monthly pregnancy tests (4, 5.1, 8.1)

PEGASYS/COPEGUS: Patients exhibiting the following conditions should be closely monitored and may require dose reduction or discontinuation of therapy:

- Hemolytic anemia may occur with a significant initial drop in hemoglobin. This may result in worsening cardiac disease leading to fatal or nonfatal myocardial infarctions (5.2, 6.1)
- Risk of hepatic failure and death: Monitor hepatic function during treatment and discontinue treatment for hepatic decompensation (5.3)
- Severe hypersensitivity reactions including urticaria, angioedema, bronchoconstriction, and anaphylaxis, and serious skin reactions such as Stevens-Johnson Syndrome (5.4)
- Pulmonary disorders, including pulmonary function impairment and pneumonitis, including fatal cases of pneumonia (5.5)
- Severe depression and suicidal ideation, autoimmune and infectious disorders, suppression of bone marrow function, pancreatitis, and diabetes (5)
- Bone marrow suppression with azathioprine coadministration (5.6)
- Growth impairment with combination therapy in pediatric patients (5.8)

ADVERSE REACTIONS

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

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

To report SUSPECTED ADVERSE REACTIONS, contact Genentech at 1-888-835-2555 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

DRUG INTERACTIONS

- Nucleoside analogues: Closely monitor for toxicities. Discontinue nucleoside reverse transcriptase inhibitors or reduce dose or discontinue interferon, ribavirin or both with worsening toxicities (7.1)
- Azathioprine: Concomitant use of azathioprine with ribavirin has been reported to induce severe pancytopenia and may increase the risk of azathioprine-related myelotoxicity (7.3)

USE IN SPECIFIC POPULATIONS

- **Ribavirin Pregnancy Registry (8.1)**
- Pediatrics: Safety and efficacy in pediatric patients less than 5 years old have not been established (8.4)
- Renal Impairment: Dose should be reduced in patients with creatinine clearance less than equal to 50 mL/min (8.7)
- Organ Transplant: Safety and efficacy have not been studied (8.10)

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved Medication Guide.

Revised: 08/2011

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FULL PRESCRIBING INFORMATION

WARNING: RISK OF SERIOUS DISORDERS AND RIBAVIRIN-ASSOCIATED EFFECTS

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

The primary clinical toxicity of ribavirin is hemolytic anemia. The anemia associated with ribavirin therapy may result in worsening of cardiac disease and lead to fatal and nonfatal myocardial infarctions. Patients with a history of significant or unstable cardiac disease should not be treated with COPEGUS [see *Warnings and Precautions (5.2)*, *Adverse Reactions (6.1)*, and *Dosage and Administration (2.3)*].

Significant teratogenic and/or embryocidal effects have been demonstrated in all animal species exposed to ribavirin. In addition, ribavirin has a multiple dose half-life of 12 days, and it may persist in non-plasma compartments for as long as 6 months. Therefore, ribavirin, including COPEGUS, is contraindicated in women who are pregnant and in the male partners of women who are pregnant. Extreme care must be taken to avoid pregnancy during therapy and for 6 months after completion of therapy in both female patients and in female partners of male patients who are taking ribavirin therapy. At least two reliable forms of effective contraception must be utilized during treatment and during the 6-month post treatment follow-up period [see *Contraindications (4)*, *Warnings and Precautions (5.1)*, and *Use in Specific Populations (8.1)*].

1 INDICATIONS AND USAGE

COPEGUS in combination with PEGASYS (peginterferon alfa-2a) is indicated for the treatment of patients 5 years of age and older with chronic hepatitis C (CHC) virus infection who have compensated liver disease and have not been previously treated with interferon alpha.

The following points should be considered when initiating COPEGUS combination therapy with PEGASYS:

- This indication is based on clinical trials of combination therapy in patients with CHC and compensated liver disease, some of whom had histological evidence of cirrhosis (Child-Pugh class A), and in adult patients with clinically stable HIV disease and CD4 count greater than 100 cells/mm³.
- This indication is based on achieving undetectable HCV-RNA after treatment for 24 or 48 weeks, based on HCV genotype, and maintaining a Sustained Virologic Response (SVR) 24 weeks after the last dose.
- Safety and efficacy data are not available for treatment longer than 48 weeks.
- The safety and efficacy of COPEGUS and PEGASYS therapy have not been established in liver or other organ transplant recipients, patients with decompensated liver disease, or previous non-responders to interferon therapy.
- The safety and efficacy of COPEGUS therapy for the treatment of adenovirus, RSV, parainfluenza or influenza infections have not been established. COPEGUS should not be used for these indications. Ribavirin for inhalation has a separate package insert, which should be consulted if ribavirin inhalation therapy is being considered.

2 DOSAGE AND ADMINISTRATION

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

2.1 Chronic Hepatitis C Monoinfection

Adult Patients

The recommended dose of COPEGUS tablets is provided in **Table 1**. The recommended duration of treatment for patients previously untreated with ribavirin and interferon is 24 to 48 weeks.

The daily dose of COPEGUS is 800 mg to 1200 mg administered orally in two divided doses. The dose should be individualized to the patient depending on baseline disease characteristics (e.g., genotype), response to therapy, and tolerability of the regimen (see **Table 1**).

Table 1 PEGASYS and COPEGUS Dosing Recommendations

Hepatitis C Virus (HCV) Genotype	PEGASYS Dose* (once weekly)	COPEGUS Dose (daily)	Duration
Genotypes 1, 4	180 mcg	<75 kg = 1000 mg ≥75 kg = 1200 mg	48 weeks 48 weeks
Genotypes 2, 3	180 mcg	800 mg	24 weeks

Genotypes 2 and 3 showed no increased response to treatment beyond 24 weeks (see **Table 10**).

Data on genotypes 5 and 6 are insufficient for dosing recommendations.

*See PEGASYS Package Insert for further details on PEGASYS dosing and administration, including dose modification in patients with renal impairment.

Pediatric Patients

PEGASYS is administered as 180 mcg/1.73m² x BSA once weekly subcutaneously, to a maximum dose of 180 mcg, and should be given in combination with ribavirin. The recommended treatment duration for patients with genotype 2 or 3 is 24 weeks and for other genotypes is 48 weeks.

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

Table 2 COPEGUS Dosing Recommendations for Pediatric Patients

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

*approximately 15 mg/kg/day

2.2 Chronic Hepatitis C with HIV Coinfection

Adult Patients

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

2.3 Dose Modifications

Adult and Pediatric Patients

If severe adverse reactions or laboratory abnormalities develop during combination COPEGUS/PEGASYS therapy, the dose should be modified or discontinued, if appropriate, until the adverse reactions abate or decrease in severity. If intolerance persists after dose adjustment, COPEGUS/PEGASYS therapy should be discontinued. **Table 3** provides guidelines for dose modifications and discontinuation based on the patient's hemoglobin concentration and cardiac status.

COPEGUS should be administered with caution to patients with pre-existing cardiac disease. Patients should be assessed before commencement of therapy and should be appropriately monitored during therapy. If there is any deterioration of cardiovascular status, therapy should be stopped [*see Warnings and Precautions (5.2)*].

Table 3 COPEGUS Dose Modification Guidelines in Adults and Pediatrics

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

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

Adult Patients

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

Pediatric Patients

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

2.4 Renal Impairment

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

Table 4 Dosage Modification for Renal Impairment

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

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

No data are available for pediatric subjects with renal impairment.

2.5 Discontinuation of Dosing

Discontinuation of PEGASYS/COPEGUS therapy should be considered if the patient has failed to demonstrate at least a 2 log₁₀ reduction from baseline in HCV RNA by 12 weeks of therapy, or undetectable HCV RNA levels after 24 weeks of therapy.

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

3 DOSAGE FORMS AND STRENGTHS

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

4 CONTRAINDICATIONS

COPEGUS (ribavirin) is contraindicated in:

- Women who are pregnant. COPEGUS may cause fetal harm when administered to a pregnant woman. COPEGUS is contraindicated in women who are or may become pregnant. If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to the fetus [see *Warnings and Precautions (5.1)*, *Use in Specific Populations (8.1)*, and *Patient Counseling Information (17)*].
- Men whose female partners are pregnant.
- Patients with hemoglobinopathies (e.g., thalassemia major or sickle-cell anemia).
- In combination with didanosine. Reports of fatal hepatic failure, as well as peripheral neuropathy, pancreatitis, and symptomatic hyperlactatemia/lactic acidosis have been reported in clinical trials [see *Drug Interactions (7.1)*].

COPEGUS and PEGASYS combination therapy is contraindicated in patients with:

- Autoimmune hepatitis.

- Hepatic decompensation (Child-Pugh score greater than 6; class B and C) in cirrhotic CHC monoinfected patients before treatment [see *Warnings and Precautions (5.3)*].
- Hepatic decompensation (Child-Pugh score greater than or equal to 6) in cirrhotic CHC patients coinfecting with HIV before treatment [see *Warnings and Precautions (5.3)*].

5 WARNINGS AND PRECAUTIONS

Significant adverse reactions associated with COPEGUS/PEGASYS combination therapy include severe depression and suicidal ideation, hemolytic anemia, suppression of bone marrow function, autoimmune and infectious disorders, ophthalmologic disorders, cerebrovascular disorders, pulmonary dysfunction, colitis, pancreatitis, and diabetes.

The PEGASYS Package Insert should be reviewed in its entirety for additional safety information prior to initiation of combination treatment.

5.1 Pregnancy

COPEGUS may cause birth defects and/or death of the exposed fetus. Ribavirin has demonstrated significant teratogenic and/or embryocidal effects in all animal species in which adequate studies have been conducted. These effects occurred at doses as low as one twentieth of the recommended human dose of ribavirin.

COPEGUS therapy should not be started unless a report of a negative pregnancy test has been obtained immediately prior to planned initiation of therapy. Extreme care must be taken to avoid pregnancy in female patients and in female partners of male patients. Patients should be instructed to use at least two forms of effective contraception during treatment and for 6 months after treatment has been stopped. Pregnancy testing should occur monthly during COPEGUS therapy and for 6 months after therapy has stopped [see *Boxed Warning, Contraindications (4), Use in Specific Populations (8.1), and Patient Counseling Information (17)*].

5.2 Anemia

The primary toxicity of ribavirin is hemolytic anemia, which was observed in approximately 13% of all COPEGUS/PEGASYS-treated subjects in clinical trials. Anemia associated with COPEGUS occurs within 1 to 2 weeks of initiation of therapy. Because the initial drop in hemoglobin may be significant, it is advised that hemoglobin or hematocrit be obtained pretreatment and at week 2 and week 4 of therapy or more frequently if clinically indicated. Patients should then be followed as clinically appropriate. Caution should be exercised in initiating treatment in any patient with baseline risk of severe anemia (e.g., spherocytosis, history of gastrointestinal bleeding) [see *Dosage and Administration (2.3)*].

Fatal and nonfatal myocardial infarctions have been reported in patients with anemia caused by COPEGUS. Patients should be assessed for underlying cardiac disease before initiation of ribavirin therapy. Patients with pre-existing cardiac disease should have electrocardiograms administered before treatment, and should be appropriately monitored during therapy. If there is any deterioration of cardiovascular status, therapy should be suspended or discontinued [see *Dosage and Administration (2.3)*]. Because cardiac disease may be worsened by drug-induced anemia, patients with a history of significant or unstable cardiac disease should not use COPEGUS [see *Boxed Warning and Dosage and Administration (2.3)*].

5.3 Hepatic Failure

Chronic hepatitis C (CHC) patients with cirrhosis may be at risk of hepatic decompensation and death when treated with alpha interferons, including PEGASYS. Cirrhotic CHC patients coinfecting with HIV receiving highly active antiretroviral therapy (HAART) and interferon alfa-2a with or without ribavirin appear to be at increased risk for the development of hepatic decompensation compared to patients not receiving HAART. In Study NR15961 [see *Clinical Studies (14.3)*], among 129 CHC/HIV cirrhotic patients receiving HAART, 14 (11%) of these patients across all treatment arms developed hepatic decompensation resulting in 6 deaths. All 14 patients were on NRTIs, including stavudine, didanosine, abacavir, zidovudine, and lamivudine. These small

numbers of patients do not permit discrimination between specific NRTIs or the associated risk. During treatment, patients' clinical status and hepatic function should be closely monitored for signs and symptoms of hepatic decompensation. Treatment with PEGASYS/COPEGUS should be discontinued immediately in patients with hepatic decompensation [see *Contraindications (4)*].

5.4 Hypersensitivity

Severe acute hypersensitivity reactions (e.g., urticaria, angioedema, bronchoconstriction, and anaphylaxis) have been observed during alpha interferon and ribavirin therapy. If such a reaction occurs, therapy with PEGASYS and COPEGUS should be discontinued immediately and appropriate medical therapy instituted. Serious skin reactions including vesiculobullous eruptions, reactions in the spectrum of Stevens-Johnson Syndrome (erythema multiforme major) with varying degrees of skin and mucosal involvement and exfoliative dermatitis (erythroderma) have been reported in patients receiving PEGASYS with and without ribavirin. Patients developing signs or symptoms of severe skin reactions must discontinue therapy [see *Adverse Reactions (6.2)*].

5.5 Pulmonary Disorders

Dyspnea, pulmonary infiltrates, pneumonitis, pulmonary hypertension, and pneumonia have been reported during therapy with ribavirin and interferon. Occasional cases of fatal pneumonia have occurred. In addition, sarcoidosis or the exacerbation of sarcoidosis has been reported. If there is evidence of pulmonary infiltrates or pulmonary function impairment, patients should be closely monitored and, if appropriate, combination COPEGUS/PEGASYS treatment should be discontinued.

5.6 Bone Marrow Suppression

Pancytopenia (marked decreases in RBCs, neutrophils and platelets) and bone marrow suppression have been reported in the literature to occur within 3 to 7 weeks after the concomitant administration of pegylated interferon/ribavirin and azathioprine. In this limited number of patients (n=8), myelotoxicity was reversible within 4 to 6 weeks upon withdrawal of both HCV antiviral therapy and concomitant azathioprine and did not recur upon reintroduction of either treatment alone. PEGASYS, COPEGUS, and azathioprine should be discontinued for pancytopenia, and pegylated interferon/ribavirin should not be re-introduced with concomitant azathioprine [see *Drug Interactions (7.3)*].

5.7 Pancreatitis

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

5.8 Impact on Growth in Pediatric Patients

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

5.9 Laboratory Tests

Before beginning PEGASYS/COPEGUS combination therapy, standard hematological and biochemical laboratory tests are recommended for all patients. Pregnancy screening for women of childbearing potential must be performed. Patients who have pre-existing cardiac abnormalities should have electrocardiograms administered before treatment with PEGASYS/COPEGUS.

After initiation of therapy, hematological tests should be performed at 2 weeks and 4 weeks and biochemical tests should be performed at 4 weeks. Additional testing should be performed periodically during therapy. In adult clinical studies, the CBC (including hemoglobin level and white blood cell and platelet counts) and chemistries (including liver function tests and uric acid) were measured at 1, 2, 4, 6, and 8 weeks, and then every 4 to 6 weeks or more frequently if abnormalities were found. In the pediatric clinical trial, hematological and chemistry assessments were at 1, 3, 5, and 8 weeks, then every 4 weeks. Thyroid stimulating hormone (TSH) was measured every 12 weeks. Monthly pregnancy testing should be performed during combination therapy and for 6 months after discontinuing therapy.

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

- Platelet count greater than or equal to 90,000 cells/mm³ (as low as 75,000 cells/mm³ in HCV patients with cirrhosis or 70,000 cells/mm³ in patients with CHC and HIV)
- Absolute neutrophil count (ANC) greater than or equal to 1500 cells/mm³
- TSH and T₄ within normal limits or adequately controlled thyroid function
- CD4+ cell count greater than or equal to 200 cells/mm³ or CD4+ cell count greater than or equal to 100 cells/mm³ but less than 200 cells/mm³ and HIV-1 RNA less than 5,000 cells/mm³ in patients coinfecting with HIV
- Hemoglobin greater than or equal to 12 g/dL for women and greater than or equal to 13 g/dL for men in CHC monoinfected patients
- Hemoglobin greater than or equal to 11 g/dL for women and greater than or equal to 12 g/dL for men in patients with CHC and HIV

6 ADVERSE REACTIONS

PEGASYS in combination with COPEGUS causes a broad variety of serious adverse reactions [*see Boxed Warning and Warnings and Precautions (5)*]. The most common serious or life-threatening adverse reactions induced or aggravated by COPEGUS/PEGASYS include depression, suicide, relapse of drug abuse/overdose, and bacterial infections each occurring at a frequency of less than 1%. Hepatic decompensation occurred in 2% (10/574 CHC/HIV patients [*see Warnings and Precautions (5.3)*]).

6.1 Clinical Studies Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice.

Adult Patients

In the pivotal registration trials NV15801 and NV15942, 886 patients received COPEGUS for 48 weeks at doses of 1000/1200 mg based on body weight. In these trials, one or more serious adverse reactions occurred in 10% of CHC monoinfected subjects and in 19% of CHC/HIV subjects receiving PEGASYS alone or in combination with COPEGUS. The most common serious adverse event (3% in CHC and 5% in CHC/HIV) was bacterial infection (e.g., sepsis, osteomyelitis, endocarditis, pyelonephritis, pneumonia).

Other serious adverse reactions occurred at a frequency of less than 1% and included: suicide, suicidal ideation, psychosis, aggression, anxiety, drug abuse and drug overdose, angina, hepatic dysfunction, fatty liver, cholangitis, arrhythmia, diabetes mellitus, autoimmune phenomena (e.g., hyperthyroidism, hypothyroidism, sarcoidosis, systemic lupus erythematosus, rheumatoid arthritis), peripheral neuropathy, aplastic anemia, peptic ulcer, gastrointestinal bleeding, pancreatitis, colitis, corneal ulcer, pulmonary embolism, coma, myositis, cerebral hemorrhage, thrombotic thrombocytopenic purpura, psychotic disorder, and hallucination.

The percentage of patients in clinical trials who experienced one or more adverse events was 98%. The most commonly reported adverse reactions were psychiatric reactions, including depression, insomnia, irritability,

anxiety, and flu-like symptoms such as fatigue, pyrexia, myalgia, headache and rigors. Other common reactions were anorexia, nausea and vomiting, diarrhea, arthralgias, injection site reactions, alopecia, and pruritus. **Table 5** shows rates of adverse events occurring in greater than or equal to 5% subjects receiving pegylated interferon and ribavirin combination therapy in the CHC Clinical Trial, NV15801.

Ten percent of CHC monoinfected patients receiving 48 weeks of therapy with PEGASYS in combination with COPEGUS discontinued therapy; 16% of CHC/HIV coinfecting patients discontinued therapy. The most common reasons for discontinuation of therapy were psychiatric, flu-like syndrome (e.g., lethargy, fatigue, headache), dermatologic and gastrointestinal disorders and laboratory abnormalities (thrombocytopenia, neutropenia, and anemia).

Overall 39% of patients with CHC or CHC/HIV required modification of PEGASYS and/or COPEGUS therapy. The most common reason for dose modification of PEGASYS in CHC and CHC/HIV patients was for laboratory abnormalities; neutropenia (20% and 27%, respectively) and thrombocytopenia (4% and 6%, respectively). The most common reason for dose modification of COPEGUS in CHC and CHC/HIV patients was anemia (22% and 16%, respectively).

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

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

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

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

Body System	CHC Combination Therapy Study NV15801	
	PEGASYS 180 mcg + 1000 mg or 1200 mg COPEGUS 48 weeks	Intron A + 1000 mg or 1200 mg Rebetol® 48 weeks
	N=451	N=443
	%	%
Gastrointestinal		
Nausea/Vomiting	25	29
Diarrhea	11	10
Abdominal pain	8	9
Dry mouth	4	7
Dyspepsia	6	5
Hematologic*		
Lymphopenia	14	12
Anemia	11	11
Neutropenia	27	8
Thrombocytopenia	5	<1
Metabolic and Nutritional		
Anorexia	24	26
Weight decrease	10	10
Musculoskeletal, Connective Tissue and Bone		
Myalgia	40	49
Arthralgia	22	23
Back pain	5	5
Neurological		
Headache	43	49
Dizziness (excluding vertigo)	14	14
Memory impairment	6	5
Psychiatric		
Irritability/Anxiety/Nervousness	33	38
Insomnia	30	37
Depression	20	28
Concentration impairment	10	13
Mood alteration	5	6
Resistance Mechanism Disorders		
Overall	12	10

Body System	CHC Combination Therapy Study NV15801	
	PEGASYS 180 mcg + 1000 mg or 1200 mg COPEGUS 48 weeks	Intron A + 1000 mg or 1200 mg Rebetol® 48 weeks
	N=451	N=443
	%	%
Respiratory, Thoracic and Mediastinal		
Dyspnea	13	14
Cough	10	7
Dyspnea exertional	4	7
Skin and Subcutaneous Tissue		
Alopecia	28	33
Pruritus	19	18
Dermatitis	16	13
Dry skin	10	13
Rash	8	5
Sweating increased	6	5
Eczema	5	4
Visual Disorders		
Vision blurred	5	2

* Severe hematologic abnormalities (lymphocyte less than 500 cells/mm³; hemoglobin less than 10 g/dL; neutrophil less than 750 cells/mm³; platelet less than 50,000 cells/mm³).

Pediatric Subjects

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

Growth inhibition was observed in pediatric subjects. During combination therapy for up to 48 weeks with PEGASYS and COPEGUS, negative changes in weight for age z-score and height for age z-score after 48 weeks of therapy compared with baseline were observed [*see Warnings and Precautions (5.8)*].

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

System Organ Class	Study NV17424	
	PEGASYS 180 mcg/1.73 m ² x BSA + COPEGUS 15 mg/kg (N=55)	PEGASYS 180 mcg/1.73 m ² x BSA + Placebo** (N=59)
	%	%
General disorders and administration site conditions		
Influenza like illness	91	81
Injection site reaction	44	42
Fatigue	25	20
Irritability	24	14
Gastrointestinal disorders		
Gastrointestinal disorder	49	44
Nervous system disorders		
Headache	51	39
Skin and subcutaneous tissue disorders		
Rash	15	10
Pruritus	11	12
Musculoskeletal, connective tissue and bone disorders		
Musculoskeletal pain	35	29
Psychiatric disorders		
Insomnia	9	12
Metabolism and nutrition disorders		
Decreased appetite	11	14

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

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

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

Common Adverse Reactions in CHC with HIV Coinfection (Adults)

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

Laboratory Test Abnormalities

Adult Patients

Anemia due to hemolysis is the most significant toxicity of ribavirin therapy. Anemia (hemoglobin less than 10 g/dL) was observed in 13% of all COPEGUS and PEGASYS combination-treated patients in clinical trials. The maximum drop in hemoglobin occurred during the first 8 weeks of initiation of ribavirin therapy [*see Dosage and Administration (2.3)*].

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

Laboratory Parameter	PEGASYS + Ribavirin 1000/1200 mg 48 wks (N=887)	Intron A + Ribavirin 1000/1200 mg 48 wks (N=443)
Neutrophils (cells/mm³)		
1,000 <1,500	34%	38%
500 <1,000	49%	21%
<500	5%	1%
Platelets (cells/mm³)		
50,000 - <75,000	11%	4%
20,000 - <50,000	5%	< 1%
<20,000	0	0
Hemoglobin (g/dL)		
8.5 - 9.9	11%	11%
<8.5	2%	< 1%

Pediatric Patients

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

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

Laboratory Parameter	PEGASYS 180 mcg/1.73 m ² x BSA + COPEGUS 15 mg/kg (N=55)	PEGASYS 180 mcg/1.73 m ² x BSA + Placebo* (N=59)
Neutrophils (cells/mm³)		
1,000 - <1,500	31%	39%
750 - <1,000	27%	17%
500 - <750	25%	15%
<500	7%	5%
Platelets (cells/mm³)		
75,000 - <100,000	4%	2%
50,000 - <75,000	0%	2%
<50,000	0%	0%
Hemoglobin (g/dL)		
8.5 - <10	7%	3%
<8.5	0%	0%

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

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

6.2 Postmarketing Experience

The following adverse reactions have been identified and reported during post-approval use of PEGASYS/COPEGUS combination therapy. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Blood and Lymphatic System disorders

Pure red cell aplasia

Ear and Labyrinth disorders

Hearing impairment, hearing loss

Eye disorders

Serous retinal detachment

Immune disorders

Liver and renal graft rejection

Metabolism and Nutrition disorders

Dehydration

Skin and Subcutaneous Tissue disorders

Stevens-Johnson Syndrome (SJS)

Toxic epidermal necrolysis (TEN)

7 DRUG INTERACTIONS

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

7.1 Nucleoside Reverse Transcriptase Inhibitors (NRTIs)

In vitro data indicate ribavirin reduces phosphorylation of lamivudine, stavudine, and zidovudine. However, no pharmacokinetic (e.g., plasma concentrations or intracellular triphosphorylated active metabolite concentrations) or pharmacodynamic (e.g., loss of HIV/HCV virologic suppression) interaction was observed when ribavirin and lamivudine (n=18), stavudine (n=10), or zidovudine (n=6) were co-administered as part of a multi-drug regimen to HCV/HIV coinfecting patients.

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

Patients receiving PEGASYS/COPEGUS and NRTIs should be closely monitored for treatment associated toxicities. Physicians should refer to prescribing information for the respective NRTIs for guidance regarding toxicity management. In addition, dose reduction or discontinuation of PEGASYS, COPEGUS or both should also be considered if worsening toxicities are observed, including hepatic decompensation (e.g., Child-Pugh greater than or equal to 6) [*see Warnings and Precautions (5.3) and Dosage and Administration (2.3)*].

Didanosine

Co-administration of COPEGUS and didanosine is contraindicated. Didanosine or its active metabolite (dideoxyadenosine 5'-triphosphate) concentrations are increased when didanosine is co-administered with ribavirin, which could cause or worsen clinical toxicities. Reports of fatal hepatic failure, as well as peripheral neuropathy, pancreatitis, and symptomatic hyperlactatemia/lactic acidosis have been reported in clinical trials [*see Contraindications (4)*].

Zidovudine

In Study NR15961, patients who were administered zidovudine in combination with PEGASYS/COPEGUS developed severe neutropenia (ANC less than 500) and severe anemia (hemoglobin less than 8 g/dL) more frequently than similar patients not receiving zidovudine (neutropenia 15% vs. 9%) (anemia 5% vs. 1%). Discontinuation of zidovudine should be considered as medically appropriate.

7.2 Drugs Metabolized by Cytochrome P450

In vitro studies indicate that ribavirin does not inhibit CYP 2C9, CYP 2C19, CYP 2D6 or CYP 3A4.

7.3 Azathioprine

The use of ribavirin to treat chronic hepatitis C in patients receiving azathioprine has been reported to induce severe pancytopenia and may increase the risk of azathioprine-related myelotoxicity. Inosine monophosphate dehydrogenase (IMDH) is required for one of the metabolic pathways of azathioprine. Ribavirin is known to inhibit IMDH, thereby leading to accumulation of an azathioprine metabolite, 6-methylthioinosine monophosphate (6-MTITP), which is associated with myelotoxicity (neutropenia, thrombocytopenia, and anemia). Patients receiving azathioprine with ribavirin should have complete blood counts, including platelet counts, monitored weekly for the first month, twice monthly for the second and third months of treatment, then monthly or more frequently if dosage or other therapy changes are necessary [see *Warnings and Precautions (5.7)*].

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

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

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

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

Treatment and Post treatment: Potential Risk to the Fetus

Ribavirin is known to accumulate in intracellular components from where it is cleared very slowly. It is not known whether ribavirin is contained in sperm, and if so, will exert a potential teratogenic effect upon fertilization of the ova. However, because of the potential human teratogenic effects of ribavirin, male patients should be advised to take every precaution to avoid risk of pregnancy for their female partners.

COPEGUS should not be used by pregnant women or by men whose female partners are pregnant. Female patients of childbearing potential and male patients with female partners of childbearing potential should not receive COPEGUS unless the patient and his/her partner are using effective contraception (two reliable forms) during therapy and for 6 months post therapy [see *Contraindications (4)*].

Ribavirin Pregnancy Registry

A Ribavirin Pregnancy Registry has been established to monitor maternal-fetal outcomes of pregnancies of female patients and female partners of male patients exposed to ribavirin during treatment and for 6 months following cessation of treatment. Healthcare providers and patients are encouraged to report such cases by calling 1-800-593-2214.

8.3 Nursing Mothers

It is not known whether ribavirin is excreted in human milk. Because many drugs are excreted in human milk and to avoid any potential for serious adverse reactions in nursing infants from ribavirin, a decision should be made either to discontinue nursing or therapy with COPEGUS, based on the importance of the therapy to the mother.

8.4 Pediatric Use

Pharmacokinetic evaluations in pediatric patients have not been performed.

Safety and effectiveness of COPEGUS have not been established in patients below the age of 5 years.

8.5 Geriatric Use

Clinical studies of COPEGUS and PEGASYS did not include sufficient numbers of subjects aged 65 or over to determine whether they respond differently from younger subjects. Specific pharmacokinetic evaluations for ribavirin in the elderly have not been performed. The risk of toxic reactions to this drug may be greater in patients with impaired renal function. The dose of COPEGUS should be reduced in patients with creatinine clearance less than or equal to 50 mL/min; and the dose of PEGASYS should be reduced in patients with creatinine clearance less than 30 mL/min [see *Dosage and Administration (2.5); Use in Specific Populations (8.7)*].

8.6 Race

A pharmacokinetic study in 42 subjects demonstrated there is no clinically significant difference in ribavirin pharmacokinetics among Black (n=14), Hispanic (n=13) and Caucasian (n=15) subjects.

8.7 Renal Impairment

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

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

Subjects with moderate (n=17) or severe (n=14) renal impairment did not tolerate 600 mg or 400 mg daily doses of COPEGUS, respectively, due to COPEGUS-related adverse reactions, mainly anemia, and exhibited 20 to 30% higher ribavirin plasma exposures (despite frequent dose modifications) compared to subjects with normal renal function (creatinine clearance greater than 80 mL/min) receiving the standard dose of COPEGUS. Discontinuation rates were higher in subjects with severe renal impairment compared to that observed in subjects with moderate renal impairment or normal renal function. Pharmacokinetic modeling and simulation indicates that a dose of 200 mg daily in patients with severe renal impairment and a dose of 200 mg daily alternating with 400 mg the following day in patients with moderate renal impairment will provide plasma ribavirin exposure similar to patients with normal renal function receiving the approved regimen of COPEGUS. These doses have not been studied in patients [see *Dosage and Administration (2.4), Use in Specific Populations (8.7), and Clinical Pharmacology (12.3)*].

Based on the pharmacokinetic and safety results from this trial, patients with creatinine clearance less than or equal to 50 mL/min should receive a reduced dose of COPEGUS; and patients with creatinine clearance less than 30 mL/min should receive a reduced dose of PEGASYS. The clinical and hematologic status of patients with creatinine clearance less than or equal to 50 mL/min receiving COPEGUS should be carefully monitored. Patients with clinically significant laboratory abnormalities or adverse reactions which are persistently severe or worsening should have therapy withdrawn. [see *Dosage and Administration (2.5), Clinical Pharmacology (12.3), and PEGASYS Package Insert*].

8.8 Hepatic Impairment

The effect of hepatic impairment on the pharmacokinetics of ribavirin following administration of COPEGUS has not been evaluated. The clinical trials of COPEGUS were restricted to patients with Child-Pugh class A disease.

8.9 Gender

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

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

8.10 Organ Transplant Recipients

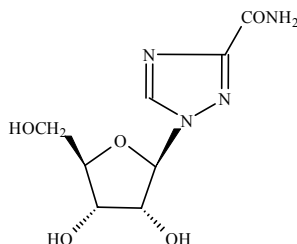
The safety and efficacy of PEGASYS and COPEGUS treatment have not been established in patients with liver and other transplantations. As with other alpha interferons, liver and renal graft rejections have been reported on PEGASYS, alone or in combination with COPEGUS [see *Adverse Reactions (6.2)*].

10 OVERDOSAGE

No cases of overdose with COPEGUS have been reported in clinical trials. Hypocalcemia and hypomagnesemia have been observed in persons administered greater than the recommended dosage of ribavirin. In most of these cases, ribavirin was administered intravenously at dosages up to and in some cases exceeding four times the recommended maximum oral daily dose.

11 DESCRIPTION

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



The empirical formula of ribavirin is C₈H₁₂N₄O₅ and the molecular weight is 244.2. Ribavirin is a white to off-white powder. It is freely soluble in water and slightly soluble in anhydrous alcohol.

COPEGUS (ribavirin) is available as a light pink to pink colored, flat, oval-shaped, film-coated tablet for oral administration. Each tablet contains 200 mg of ribavirin and the following inactive ingredients: pregelatinized starch, microcrystalline cellulose, sodium starch glycolate, cornstarch, and magnesium stearate. The coating of the tablet contains Chromatone-P[®] or Opadry[®] Pink (made by using hydroxypropyl methyl cellulose, talc, titanium dioxide, synthetic yellow iron oxide, and synthetic red iron oxide), ethyl cellulose (ECD-30), and triacetin.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

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

12.3 Pharmacokinetics

Multiple dose ribavirin pharmacokinetic data are available for HCV patients who received ribavirin in combination with peginterferon alfa-2a. Following administration of 1200 mg/day with food for 12 weeks mean \pm SD (n=39; body weight greater than 75 kg) AUC_{0-12hr} was 25,361 \pm 7110 ng·hr/mL and C_{max} was 2748 \pm 818 ng/mL. The average time to reach C_{max} was 2 hours. Trough ribavirin plasma concentrations

following 12 weeks of dosing with food were 1662 ± 545 ng/mL in HCV infected patients who received 800 mg/day (n=89), and 2112 ± 810 ng/mL in patients who received 1200 mg/day (n=75; body weight greater than 75 kg).

The terminal half-life of ribavirin following administration of a single oral dose of COPEGUS is about 120 to 170 hours. The total apparent clearance following administration of a single oral dose of COPEGUS is about 26 L/h. There is extensive accumulation of ribavirin after multiple dosing (twice daily) such that the C_{max} at steady state was four-fold higher than that of a single dose.

Effect of Food on Absorption of Ribavirin

Bioavailability of a single oral dose of ribavirin was increased by co-administration with a high-fat meal. The absorption was slowed (T_{max} was doubled) and the AUC_{0-192h} and C_{max} increased by 42% and 66%, respectively, when COPEGUS was taken with a high-fat meal compared with fasting conditions [see *Dosage and Administration (2.1) and Patient Counseling Information (17)*].

Elimination and Metabolism

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

Renal Impairment

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

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

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

12.4 Microbiology

Mechanism of Action

The mechanism by which ribavirin contributes to its antiviral efficacy in the clinic is not fully understood. Ribavirin has direct antiviral activity in tissue culture against many RNA viruses. Ribavirin increases the mutation frequency in the genomes of several RNA viruses and ribavirin triphosphate inhibits HCV polymerase in a biochemical reaction.

Antiviral Activity in Cell Culture

In the stable HCV cell culture model system (HCV replicon), ribavirin inhibited autonomous HCV RNA replication with a 50% effective concentration (EC_{50}) value of 11-21 mcM. In the same model, PEG-IFN α -2a also inhibited HCV RNA replication, with an EC_{50} value of 0.1-3 ng/mL. The combination of PEG-IFN α -2a and ribavirin was more effective at inhibiting HCV RNA replication than either agent alone.

Resistance

Different HCV genotypes display considerable clinical variability in their response to PEG-IFN- α and ribavirin therapy. Viral genetic determinants associated with the variable response have not been definitively identified.

Cross-resistance

Cross-resistance between IFN α and ribavirin has not been observed.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis

In a p53 (+/-) mouse carcinogenicity study up to the maximum tolerated dose of 100 mg/kg/day, ribavirin was not oncogenic. Ribavirin was also not oncogenic in a rat 2-year carcinogenicity study at doses up to the maximum tolerated dose of 60 mg/kg/day. On a body surface area basis, these doses are approximately 0.5 and 0.6 times the maximum recommended daily human dose of ribavirin, respectively.

Mutagenesis

Ribavirin demonstrated mutagenic activity in the in vitro mouse lymphoma assay. No clastogenic activity was observed in an in vivo mouse micronucleus assay at doses up to 2000 mg/kg. However, results from studies published in the literature show clastogenic activity in the in vivo mouse micronucleus assay at oral doses up to 2000 mg/kg. A dominant lethal assay in rats was negative, indicating that if mutations occurred in rats they were not transmitted through male gametes. However, potential carcinogenic risk to humans cannot be excluded.

Impairment of Fertility

In a fertility study in rats, ribavirin showed a marginal reduction in sperm counts at the dose of 100 mg/kg/day with no effect on fertility. Upon cessation of treatment, total recovery occurred after 1 spermatogenesis cycle. Abnormalities in sperm were observed in studies in mice designed to evaluate the time course and reversibility of ribavirin-induced testicular degeneration at doses of 15 to 150 mg/kg/day (approximately 0.1 to 0.8 times the maximum recommended daily human dose of ribavirin) administered for 3 to 6 months. Upon cessation of treatment, essentially total recovery from ribavirin-induced testicular toxicity was apparent within 1 or 2 spermatogenic cycles.

Female patients of childbearing potential and male patients with female partners of childbearing potential should not receive COPEGUS unless the patient and his/her partner are using effective contraception (two reliable forms). Based on a multiple dose half-life ($t_{1/2}$) of ribavirin of 12 days, effective contraception must be utilized for 6 months post therapy (i.e., 15 half-lives of clearance for ribavirin).

No reproductive toxicology studies have been performed using PEGASYS in combination with COPEGUS. However, peginterferon alfa-2a and ribavirin when administered separately, each has adverse effects on reproduction. It should be assumed that the effects produced by either agent alone would also be caused by the combination of the two agents.

13.2 Animal Toxicology

In a study in rats, it was concluded that dominant lethality was not induced by ribavirin at doses up to 200 mg/kg for 5 days (up to 1.7 times the maximum recommended human dose of ribavirin).

Long-term studies in the mouse and rat (18 to 24 months; dose 20 to 75, and 10 to 40 mg/kg/day, respectively, approximately 0.1 to 0.4 times the maximum daily human dose of ribavirin) have demonstrated a relationship between chronic ribavirin exposure and an increased incidence of vascular lesions (microscopic hemorrhages) in mice. In rats, retinal degeneration occurred in controls, but the incidence was increased in ribavirin-treated rats.

14 CLINICAL STUDIES

14.1 Chronic Hepatitis C Patients

Adult Patients

The safety and effectiveness of PEGASYS in combination with COPEGUS for the treatment of hepatitis C virus infection were assessed in two randomized controlled clinical trials. All patients were adults, had compensated liver disease, detectable hepatitis C virus, liver biopsy diagnosis of chronic hepatitis, and were previously untreated with interferon. Approximately 20% of patients in both studies had compensated cirrhosis (Child-Pugh class A). Patients coinfecting with HIV were excluded from these studies.

In Study NV15801, patients were randomized to receive either PEGASYS 180 mcg subcutaneous once weekly with an oral placebo, PEGASYS 180 mcg once weekly with COPEGUS 1000 mg by mouth (body weight less than 75 kg) or 1200 mg by mouth (body weight greater than or equal to 75 kg) or interferon alfa-2b 3 MIU subcutaneous three times a week plus ribavirin 1000 mg or 1200 mg by mouth. All patients received 48 weeks of therapy followed by 24 weeks of treatment-free follow-up. COPEGUS or placebo treatment assignment was blinded. Sustained virological response was defined as undetectable (less than 50 IU/mL) HCV RNA on or after study week 68. PEGASYS in combination with COPEGUS resulted in a higher SVR compared to PEGASYS alone or interferon alfa-2b and ribavirin (**Table 9**). In all treatment arms, patients with viral genotype 1, regardless of viral load, had a lower response rate to PEGASYS in combination with COPEGUS compared to patients with other viral genotypes.

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

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

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

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

Sustained Virologic Response (SVR) and HCV Genotype

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

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

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

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

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

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

Pediatric Patients

Previously untreated pediatric subjects 5 through 17 years of age (55% less than 12 years old) with chronic hepatitis C, compensated liver disease and detectable HCV RNA were treated with COPEGUS approximately 15 mg/kg/day plus PEGASYS 180 mcg/1.73 m² x body surface area once weekly for 48 weeks. All subjects were followed for 24 weeks post-treatment. Sustained virological response (SVR) was defined as undetectable (less than 50 IU/mL) HCV RNA on or after study week 68. A total of 114 subjects were randomized to receive either combination treatment of COPEGUS plus PEGASYS or PEGASYS monotherapy; subjects failing PEGASYS monotherapy at 24 weeks or later could receive open-label COPEGUS plus PEGASYS. The initial randomized arms were balanced for demographic factors; 55 subjects received initial combination treatment of COPEGUS plus PEGASYS and 59 received PEGASYS plus placebo; in the overall intent-to-treat population, 45% were female, 80% were Caucasian, and 81% were infected with HCV genotype 1. The SVR results are summarized in Table 11.

Table 11 Sustained Virologic Response (Study NV17424)

	PEGASYS 180 mcg/1.73 m ² x BSA + COPEGUS 15 mg/kg* (N=55)	PEGASYS 180 mcg/1.73 m ² x BSA + Placebo* (N=59)
All HCV genotypes**	29 (53%)	12 (20%)
HCV genotype 1	21/45 (47%)	8/47 (17%)
HCV non-genotype 1***	8/10 (80%)	4/12 (33%)

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

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

***Includes HCV genotypes 2,3 and others

14.2 Other Treatment Response Predictors

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

In studies NV15801 and NV15942, lack of early virologic response by 12 weeks (defined as HCV RNA undetectable or greater than 2 log₁₀ lower than baseline) was grounds for discontinuation of treatment. Of patients who lacked an early viral response by 12 weeks and completed a recommended course of therapy despite a protocol-defined option to discontinue therapy, 5/39 (13%) achieved an SVR. Of patients who lacked an early viral response by 24 weeks, 19 completed a full course of therapy and none achieved an SVR.

14.3 Chronic Hepatitis C/HIV Coinfected Patients

In Study NR15961, patients with CHC/HIV were randomized to receive either PEGASYS 180 mcg subcutaneous once weekly plus an oral placebo, PEGASYS 180 mcg once weekly plus COPEGUS 800 mg by mouth daily or interferon alfa-2a, 3 MIU subcutaneous three times a week plus COPEGUS 800 mg by mouth daily. All patients received 48 weeks of therapy and sustained virologic response (SVR) was assessed at 24 weeks of treatment-free follow-up. COPEGUS or placebo treatment assignment was blinded in the PEGASYS treatment arms. All patients were adults, had compensated liver disease, detectable hepatitis C virus, liver biopsy diagnosis of chronic hepatitis C, and were previously untreated with interferon. Patients also had CD4+ cell count greater than or equal to 200 cells/mm³ or CD4+ cell count greater than or equal to 100 cells/mm³ but less than 200 cells/mm³ and HIV-1 RNA less than 5000 copies/mL, and stable status of HIV. Approximately 15% of patients in the study had cirrhosis. Results are shown in **Table 12**.

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

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

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

Of the patients who did not demonstrate either undetectable HCV RNA or at least a 2 log₁₀ reduction from baseline in HCV RNA titer by 12 weeks of PEGASYS and COPEGUS combination therapy, 2% (2/85) achieved an SVR.

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

16 HOW SUPPLIED/STORAGE AND HANDLING

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

Storage and Handling

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

17 PATIENT COUNSELING INFORMATION

- “See FDA-approved patient labeling (Medication Guide)”

Pregnancy

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

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

Anemia

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

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

Patients should be advised to take COPEGUS with food.

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

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

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

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

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

MEDICATION GUIDE

COPEGUS® (Co-PEG-UHS)

(ribavirin)

Tablets

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

Also read the Medication Guide for PEGASYS (peginterferon alfa-2a).

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

1. **You should not take COPEGUS alone to treat chronic hepatitis C infection.** COPEGUS should be used with PEGASYS to treat chronic hepatitis C infection.
2. **COPEGUS may cause you to have a blood problem (hemolytic anemia) that can worsen any heart problems you have, and cause you to have a heart attack or die.** Tell your healthcare provider if you have ever had any heart problems. COPEGUS may not be right for you. If you have chest pain while you take COPEGUS, get emergency medical attention right away.
3. **COPEGUS may cause birth defects or death of your unborn baby.** If you are pregnant or your sexual partner is pregnant, do not take COPEGUS. You or your sexual partner should not become pregnant while you take COPEGUS and for 6 months after treatment is over. You must use two forms of birth control when you take COPEGUS and for the 6 months after treatment.
 - Females must have a pregnancy test before starting COPEGUS, every month while treated with COPEGUS, and every month for the 6 months after treatment with COPEGUS.
 - **If you or your female sexual partner becomes pregnant** while taking COPEGUS or within 6 months after you stop taking COPEGUS, tell your healthcare provider right away. You or your healthcare provider should contact the **Ribavirin Pregnancy Registry by calling 1-800-593-2214**. The Ribavirin Pregnancy Registry collects information about what happens to mothers and their babies if the mother takes COPEGUS while she is pregnant.

What is COPEGUS?

COPEGUS is a prescription medicine used with another medicine called PEGASYS (peginterferon alfa-2a) to treat chronic (lasting a long time) hepatitis C infection in people 5 years and older whose liver still works normally, and who have not been treated before with a medicine called an interferon alpha. It is not known if COPEGUS is safe and will work in children under 5 years of age.

Who should not take COPEGUS?

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

Do not take COPEGUS if you:

- **have certain types of hepatitis** caused by your immune system attacking your liver (autoimmune hepatitis)
- **have certain blood disorders, such as thalassemia major or sickle-cell anemia (hemoglobinopathies)**
- **take didanosine (Videx or Videx EC)**

Talk to your healthcare provider before starting treatment with COPEGUS if you have any of these medical conditions.

What should I tell my healthcare provider before taking COPEGUS?

Before you take COPEGUS, tell your healthcare provider if you have or have had:

- **treatment for hepatitis C that did not work for you**
- **serious allergic reactions to COPEGUS or to any of the ingredients in COPEGUS.** See the end of this Medication Guide for a list of ingredients.
- **breathing problems.** COPEGUS may cause or worsen your breathing problems you already have.
- **vision problems.** COPEGUS may cause eye problems or worsen eye problems you already have. You should have an eye exam before you start treatment with COPEGUS.
- **certain blood disorders such as anemia**
- **high blood pressure, heart problems or have had a heart attack.** Your healthcare provider should test your blood and heart before you start treatment with COPEGUS.

- **thyroid problems**
- **diabetes.** COPEGUS and PEGASYS combination therapy may make your diabetes worse or harder to treat.
- **liver problems** other than hepatitis C virus infection
- **human immunodeficiency virus (HIV) or other immunity problems**
- **mental health problems**, including depression or thoughts of suicide
- **kidney problems**
- **an organ transplant**
- **drug addiction or abuse**
- **infection with hepatitis B virus**
- **any other medical condition**
- **are breast feeding.** It is not known if COPEGUS passes into your breast milk. You and your healthcare provider should decide if you will take COPEGUS or breast-feed.

Tell your healthcare provider about all the medicines you take, including prescription and non-prescription medicines, vitamins and herbal supplements. Some medicines can cause serious side effects if taken while you also take COPEGUS. Some medicines may affect how COPEGUS works or COPEGUS may affect how your other medicines work.

Especially tell your healthcare provider if you take any medicines to treat HIV, including didanosine (Videx or Videx EC), or if you take azathioprine (Imuran or Azasan).

Know the medicines you take. Keep a list of them to show your healthcare provider or pharmacist when you get a new medicine.

How should I take COPEGUS?

- Take COPEGUS exactly as your healthcare provider tells you. Your healthcare provider will tell you how much COPEGUS to take and when to take it. For children 5 years of age and older your healthcare provider will prescribe the dose of COPEGUS based on weight.
- Take COPEGUS with food.
- If you miss a dose of COPEGUS, take the missed dose as soon as possible during the same day. Do not double the next dose. If you have questions about what to do, call your healthcare provider.
- If you take too much COPEGUS, call your healthcare provider or local Poison Control Center right away, or go the nearest hospital emergency room right away.
- Your healthcare provider should do blood tests before you start treatment with COPEGUS, at weeks 2 and 4 of treatment, and then as needed to see how well you are tolerating treatment and to check for side effects. Your healthcare provider may change your dose of COPEGUS based on blood test results or side effects you may have.
- If you have heart problems, your healthcare provider should check your heart by doing an electrocardiogram before you start treatment with COPEGUS, and if needed during treatment.

What should I avoid while taking COPEGUS?

- **COPEGUS can make you feel tired, dizzy, or confused. You should not drive or operate machinery if you have any of these symptoms.**
- **Do not drink alcohol**, including beer, wine, and liquor. This may make your liver disease worse.

What are the possible side effects of COPEGUS?

COPEGUS may cause serious side effects including:

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

- **Swelling and irritation of your pancreas (pancreatitis).** You may have stomach pain, nausea, vomiting or diarrhea.

- **Severe allergic reactions.** Symptoms may include hives, wheezing, trouble breathing, chest pain, swelling of your mouth, tongue, or lips, or severe rash.
- **Serious breathing problems.** Difficulty breathing may be a sign of a serious lung infection (pneumonia) that can lead to death.
- **Serious eye problems** that may lead to vision loss or blindness.
- **Liver problems.** Some people may get worsening of liver function. Tell your healthcare provider right away if you have any of these symptoms: stomach bloating, confusion, brown urine, and yellow eyes.
- **Severe depression**
- **Suicidal thoughts and attempts**
- **Effect on growth in children.** Children can experience a delay in weight gain and height increase while being treated with PEGASYS and COPEGUS. Catch-up in growth happens after treatment stops, but some children may not reach the height that they were expected to have before treatment. Talk to your healthcare provider if you are concerned about your child's growth during treatment with PEGASYS and COPEGUS.

Call your healthcare provider or get medical help right away if you have any of the symptoms listed above. These may be signs of a serious side effect of COPEGUS treatment.

Common side effects of COPEGUS taken with PEGASYS include:

- flu-like symptoms-feeling tired, headache, shaking along with high temperature (fever), and muscle or joint aches
- mood changes, feeling irritable, anxiety, and difficulty sleeping
- loss of appetite, nausea, vomiting, and diarrhea
- hair loss
- itching

Tell your healthcare provider about any side effect that bothers you or that does not go away.

These are not all the possible side effects of COPEGUS treatment. For more information, ask your healthcare provider or pharmacist.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

You may also report side effects to Genentech at 1-888-835-2555.

How should I store COPEGUS?

- Store COPEGUS tablets between 59°F and 86°F (15°C and 30°C).
- Keep the bottle tightly closed.

Keep COPEGUS and all medicines out of the reach of children.

General information about the safe and effective use of COPEGUS

It is not known if treatment with COPEGUS in combination with PEGASYS will prevent an infected person from spreading the hepatitis C virus to another person while on treatment.

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

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

What are the ingredients in COPEGUS?

Active Ingredient: ribavirin

Inactive Ingredients: The core of the tablet contains pregelatinized starch, microcrystalline cellulose, sodium starch glycolate, cornstarch, and magnesium stearate. The coating of the tablet contains Chromatone-P or Opadry Pink (made by using hydroxypropyl methyl cellulose, talc, titanium dioxide, synthetic yellow iron oxide, and synthetic red iron oxide), ethyl cellulose (ECD-30), and triacetin.

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

MG Revised: August 2011

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HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use PEGASYS safely and effectively. See full prescribing information for PEGASYS.

PEGASYS® (peginterferon alfa-2a)
Solution for Subcutaneous Injection
Initial U.S. Approval: 2002

WARNING: RISK OF SERIOUS DISORDERS AND RIBAVIRIN ASSOCIATED EFFECTS

See full prescribing information for complete boxed warning.

- May cause or aggravate fatal or life-threatening neuropsychiatric, autoimmune, ischemic, and infectious disorders. Monitor closely and withdraw therapy with persistently severe or worsening signs or symptoms of the above disorders (5)

Use with Ribavirin

- Ribavirin may cause birth defects and fetal death; avoid pregnancy in female patients and female partners of male patients (5.1, 8.1)

RECENT MAJOR CHANGES

Boxed Warning	02/2011
Indications and Usage, Chronic Hepatitis C (1.1)	08/2011
Dosage and Administration	
Preparation and Administration (2.8)	02/2011
Renal Impairment (2.5)	08/2011
Chronic Hepatitis C (2.1)	08/2011
Dose Modifications (2.4)	08/2011
Contraindications (4)	02/2011
Warnings and Precautions	
Use with Ribavirin including COPEGUS (5.1)	02/2011
Hepatic Failure and Hepatitis Exacerbations (5.9)	02/2011
Impact on Growth in Pediatric Patients (5.15)	08/2011
Laboratory Tests (5.17)	08/2011

INDICATIONS AND USAGE

PEGASYS is an antiviral indicated for:

Treatment of Chronic Hepatitis C (CHC) in patients 5 years of age and older with compensated liver disease not previously treated with interferon alpha, in patients with histological evidence of cirrhosis and compensated liver disease, and in adults with CHC/HIV coinfection and CD4 count greater than 100 cells/mm³ (1.1)

- Combination Therapy with COPEGUS is recommended unless patient has contraindication to or significant intolerance to COPEGUS (1.1)

PEGASYS Monotherapy is indicated for:

- Treatment of adult patients with HBeAg positive and HBeAg negative chronic hepatitis B who have compensated liver disease and evidence of viral replication and liver inflammation (1.2)

DOSAGE AND ADMINISTRATION

- PEGASYS is administered by subcutaneous injection
- In adult patients with CHC or chronic hepatitis B, PEGASYS is dosed as 180 mcg per week and the length of treatment depends on indication, genotype, and whether it is administered with COPEGUS (2.2, 2.3, 2.4)
- In pediatric patients with CHC, PEGASYS is dosed as 180 mcg/1.73 m² x BSA per week, in combination with COPEGUS, and the length of treatment depends on genotype (2.1)
- Dose reduction is recommended in patients experiencing certain laboratory abnormalities, adverse reactions or renal impairment (2.5, 12.3)

DOSAGE FORMS AND STRENGTHS

- 180 mcg/mL Vial for single use (3)
- 180 mcg/0.5 mL Prefilled Syringe for single use (3)

CONTRAINDICATIONS

- Autoimmune hepatitis (4)
- Hepatic decompensation in patients with cirrhosis (4)
- Use in neonates/infants (4)
- Known hypersensitivity reactions such as urticaria, angioedema, bronchoconstriction and anaphylaxis to alpha interferons or any component of the product (4, 5)

Additional contraindications for use with ribavirin:

- Pregnant women and men whose female partners are pregnant in combination therapy with COPEGUS (4, 8.1)
- Hemoglobinopathies (e.g., thalassemia major, sickle cell disease) (4)
- Coadministration with didanosine

WARNINGS AND PRECAUTIONS

Use with Ribavirin

- Birth defects and fetal death: patients must have a negative pregnancy test prior to therapy, use 2 or more forms of contraception, and have monthly pregnancy tests (5.1)
 - Hemolytic anemia (5.1)
 - History of significant or unstable cardiac disease (5.3)
- Patients exhibiting the following events should be closely monitored and may require dose reduction or discontinuation of therapy:
- Neuropsychiatric events (5.2)
 - Autoimmune and endocrine disorders (including thyroid disorders; hyperglycemia) (5.5, 5.6)
 - Ophthalmologic disorders (5.7)
 - Cerebrovascular disorders (5.8)
 - Hepatic decompensation in cirrhotic patients. Exacerbation of hepatitis during hepatitis B treatment (5.9)
 - Pulmonary disorders (5.10)
 - Infections (bacterial, viral, fungal) (5.11)
 - Bone marrow suppression (5.4)
 - Colitis and pancreatitis (5.12, 5.13)
 - Hypersensitivity and serious skin reactions including Stevens-Johnson Syndrome (5.14)
 - Growth impairment with combination therapy in pediatric patients (5.15)
 - Peripheral neuropathy when used in combination with telbivudine (5.16)

ADVERSE REACTIONS

The most common adverse reactions (incidence greater than 40%) are fatigue/asthenia, pyrexia, myalgia, and headache. (6.1)

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

To report SUSPECTED ADVERSE REACTIONS, contact Genentech at 1-888-835-2555 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

DRUG INTERACTIONS

- Drugs metabolized by CYP1A2: monitor for increased serum levels of theophylline and adjust dose accordingly (7.2)
- Methadone: monitor for signs and symptoms of methadone toxicity (7.3)
- Nucleoside analogues: closely monitor for toxicities and dose reduce or discontinue PEGASYS/COPEGUS or both should event worsen (7.4)
- Zidovudine: monitor for worsening neutropenia and/or anemia with PEGASYS/COPEGUS (7.4)
- Azathioprine (7.4)

USE IN SPECIFIC POPULATIONS

- Ribavirin Pregnancy Registry (8.1)
- Pediatrics: Safety and efficacy in pediatric patients less than 5 years old have not been established (8.4)
- Geriatric patients: Neuropsychiatric, cardiac, and systemic (flu-like) adverse reactions may be more severe (8.5)
- Hepatic patients: Clinical status and hepatic function should be closely monitored and treatment should be immediately discontinued if decompensation occurs (8.6)
- Renal Impairment: PEGASYS dose should be reduced in patients with creatinine clearance less than 30 mL/min (2.5, 8.7)
- Organ Transplant: safety and efficacy have not been studied (8.8)
- Chronic Hepatitis B: safety and efficacy have not been established in hepatitis B patients coinfecting with HCV or HIV (8.9)

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved Medication Guide.

Revised: 08/2011

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FULL PRESCRIBING INFORMATION

WARNING: RISK OF SERIOUS DISORDERS AND RIBAVIRIN-ASSOCIATED EFFECTS

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 Precautions (5.2, 5.5, 5.8, 5.11, 5.14, 5.16), Adverse Reactions (6.1) and Nonclinical Toxicology (13.1)*].

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. [See *COPEGUS Package Insert for additional information and other WARNINGS.*]

1 INDICATIONS AND USAGE

1.1 Chronic Hepatitis C

PEGASYS, peginterferon alfa-2a, alone or in combination with COPEGUS, is indicated for the treatment of patients 5 years of age and older with chronic hepatitis C (CHC) virus infection who have compensated liver disease and have not been previously treated with interferon alpha. Efficacy has been demonstrated in subjects with compensated liver disease and histological evidence of cirrhosis (Child-Pugh class A) and in adult subjects with clinically stable HIV disease and CD4 count greater than 100 cells/mm³.

The following points should be considered when initiating therapy with PEGASYS and COPEGUS:

- Use of PEGASYS monotherapy is not recommended for treatment of CHC unless a patient has a contraindication to or significant intolerance to ribavirin. Combination therapy provides substantially better response rates than monotherapy [see *Clinical Studies (14)*].
- Safety and efficacy have not been demonstrated for treatment longer than 48 weeks.
- The safety and efficacy have not been established in liver or other organ transplant recipients [see *Use in Specific Populations (8.7)*].

1.2 Chronic Hepatitis B

PEGASYS is indicated for the treatment of adult patients with HBeAg positive and HBeAg negative chronic hepatitis B who have compensated liver disease and evidence of viral replication and liver inflammation.

2 DOSAGE AND ADMINISTRATION

PEGASYS is administered by subcutaneous injection in the abdomen or thigh. See COPEGUS Package Insert for all instructions regarding COPEGUS dosing and administration.

2.1 Chronic Hepatitis C

Adult Patients

PEGASYS Monotherapy:

The recommended dose of PEGASYS monotherapy for chronic hepatitis C is 180 mcg (1 mL vial or 0.5 mL prefilled syringe) once weekly for 48 weeks.

PEGASYS/COPEGUS Combination Therapy:

The recommended dose of PEGASYS when used in combination with ribavirin for chronic hepatitis C is 180 mcg (1 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 1**).

The daily dose of COPEGUS is 800 mg to 1200 mg administered orally in two divided doses.

COPEGUS should be taken with food.

Table 1 PEGASYS and COPEGUS Dosing Recommendations

Hepatitis C virus Genotype	PEGASYS Dose (once weekly)	COPEGUS Dose (daily)	Duration
Genotypes 1, 4	180 mcg	<75 kg = 1000 mg	48 weeks
		≥75 kg = 1200 mg	48 weeks
Genotypes 2, 3	180 mcg	800 mg	24 weeks

Genotypes 2 and 3 showed no increased response to treatment beyond 24 weeks (see **Table 13**). Data on genotypes 5 and 6 are insufficient for dosing recommendations.

Pediatric Patients

PEGASYS/COPEGUS Combination Therapy:

PEGASYS is administered as 180 mcg/1.73 m² x BSA subcutaneously once weekly, to a maximum dose of 180 mcg, and should be given in combination with COPEGUS. The recommended treatment duration for patients with genotype 2 or 3 is 24 weeks and for other genotypes is 48 weeks.

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

Table 2 COPEGUS Dosing Recommendations for Pediatric Patients

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

*approximately 15 mg/kg/day

2.2 Chronic Hepatitis C with HIV Coinfection

Adult Patients

PEGASYS Monotherapy:

The recommended dose of PEGASYS monotherapy for chronic hepatitis C in patients coinfecting with HIV is 180 mcg (1 mL vial or 0.5 mL prefilled syringe) once weekly for 48 weeks.

PEGASYS/COPEGUS Combination Therapy:

The recommended dose when used in combination with ribavirin is PEGASYS 180 mcg once weekly and COPEGUS 800 mg orally daily given in two divided doses for a total of 48 weeks, regardless of genotype.

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

2.3 Chronic Hepatitis B

Adult Patients

PEGASYS Monotherapy:

The recommended dose of PEGASYS monotherapy for hepatitis B is 180 mcg (1 mL vial or 0.5 mL prefilled syringe) once weekly for 48 weeks.

2.4 Dose Modifications

If severe adverse reactions or laboratory abnormalities develop during combination PEGASYS/COPEGUS therapy, the dose should be modified until the adverse reactions abate. If intolerance persists after dose adjustment, PEGASYS/COPEGUS therapy should be discontinued. **Table 3, Table 4, Table 5, and Table 6** provide guidelines for dose modifications and discontinuation of PEGASYS/COPEGUS based on laboratory abnormalities, patient's depression status, and cardiac status.

Adult Patients

When dose modification of PEGASYS is required for adverse reactions (clinical and/or laboratory), initial dose reduction to 135 mcg (which is 0.75 mL for the vials or adjustment to the corresponding graduation mark for the syringes) is recommended. Dose reduction to 90 mcg (which is 0.5 mL for the vials or adjustment to the corresponding graduation mark for the syringes) may be needed if the adverse reaction persists or recurs. Following improvement of the adverse reaction, re-escalation of the dose may be considered [*see Warnings and Precautions (5) and Adverse Reactions (6)*].

Table 3 PEGASYS Hematological Dose Modification Guidelines

Laboratory Values	Recommended Dose
ANC <750 cells/mm ³	Reduce to 135 mcg
ANC <500 cells/mm ³	Discontinue treatment until ANC values return to more than 1000 cells/mm ³ . Reinstigate at 90 mcg and monitor ANC.
Platelet <50,000 cells/mm ³	Reduce to 90 mcg
Platelet <25,000 cells/mm ³	Discontinue treatment

Table 4 Guidelines for Modification or Discontinuation of PEGASYS and for Scheduling Visits for Adults Patients with Depression

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

Pediatric Patients

If toxicities occur which may be related to PEGASYS or COPEGUS administration, the dose of one or both drugs can be modified. Additionally, COPEGUS or PEGASYS plus COPEGUS combination therapy can be discontinued. COPEGUS should never be given as monotherapy. Recommendations for dose modifications in pediatric patients for toxicities associated with PEGASYS administration are presented in **Table 5**.

When dose modification is required for moderate to severe adverse reactions (clinical or laboratory), modification to 135 mcg/1.73 m² x BSA is generally adequate. However, in some cases, dose modification to 90 mcg/1.73 m² x BSA or 45 mcg/1.73 m² x BSA may be needed. Up to 3 dose modifications for toxicity can be made before discontinuation is considered. These modifications apply to pediatric patients with depression, who can be managed similar to the algorithm for adult patients outlined in **Table 4**.

Guidelines for dose modification based on neutropenia, increased ALT levels, and decreased platelet counts for pediatric patients are provided in **Table 5**.

Table 5 PEGASYS Dose Modification for Neutropenia, Increased ALT and Decreased Platelets in Pediatric Patients

	PEGASYS Dose Modification
Neutropenia	<p>750-999 cells/mm³: Week 1-2 - immediate modification to 135 mcg/1.73 m² x BSA; Week 3-48: no modification.</p> <p>500-749 cells/mm³: Week 1-2 - delay or hold dose until >750 cells/mm³ then resume dose with a modification to 135 mcg/1.73 m² x BSA, assess weekly x 3 to verify WBC's >750 cells/mm³; Week 3-48 - immediate modification to 135 mcg/1.73 m² x BSA.</p> <p>250-499 cells/mm³: Week 1-2 - delay or hold dose until >750 cells/mm³ then resume dose with a modification to 90 mcg/1.73 m² x BSA; Week 3-48 - delay or hold dose until >750 cells/mm³ then resume dose with a modification to 135 mcg/1.73 m² x BSA.</p> <p><250 cells/mm³ (or febrile neutropenia) discontinue treatment.</p>
Increased alanine transaminase (ALT)	<p>For persistent or increasing elevations ≥5 but <10 x ULN, modify dose with a modification to 135 mcg/1.73 m² x BSA. Monitor weekly, further modifying dose if necessary, until stable or ALT level decreases</p> <p>For persistent ALT values ≥10 x ULN discontinue treatment.</p>
Decreased platelet count	<p>Platelet <50,000 cells/mm³: Modify dose to 90 mcg/1.73 m² x BSA</p>

COPEGUS Dose Modifications

See COPEGUS Package Insert for all instructions regarding COPEGUS dosing and administration.

Adult and Pediatric Patients

Table 6 COPEGUS Dose Modification Guidelines in Adults and Pediatrics

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

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

Adult Patients

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

Pediatric Patients

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

2.5 Renal Impairment

In patients with CrCL less than 30 mL/min, including patients with end-stage renal disease requiring hemodialysis, dose reduction to 135 mcg PEGASYS is recommended. Signs and symptoms of interferon toxicity should be closely monitored. If severe adverse reactions or laboratory abnormalities develop, the dose of PEGASYS may be reduced to 90 mcg until the adverse reactions abate. If intolerance persists after dose adjustment, PEGASYS/COPEGUS therapy should be discontinued.

Renal function should be evaluated in all patients on COPEGUS. The dose of COPEGUS should be reduced for patients with creatinine clearance less than or equal to 50 mL/min [see *Clinical Pharmacology (12.3) and COPEGUS Package Insert*].

Table 7 Dose Modification for Renal Impairment

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

No data are available for pediatric subjects with renal impairment.

2.6 Liver Function

Adult Patients

If ALT increases are progressive despite dose reduction or accompanied by increased bilirubin or evidence of hepatic decompensation, therapy should be immediately discontinued.

In chronic hepatitis C patients with progressive ALT increases above baseline values, the dose of PEGASYS should be reduced to 135 mcg and more frequent monitoring of liver function should be performed. After PEGASYS dose reduction or withholding, therapy can be resumed after ALT flares subside.

In chronic hepatitis B patients with elevations in ALT (greater than 5 x ULN), more frequent monitoring of liver function should be performed and consideration should be given to either reducing the dose of PEGASYS to 135 mcg or temporarily discontinuing treatment. After PEGASYS dose reduction or withholding, therapy can be resumed after ALT flares subside.

In adult patients with persistent, severe (ALT greater than 10 times above the upper limit of normal) hepatitis B flares, consideration should be given to discontinuation of treatment.

2.7 Discontinuation of Dosing

Discontinuation of therapy should be considered if the patient has failed to demonstrate at least a 2 log₁₀ reduction from baseline in HCV RNA titer by 12 weeks of therapy or undetectable HCV RNA after 24 weeks of therapy [see *Clinical Studies (14)*].

During treatment, patients' clinical status and hepatic function should be closely monitored, and PEGASYS treatment should be immediately discontinued if decompensation is observed [see *Contraindications (4)*].

Patients should be monitored for serious adverse events, some of which may become life threatening. Patients with persistently severe or worsening signs or symptoms should have their therapy withdrawn [see *Boxed Warning*].

2.8 Preparation and Administration

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 has been trained in proper injection technique [see *illustrated FDA Approved 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.

Discard unused portion of PEGASYS in single-use vials or prefilled syringes in excess of the labeled volume. Use only one vial or prefilled syringe per dose.

3 DOSAGE FORMS AND STRENGTHS

- Vial for single use: 180 mcg/mL
- Prefilled Syringe for single use: 180 mcg/0.5 mL

4 CONTRAINDICATIONS

PEGASYS is contraindicated in patients with:

- Patients with known hypersensitivity reactions such as urticaria, angioedema, bronchoconstriction, anaphylaxis, or Stevens-Johnson syndrome to alpha interferons, including PEGASYS, or any of its components.
- Autoimmune hepatitis
- Hepatic decompensation (Child-Pugh score greater than 6 [class B and C]) in cirrhotic patients before treatment
- Hepatic decompensation with Child-Pugh score greater than or equal to 6 in cirrhotic CHC patients coinfecting with HIV before 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 which are sometimes fatal in neonates and infants.

PEGASYS/COPEGUS combination therapy is additionally contraindicated in:

- Women who are pregnant
- Men whose female partners are pregnant
- Patients with known hypersensitivity (urticaria, angioedema, bronchoconstriction, and anaphylaxis) to COPEGUS or to any component of the tablet
- Patients with hemoglobinopathies (e.g., thalassemia major, sickle-cell anemia)
- Combination with didanosine. Reports of fatal hepatic failure, as well as peripheral neuropathy, pancreatitis, and symptomatic hyperlactatemia/lactic acidosis have been reported in clinical trials [*see Drug Interactions (7.4)*].

5 WARNINGS AND PRECAUTIONS

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*].

5.1 Use with Ribavirin including COPEGUS

Pregnancy

COPEGUS 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 6 months after treatment has concluded. Routine monthly pregnancy tests must be performed during this time [*see Boxed Warning, Contraindications (4), Patient Counseling Information (17) and COPEGUS Package Insert*].

Anemia

The primary toxicity of COPEGUS is hemolytic anemia. Hemoglobin less than 10 g/dL was observed in approximately 13% of COPEGUS and PEGASYS treated subjects in chronic hepatitis C clinical trials. 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. Caution should be exercised in initiating treatment in any patient with baseline risk of severe anemia (e.g., spherocytosis, history of GI bleeding).

Fatal and nonfatal myocardial infarctions have been reported in patients with anemia caused by COPEGUS. Patients should be assessed for underlying cardiac disease before initiation of COPEGUS therapy. Patients with pre-existing cardiac disease should have electrocardiograms administered before treatment, and should be appropriately monitored during therapy. If there is any deterioration of cardiovascular status, therapy should be suspended or discontinued [see *Dosage and Administration (2.6)*]. 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*].

5.2 Neuropsychiatric

Life-threatening or fatal neuropsychiatric reactions may manifest in all patients receiving therapy with PEGASYS and include suicide, suicidal ideation, homicidal 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 all 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 (6.1) and Dosage and Administration (2.5)*].

5.3 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 receive PEGASYS/COPEGUS [see *Warnings and Precautions (5.15) and COPEGUS Package Insert*].

5.4 Bone Marrow Suppression

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 *Warnings and Precautions (5.1)*].

PEGASYS/COPEGUS should be used with caution in patients with baseline neutrophil counts less than $1,500 \text{ cells/mm}^3$, with baseline platelet counts less than $90,000 \text{ cells/mm}^3$ or baseline hemoglobin less than 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 (2.6)*].

Severe neutropenia and thrombocytopenia occur with a greater incidence in HIV coinfecting patients than mono-infected patients and may result in serious infections or bleeding [see *Adverse Reactions (6.1)*].

Pancytopenia (marked decreases in RBCs, neutrophils and platelets) and bone marrow suppression have been reported in the literature to occur within 3 to 7 weeks after the concomitant administration of pegylated interferon/ribavirin and azathioprine. In this limited number of patients (n=8), myelotoxicity was reversible within 4 to 6 weeks upon withdrawal of both HCV antiviral therapy and concomitant azathioprine and did not recur upon reintroduction of either treatment alone. PEGASYS, COPEGUS, and azathioprine should be discontinued for pancytopenia, and pegylated interferon/ribavirin should not be re-introduced with concomitant azathioprine [see *Drug Interactions (7)*].

5.5 Autoimmune Disorders

Development or exacerbation of autoimmune disorders including myositis, hepatitis, thrombotic thrombocytopenic purpura, idiopathic thrombocytopenic purpura, 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.

5.6 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.

5.7 Ophthalmologic Disorders

Decrease or loss of vision, retinopathy including macular edema, retinal artery or vein thrombosis, retinal hemorrhages and cotton wool spots, optic neuritis, papilledema and serous retinal detachment 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 (e.g., 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.

5.8 Cerebrovascular Disorders

Ischemic and hemorrhagic cerebrovascular events have been observed in patients treated with interferon alfa-based therapies, including PEGASYS. Events occurred in patients with few or no reported risk factors for stroke, including patients less than 45 years of age. Because these are spontaneous reports, estimates of frequency cannot be made and a causal relationship between interferon alfa-based therapies and these events is difficult to establish.

5.9 Hepatic Failure and Hepatitis Exacerbations

Chronic hepatitis C (CHC) patients with cirrhosis may be at risk of hepatic decompensation and death when treated with alpha interferons, including PEGASYS. Cirrhotic CHC patients coinfecting with HIV receiving highly active antiretroviral therapy (HAART) and interferon alfa-2a with or without ribavirin appear to be at increased risk for the development of hepatic decompensation compared to patients not receiving HAART. In Study 6 [see *Clinical Studies (14.3)*], among 129 CHC/HIV cirrhotic subjects receiving HAART, 14 (11%) of these subjects across all treatment arms developed hepatic decompensation resulting in 6 deaths. All 14 subjects were on NRTIs, including stavudine, didanosine, abacavir, zidovudine, and lamivudine. These small numbers of patients do not permit discrimination between specific NRTIs for the associated risk. During treatment, patients' clinical status and hepatic function should be closely monitored, and PEGASYS/COPEGUS treatment should be immediately discontinued in patients with hepatic decompensation [see *Contraindications (4)*].

Exacerbations of hepatitis during hepatitis B therapy are not uncommon and are characterized by transient and potentially severe increases in serum ALT. Chronic hepatitis B subjects experienced transient acute exacerbations (flares) of hepatitis B (ALT elevation greater than 10-fold higher than the upper limit of normal) during PEGASYS treatment (12% and 18%) and post-treatment (7% and 12%) in HBeAg negative and HBeAg positive subjects, respectively. Marked transaminase flares while on PEGASYS therapy have been accompanied by other liver test abnormalities. Patients experiencing ALT flares should receive more frequent monitoring of liver function. PEGASYS dose reduction should be considered in patients experiencing transaminase flares. If ALT increases are progressive despite reduction of PEGASYS dose or are accompanied by increased bilirubin or evidence of hepatic decompensation, PEGASYS should be immediately discontinued [see *Adverse Reactions (6.1) and Dosage and Administration (2.5)*].

5.10 Pulmonary Disorders

Dyspnea, pulmonary infiltrates, pneumonia, bronchiolitis obliterans, interstitial pneumonitis, pulmonary hypertension and sarcoidosis, some resulting in respiratory failure and/or patient deaths, may be induced or aggravated by PEGASYS or alpha interferon therapy. Recurrence of respiratory failure has been observed with interferon rechallenge. PEGASYS combination treatment should be suspended in patients who develop pulmonary infiltrates or pulmonary function impairment. Patients who resume interferon treatment should be closely monitored.

5.11 Infections

While fever may be associated with the flu-like syndrome reported commonly during interferon therapy, other causes of high or persistent fever must be ruled out, particularly in patients with neutropenia. Serious and severe infections (bacterial, viral, or fungal), some fatal, have been reported during treatment with alpha interferons including PEGASYS. Appropriate anti-infective therapy should be started immediately and discontinuation of therapy should be considered.

5.12 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.

5.13 Pancreatitis

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

5.14 Hypersensitivity

Severe acute hypersensitivity reactions (e.g., urticaria, angioedema, bronchoconstriction, and anaphylaxis) have been observed during alpha interferon and ribavirin therapy. If such reaction occurs, therapy with PEGASYS/COPEGUS should be discontinued and appropriate medical therapy immediately instituted. Serious skin reactions including vesiculobullous eruptions, reactions in the spectrum of Stevens-Johnson Syndrome (erythema multiforme major) with varying degrees of skin and mucosal involvement and exfoliative dermatitis (erythroderma) have been reported in patients receiving PEGASYS with and without ribavirin. Patients developing signs or symptoms of severe skin reactions must discontinue therapy [*see Adverse Reactions (6.2)*].

5.15 Impact on Growth in Pediatric Patients

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

5.16 Peripheral Neuropathy

Peripheral neuropathy has been reported when alpha interferons were given in combination with telbivudine. In one clinical trial, an increased risk and severity of peripheral neuropathy was observed with the combination use of telbivudine and PEGASYS as compared to telbivudine alone. The safety and efficacy of telbivudine in combination with interferons for the treatment of chronic hepatitis B has not been demonstrated.

5.17 Laboratory Tests

Before beginning PEGASYS or PEGASYS/COPEGUS combination therapy, standard hematological and biochemical laboratory tests are recommended for all patients. Pregnancy screening for women of childbearing potential must be performed. Patients who have pre-existing cardiac abnormalities should have electrocardiograms administered before treatment with PEGASYS/COPEGUS.

After initiation of therapy, hematological tests should be performed at 2 weeks and 4 weeks and biochemical tests should be performed at 4 weeks. Additional testing should be performed periodically during therapy. In adult clinical studies, the CBC (including hemoglobin level and white blood cell and platelet counts) and chemistries (including liver function tests and uric acid) were measured at 1, 2, 4, 6, and 8 weeks, and then every 4 to 6 weeks or more frequently if abnormalities were found. In a pediatric clinical trial, hematological and chemistry assessments were at 1, 3, 5, and 8 weeks, then every 4 weeks. Thyroid stimulating hormone (TSH) was measured every 12 weeks. Monthly pregnancy testing should be performed during combination therapy and for 6 months after discontinuing therapy.

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

- Platelet count greater than or equal to 90,000 cells/mm³ (as low as 75,000 cells/mm³ in HCV subjects with cirrhosis or 70,000 cells/mm³ in subjects with CHC and HIV)
- Absolute neutrophil count (ANC) greater than or equal to 1,500 cells/mm³
- Serum creatinine concentration less than 1.5 x upper limit of normal
- TSH and T₄ within normal limits or adequately controlled thyroid function
- CD4+ cell count greater than or equal to 200 cells/mm³ or CD4+ cell count greater than or equal to 100 cells/mm³ but less than 200 cells/mm³ and HIV-1 RNA less than 5,000 copies/mL in subjects coinfecting with HIV
- Hemoglobin greater than or equal to 12 g/dL for women and greater than or equal to 13 g/dL for men in CHC monoinfected subjects
- Hemoglobin greater than or equal to 11 g/dL for women and greater than or equal to 12 g/dL for men in subjects with CHC and HIV

6 ADVERSE REACTIONS

In clinical trials, a broad variety of serious adverse reactions were observed in 1,010 subjects who received PEGASYS at doses of 180 mcg for 48 weeks, alone or in combination with COPEGUS [see *Boxed Warning and Warnings and Precautions (5)*]. The most common life-threatening or fatal events induced or aggravated by PEGASYS and COPEGUS include depression, suicide, relapse of drug abuse/overdose, and bacterial infections, each occurring at a frequency of less than 1%. Hepatic decompensation occurred in 2% (10/574) of CHC/HIV subjects [see *Warnings and Precautions (5.9)*].

6.1 Clinical Trials Experience

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, and may not reflect the rates observed in clinical practice.

Adult Subjects

In all hepatitis C studies, one or more serious adverse reactions occurred in 10% of CHC monoinfected subjects and in 19% of CHC/HIV subjects receiving PEGASYS alone or in combination with COPEGUS. The most common serious adverse event (3% in CHC and 5% in CHC/HIV) was bacterial infection (e.g., sepsis, osteomyelitis, endocarditis, pyelonephritis, pneumonia). Other SAEs occurred at a frequency of less than 1% and included: suicide, suicidal ideation, aggression, anxiety, drug abuse and drug overdose, angina, hepatic dysfunction, fatty liver, cholangitis, arrhythmia, diabetes mellitus, autoimmune phenomena (e.g.,

hyperthyroidism, hypothyroidism, sarcoidosis, systemic lupus erythematosus, rheumatoid arthritis), peripheral neuropathy, aplastic anemia, peptic ulcer, gastrointestinal bleeding, pancreatitis, colitis, corneal ulcer, pulmonary embolism, coma, myositis, cerebral hemorrhage, thrombotic thrombocytopenic purpura, psychotic disorder, and hallucination.

In clinical trials, 98 to 99 percent of subjects experienced one or more adverse events. For hepatitis C subjects, the most commonly reported adverse reactions were psychiatric reactions, including depression, insomnia, irritability, anxiety, and flu-like symptoms such as fatigue, pyrexia, myalgia, headache, and rigors. Other common reactions were anorexia, nausea and vomiting, diarrhea, arthralgias, injection site reactions, alopecia, and pruritus. **Table 8** displays pooled rates of adverse events occurring in greater than 5% of subjects in the PEGASYS monotherapy and PEGASYS/COPEGUS combination therapy clinical trials.

Overall 11% of CHC monoinfected subjects receiving 48 weeks of therapy with PEGASYS either alone or in combination with COPEGUS discontinued therapy; 16% of CHC/HIV coinfecting subjects discontinued therapy. The most common reasons for discontinuation of therapy were psychiatric, flu-like syndrome (e.g., lethargy, fatigue, headache), dermatologic and gastrointestinal disorders, and laboratory abnormalities (thrombocytopenia, neutropenia, and anemia).

Overall 39% of subjects with CHC or CHC/HIV required modification of PEGASYS and/or COPEGUS therapy. The most common reasons for dose modification of PEGASYS in CHC and CHC/HIV subjects was for laboratory abnormalities, neutropenia (20% and 27%, respectively) and thrombocytopenia (4% and 6%, respectively). The most common reason for dose modification of COPEGUS in CHC and CHC/HIV subjects was anemia (22% and 16%, respectively). PEGASYS dose was reduced in 12% of subjects receiving 1000 mg to 1200 mg COPEGUS for 48 weeks and in 7% of subjects receiving 800 mg COPEGUS for 24 weeks. COPEGUS dose was reduced in 21% of subjects receiving 1000 mg to 1200 mg COPEGUS for 48 weeks and in 12% of subjects receiving 800 mg COPEGUS for 24 weeks.

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

Table 8 Adverse Reactions Occurring in greater than or equal to 5% of Subjects in Chronic Hepatitis C Clinical Trials (Pooled Studies 1, 2, 3, and Study 4)

Body System	CHC Monotherapy (Pooled Studies 1-3)		CHC Combination Therapy Study 4	
	PEGASYS 180 mcg 48 week†	ROFERON-A Either 3 MIU* or 6/3 MIU* of ROFERON-A 48 week†	PEGASYS 180 mcg + 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

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

	CHC Monotherapy (Pooled Studies 1-3)		CHC Combination Therapy Study 4	
Body System	PEGASYS 180 mcg 48 week†	ROFERON-A Either 3 MIU* or 6/3 MIU* of ROFERON-A 48 week†	PEGASYS 180 mcg + 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
	%	%	%	%
Resistance Mechanism Disorders				
Overall	10	6	12	10
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
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

*An induction dose of 6 million international units (MIU) three times a week for the first 12 weeks followed by 3 million international units three times a week for 36 weeks given subcutaneously.

† Pooled studies 1, 2, and 3

**Study 4

‡ Severe hematologic abnormalities (lymphocyte less than 500 cells/mm³; hemoglobin less than 10 g/dL; neutrophil less than 750 cells/mm³; platelet less than 50,000 cells/mm³).

Pediatric Subjects

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

Growth inhibition was observed in pediatric subjects. During combination therapy for up to 48 weeks with PEGASYS and COPEGUS, negative changes in weight for age z-score and height for age z-score after 48 weeks of therapy compared with baseline were observed [see *Warnings and Precautions (5.15)*].

Table 9 Percentage of Pediatric Subjects with Adverse Reactions* During First 24 Weeks of Treatment by Treatment Group (in at Least 10% of Subjects)

System Organ Class	Study NV17424	
	PEGASYS 180 mcg/1.73 m ² x BSA + COPEGUS 15 mg/kg (N=55)	PEGASYS 180 mcg/1.73 m ² x BSA + Placebo** (N=59)
	%	%
General disorders and administration site conditions		
Influenza like illness	91	81
Injection site reaction	44	42
Fatigue	25	20
Irritability	24	14
Gastrointestinal disorders		
Gastrointestinal disorder	49	44
Nervous system disorders		
Headache	51	39
Skin and subcutaneous tissue disorders		
Rash	15	10
Pruritus	11	12
Musculoskeletal, connective tissue and bone disorders		
Musculoskeletal pain	35	29
Psychiatric disorders		
Insomnia	9	12
Metabolism and nutrition disorders		
Decreased appetite	11	14

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

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

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

CHC with HIV Coinfection (Adults)

The adverse event profile of coinfecting subjects treated with PEGASYS/COPEGUS in Study 6 was generally similar to that shown for mono-infected subjects in Study 4 (**Table 8**). Events occurring more frequently in

coinfecting subjects were neutropenia (40%), anemia (14%), thrombocytopenia (8%), weight decrease (16%), and mood alteration (9%).

Chronic Hepatitis B

In clinical trials of 48 week treatment duration, the adverse event profile of PEGASYS in chronic hepatitis B was similar to that seen in CHC PEGASYS monotherapy use, except for exacerbations of hepatitis [see *Warnings and Precautions (5.9)*]. Six percent of PEGASYS treated subjects in the hepatitis B studies experienced one or more serious adverse events.

The most common or important serious adverse events, all of which occurred at a frequency of less than or equal to 1%, in the hepatitis B studies were infections (sepsis, appendicitis, tuberculosis, influenza), hepatitis B flares, and thrombotic thrombocytopenic purpura.

One serious adverse event of anaphylactic shock occurred in a dose ranging study of 191 subjects in a subject taking a higher than approved dose of PEGASYS.

The most commonly observed adverse reactions in the PEGASYS and lamivudine groups, respectively, were pyrexia (54% vs. 4%), headache (27% vs. 9%), fatigue (24% vs. 10%), myalgia (26% vs. 4%), alopecia (18% vs. 2%), and anorexia (16% vs. 3%).

Overall 5% of hepatitis B subjects discontinued PEGASYS therapy and 40% of subjects required modification of PEGASYS dose. The most common reason for dose modification in subjects receiving PEGASYS therapy was for laboratory abnormalities including neutropenia (20%), thrombocytopenia (13%), and ALT elevation (11%).

Laboratory Values

Adult Patients

The laboratory test values observed in the hepatitis B trials (except where noted below) were similar to those seen in the PEGASYS monotherapy CHC trials.

Neutrophils

In the hepatitis C studies, decreases in neutrophil count below normal were observed in 95% of all subjects treated with PEGASYS either alone or in combination with COPEGUS. Severe potentially life-threatening neutropenia (ANC less than 500 cells/mm³) occurred in 5% of CHC subjects and 12% of CHC/HIV subjects receiving PEGASYS either alone or in combination with COPEGUS. Modification of PEGASYS dose for neutropenia occurred in 17% of subjects receiving PEGASYS monotherapy and 22% of subjects receiving PEGASYS/COPEGUS combination therapy. In the CHC/HIV subjects 27% required modification of interferon dosage for neutropenia. Two percent of subjects with CHC and 10% of subjects with CHC/HIV required permanent reductions of PEGASYS dosage and less than 1% required permanent discontinuation. Median neutrophil counts return to pre-treatment levels 4 weeks after cessation of therapy [see *Dosage and Administration (2.5)*].

Lymphocytes

Decreases in lymphocyte count are induced by interferon alpha therapy. PEGASYS plus COPEGUS combination therapy induced decreases in median total lymphocyte counts (56% in CHC and 40% in CHC/HIV, with median decrease of 1170 cells/mm³ in CHC and 800 cells/mm³ in CHC/HIV). In the hepatitis C studies, lymphopenia was observed during both monotherapy (81%) and combination therapy with PEGASYS and COPEGUS (91%). Severe lymphopenia (less than 500 cells/mm³) occurred in approximately 5% of all monotherapy subjects and 14% of all combination PEGASYS and COPEGUS therapy recipients. Dose adjustments were not required by protocol. The clinical significance of the lymphopenia is not known.

In CHC with HIV coinfection, CD4 counts decreased by 29% from baseline (median decrease of 137 cells/mm³) and CD8 counts decreased by 44% from baseline (median decrease of 389 cells/mm³) in the

PEGASYS plus COPEGUS combination therapy arm. Median lymphocyte CD4 and CD8 counts return to pre-treatment levels after 4 to 12 weeks of the cessation of therapy. CD4% did not decrease during treatment.

Platelets

In the hepatitis C studies, platelet counts decreased in 52% of CHC subjects and 51% of CHC/HIV subjects treated with PEGASYS alone (respectively median decrease of 41% and 35% from baseline), and in 33% of CHC subjects and 47% of CHC/HIV subjects receiving combination therapy with COPEGUS (median decrease of 30% from baseline). Moderate to severe thrombocytopenia (less than 50,000 cells/mm³) was observed in 4% of CHC and 8% of CHC/HIV subjects. Median platelet counts return to pre-treatment levels 4 weeks after the cessation of therapy.

Hemoglobin

In the hepatitis C studies, the hemoglobin concentration decreased below 12 g/dL in 17% (median Hgb reduction of 2.2 g/dL) of monotherapy and 52% (median Hgb reduction of 3.7 g/dL) of combination therapy subjects. Severe anemia (Hgb less than 10 g/dL) was encountered in 13% of all subjects receiving combination therapy and in 2% of CHC subjects and 8% of CHC/HIV subjects receiving PEGASYS monotherapy. Dose modification for anemia in COPEGUS recipients treated for 48 weeks occurred in 22% of CHC subjects and 16% of CHC/HIV subjects [see *Dosage and Administration* (2.6)].

Triglycerides

Triglyceride levels are elevated in subjects receiving alfa interferon therapy and were elevated in the majority of subjects participating in clinical studies receiving either PEGASYS alone or in combination with COPEGUS. Random levels greater than or equal to 400 mg/dL were observed in about 20% of CHC subjects. Severe elevations of triglycerides (greater than 1000 mg/dL) occurred in 2% of CHC monoinfected subjects.

In HCV/HIV coinfecting subjects, fasting levels greater than or equal to 400 mg/dL were observed in up to 36% of subjects receiving either PEGASYS alone or in combination with COPEGUS. Severe elevations of triglycerides (greater than 1000 mg/dL) occurred in 7% of coinfecting subjects.

ALT Elevations

Chronic Hepatitis C

One percent of subjects in the hepatitis C trials experienced marked elevations (5- to 10-fold above the upper limit of normal) in ALT levels during treatment and follow-up. 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* (2.5)].

Chronic Hepatitis B

Transient ALT elevations are common during hepatitis B therapy with PEGASYS. Twenty-five percent and 27% of subjects experienced elevations of 5 to 10 x ULN and 12% and 18% had elevations of greater than 10 x ULN during treatment of HBeAg negative and HBeAg positive disease, respectively. Flares have been accompanied by elevations of total bilirubin and alkaline phosphatase and less commonly with prolongation of PT and reduced albumin levels. Eleven percent of subjects had dose modifications due to ALT flares and less than 1% of subjects were withdrawn from treatment [see *Warnings and Precautions* (5.9) and *Dosage and Administration* (2.5)].

ALT flares of 5 to 10 x ULN occurred in 13% and 16% of subjects, while ALT flares of greater than 10 x ULN occurred in 7% and 12% of subjects in HBeAg negative and HBeAg positive disease, respectively, after discontinuation of PEGASYS therapy.

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. In the hepatitis C studies, hypothyroidism or hyperthyroidism requiring treatment, dose modification or discontinuation occurred in 4% and 1% of PEGASYS treated subjects and 4% and 2% of PEGASYS and COPEGUS treated subjects, respectively. Approximately half of the subjects, who developed thyroid abnormalities during PEGASYS treatment, still had abnormalities during the follow-up period [see *Warnings and Precautions (5.6)*].

Pediatric Patients

Decreases in hemoglobin, neutrophils and platelets may require dose reduction or permanent discontinuation from treatment [see *Dosage and Administration (2.7)*]. Most laboratory abnormalities noted during the clinical trial returned to baseline levels shortly after completion of treatment.

Table 10 Selected Hematologic Abnormalities During First 24 Weeks of Treatment by Treatment Group in Previously Untreated Pediatric Subjects

Laboratory Parameter	PEGASYS 180 mcg/1.73 m ² x BSA + COPEGUS 15 mg/kg (N=55)	PEGASYS 180 mcg/1.73 m ² x BSA + Placebo* (N=59)
Neutrophils (cells/mm³)		
1,000 - <1,500	31%	39%
750 - <1,000	27%	17%
500 - <750	25%	15%
<500	7%	5%
Platelets (cells/mm³)		
75,000 - <100,000	4%	2%
50,000 - <75,000	0%	2%
< 50,000	0%	0%
Hemoglobin (g/dL)		
8.5-<10	7%	3%
<8.5	0%	0%

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

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

6.2 Immunogenicity

Chronic Hepatitis C

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

Chronic Hepatitis B

Twenty-nine percent (42/143) of hepatitis B subjects treated with PEGASYS for 24 weeks developed binding antibodies to interferon alfa-2a, as assessed by an ELISA assay. Thirteen percent of subjects (19/143) receiving PEGASYS developed low-titer neutralizing antibodies (using an assay with 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 subjects 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 other products may be misleading.

6.3 Postmarketing Experience

The following adverse reactions have been identified and reported during post-approval use of PEGASYS therapy. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Blood and Lymphatic System disorders

pure red cell aplasia

Ear and Labyrinth Disorders

hearing impairment, hearing loss

Immune system disorders

Liver graft rejection and renal graft rejection [see *Warnings and Precautions (5.9) and Use in Specific Populations (8.8)*].

Metabolism and Nutrition Disorders

dehydration

Skin and subcutaneous tissue disorders

serious skin reactions

Neurological

seizures

7 DRUG INTERACTIONS

7.1 Drugs Metabolized by Cytochrome P450

There was no effect on the pharmacokinetics of representative drugs metabolized by CYP 2C9, CYP 2C19, CYP 2D6 or CYP 3A4.

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.

7.2 Theophylline

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.

7.3 Methadone

In a PK study of HCV subjects 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. The clinical significance of this finding is unknown; however, patients should be monitored for the signs and symptoms of methadone toxicity.

The pharmacokinetics of concomitant administration of methadone and PEGASYS were evaluated in 24 PEGASYS naive chronic hepatitis C (CHC) subjects (15 male, 9 female) who received 180 mcg PEGASYS subcutaneously weekly. All subjects were on stable methadone maintenance therapy (median dose 95 mg, range 30 mg to 150 mg) prior to receiving PEGASYS. Mean methadone PK parameters were 10% to 15% higher after

4 weeks of PEGASYS treatment as compared to baseline. Methadone did not significantly alter the PK of PEGASYS as compared to a PK study of 6 chronic hepatitis C subjects not receiving methadone.

7.4 Nucleoside Analogues

In vitro data indicate ribavirin reduces phosphorylation of lamivudine, stavudine, and zidovudine. However, no pharmacokinetic (e.g., plasma concentrations or intracellular triphosphorylated active metabolite concentrations) or pharmacodynamic (e.g., loss of HCV/HIV virologic suppression) interaction was observed when ribavirin and lamivudine (n=18), stavudine (n=10), or zidovudine (n=6) were co-administered as part of a multi-drug regimen to HCV/HIV coinfecting subjects.

NRTIs

In Study 6 among the CHC/HIV coinfecting cirrhotic subjects receiving NRTIs cases of hepatic decompensation (some fatal) were observed [see *Warnings and Precautions (5.9)*].

Patients receiving PEGASYS/COPEGUS and NRTIs should be closely monitored for treatment associated toxicities. Physicians should refer to prescribing information for the respective NRTIs for guidance regarding toxicity management. In addition, dose reduction or discontinuation of PEGASYS, COPEGUS or both should also be considered if worsening toxicities are observed [see *Warnings and Precautions (5.3, 5.9) and Dosage and Administration (2.5, 2.6)*].

Didanosine

Co-administration of COPEGUS and didanosine is contraindicated. *In vitro*, didanosine and its active metabolite (dideoxyadenosine 5'-triphosphate) concentrations are increased when didanosine is co-administered with ribavirin. Reports of fatal hepatic failure, as well as peripheral neuropathy, pancreatitis, and symptomatic hyperlactatemia/lactic acidosis have been reported in clinical trials [see *Contraindications (4)*].

Zidovudine

In Study 6, subjects who were administered zidovudine in combination with PEGASYS/COPEGUS developed severe neutropenia (ANC less than 500 cells/mm³) and severe anemia (hemoglobin less than 8 g/dL) more frequently than similar subjects not receiving zidovudine (neutropenia 15% vs. 9%) (anemia 5% vs. 1%). Discontinuation of zidovudine should be considered as medically appropriate. Dose reduction or discontinuation of PEGASYS, COPEGUS or both should also be considered if worsening clinical toxicities are observed, including hepatic decompensation (e.g., Child-Pugh greater than 6).

Azathioprine

The use of ribavirin to treat chronic hepatitis C in patients receiving azathioprine has been reported to induce severe pancytopenia and may increase the risk of azathioprine-related myelotoxicity. Inosine monophosphate dehydrogenase (IMDH) is required for one of the metabolic pathways of azathioprine. Ribavirin is known to inhibit IMDH, thereby leading to accumulation of an azathioprine metabolite, 6-methylthioinosine monophosphate (6-MTITP), which is associated with myelotoxicity (neutropenia, thrombocytopenia, and anemia). Patients receiving azathioprine with ribavirin should have complete blood counts, including platelet counts, monitored weekly for the first month, twice monthly for the second and third months of treatment, then monthly or more frequently if dosage or other therapy changes are necessary [see *Warnings and Precautions (5.1)*].

Please refer to the Full Prescribing Information for ribavirin for full details on ribavirin's drug interaction potential.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category C: PEGASYS Monotherapy

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 (4)*]

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 (4)*, *Warnings and Precautions (5.1)*, and *COPEGUS Package Insert*].

Ribavirin Pregnancy Registry:

A Ribavirin Pregnancy Registry has been established to monitor maternal and fetal outcomes of pregnancies of female patients and female partners of male patients exposed to ribavirin during treatment and for 6 months following cessation of treatment. Healthcare providers and patients are encouraged to report such cases by calling 1-800-593-2214.

8.3 Nursing Mothers

It is not known whether 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.

8.4 Pediatric Use

The safety and effectiveness of PEGASYS, alone or in combination with COPEGUS in patients below the age of 5 years have not been established.

PEGASYS contains benzyl alcohol. In neonates and infants, benzyl alcohol has been reported to be associated with an increased incidence of neurological and other complications which are sometimes fatal in neonates and infants [see *Contraindications (4)*].

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

8.6 Hepatic Impairment

Chronic hepatitis C (CHC) patients with cirrhosis may be at risk of hepatic decompensation and death when treated with alpha interferons, including PEGASYS. During treatment, patients' clinical status and hepatic function should be closely monitored, and PEGASYS treatment should be immediately discontinued if decompensation (Child-Pugh score greater than or equal to 6) is observed [see *Contraindications (4)*]. Chronic hepatitis B subjects experienced transient acute exacerbations (flares) of hepatitis B (ALT elevation greater than 10-fold higher than the upper limit of normal) during PEGASYS treatment (12% and 18%) and post-treatment (7% and 12%) in HBeAg negative and HBeAg positive subjects, respectively.

8.7 Renal Impairment

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

A clinical trial evaluated treatment with PEGASYS and COPEGUS in 50 CHC subjects with moderate (creatinine clearance 30 – 50 mL/min) or severe (creatinine clearance less than 30 mL/min) renal impairment or end stage renal disease (ESRD) requiring chronic hemodialysis (HD). In 18 subjects with ESRD receiving chronic HD, PEGASYS was administered at a dose of 135 mcg once weekly. Dose reductions and temporary interruptions of PEGASYS (due to PEGASYS-related adverse reactions, mainly anemia) were observed in up to 22% ESRD/HD subjects during treatment; and 17% of these subjects discontinued PEGASYS due to PEGASYS-related adverse reactions. Only one-third of ESRD/HD subjects received PEGASYS for 48 weeks. Subjects with severe (n=14) or moderate (n=17) renal impairment received PEGASYS 180 mcg once weekly. PEGASYS discontinuation rates were 36% and 0% in subjects with severe and moderate renal impairment, respectively, compared to 0% discontinuation rate in subjects with normal renal function.

Based on the pharmacokinetic and safety results from this trial, patients with creatinine clearance less than 30 mL/min should receive a reduced dose of PEGASYS, and patients with creatinine clearance less than or equal to 50 mL/min should receive a reduced dose of COPEGUS. In addition, patients with any degree of renal impairment should be carefully monitored for laboratory abnormalities (especially decreased hemoglobin) and adverse reactions, and should undergo careful monitoring of creatinine clearance. Patients with clinically significant laboratory abnormalities or adverse reactions which are persistently severe or worsening should have therapy withdrawn [see *Dosage and Administration (2.4, 2.5)*, *Clinical Pharmacology (12.3)* and *COPEGUS Package Insert*].

8.8 Organ Transplant Recipients

The safety and efficacy of PEGASYS and COPEGUS treatment have not been established in patients with liver and other transplantations. As with other alpha interferons, liver and renal graft rejections have been reported on PEGASYS, alone or in combination with COPEGUS [see *Adverse Reactions (6.3)*].

8.9 Chronic Hepatitis B

The safety and efficacy of PEGASYS alone or in combination with COPEGUS have not been established in:

- Hepatitis B patients coinfecting with HCV or HIV
- Hepatitis C patients coinfecting with HBV or coinfecting with HIV with a CD4+ cell count less than 100 cells/mm³

10 OVERDOSAGE

There is limited experience with overdosage. The maximum dose received by any patient was 7 times the intended dose of PEGASYS (180 mcg/day for 7 days). There were no serious reactions attributed to overdosages. Weekly doses of up to 630 mcg 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.

11 DESCRIPTION

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

PEGASYS is a sterile, preservative-free, colorless to light yellow injectable solution administered subcutaneously.

180 mcg/mL Vial: Each vial contains approximately 1.2 mL of solution to deliver 1 mL of drug product. Subcutaneous (sc) administration of 1 mL of 180 mcg of drug product (expressed as the amount of interferon alfa-2a) also contains acetic acid (0.05 mg), benzyl alcohol (10 mg), polysorbate 80 (0.05 mg), sodium acetate trihydrate (2.62 mg), and sodium chloride (8 mg) at pH 6 ± 0.5 .

180 mcg/0.5 mL Prefilled Syringe: Each syringe contains 0.6 mL of solution to deliver 0.5 mL of drug product. Subcutaneous (sc) administration of 0.5 mL delivers 180 mcg of drug product (expressed as the amount of interferon alfa-2a) also contains acetic acid (0.0231 mg), benzyl alcohol (5 mg), polysorbate 80 (0.025 mg), sodium acetate trihydrate (1.3085 mg), and sodium chloride (4 mg) at pH 6 ± 0.5 .

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Pegylated recombinant human interferon alfa-2a is an inducer of the innate antiviral immune response [see *Microbiology (12.4)*].

12.2 Pharmacodynamics

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

12.3 Pharmacokinetics

Maximal serum concentrations (C_{max}) and AUC increased in a nonlinear dose related manner following administration of 90 to 270 mcg of PEGASYS. Maximal serum concentrations (C_{max}) occur between 72 to 96 hours post-dose.

Week 48 mean trough concentrations (16 ng/mL; range 4 to 28) at 168 hours post-dose are approximately 2-fold higher than week 1 mean trough concentrations (9 ng/mL; range 0 to 15). Steady-state serum levels are reached within 5 to 8 weeks of once weekly dosing. The peak to trough ratio at week 48 is approximately 2. The mean systemic clearance in healthy subjects given PEGASYS was 94 mL/h, which is approximately 100-fold lower than that for interferon alfa-2a (ROFERON[®]-A). The mean terminal half-life after subcutaneous dosing in subjects with chronic hepatitis C was 160 hours (range 84 to 353 hours) compared to 5 hours (range 3.7 to 8.5 hours) for ROFERON-A.

Special Populations

Gender and Age

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

Pediatric Patients

In a population pharmacokinetics study, 14 children 2 to 8 years of age with CHC received PEGASYS based on their body surface area (BSA of the child \times 180 mcg/1.73 m²). The clearance of PEGASYS in children was nearly 4-fold lower compared to the clearance reported in adults.

Steady-state trough levels in children with the BSA-adjusted dosing were similar to trough levels observed in adults with 180 mcg fixed dosing. Time to reach the steady state in children is approximately 12 weeks, whereas in adults, steady state is reached within 5 to 8 weeks. In these children receiving the BSA adjusted dose, the mean exposure (AUC) during the dosing interval is predicted to be 25% to 70% higher than that observed in adults receiving 180 mcg fixed dosing.

Renal Impairment

A clinical trial evaluated 50 CHC subjects with either moderate (creatinine clearance 30 to 50 mL/min) or severe (creatinine clearance less than 30 mL/min) renal impairment or end stage renal disease (ESRD) requiring chronic hemodialysis (HD). Subjects with moderate renal impairment receiving PEGASYS 180 mcg once weekly dose exhibited similar peginterferon alfa-2a plasma exposures compared to subjects with normal renal function (creatinine clearance greater than 80 mL/min) receiving the standard dose of PEGASYS. No PEGASYS dose adjustment is required for patients with mild or moderate renal impairment [*See Dosage and Administration (2.4) and Use in Specific Populations (8.7)*].

For subjects with severe renal impairment, peginterferon alfa-2a apparent clearance was 43% lower as compared to subjects with normal renal function. A reduced dose of 135 mcg once weekly PEGASYS is recommended in patients with severe renal impairment. This dose may result in 30% higher peginterferon alfa-2a exposure compared to that of the recommended dose for patients with normal renal function. Signs and symptoms of interferon toxicity should be closely monitored in patients with severe renal impairment and the dose reduced to 90 mcg once weekly as appropriate [*see Dosage and Administration (2.4, 2.5) and Use in Specific Populations (8.7)*].

In 18 subjects with ESRD receiving chronic HD, PEGASYS was administered at a dose of 135 mcg once weekly. The apparent clearance of peginterferon alfa-2a was similar between subjects with ESRD and subjects with normal renal function. Despite a lower exposure to peginterferon alfa-2a with the 135 mcg dose, subjects with ESRD had a high rate of adverse events and discontinuations of PEGASYS in the trial. Therefore, a dose of 135 mcg once weekly should be used for patients with ESRD on HD. However, the potential for reduced efficacy and increased interferon toxicity in patients with ESRD receiving chronic HD should be closely monitored. The dose may be reduced to 90 mcg once weekly as appropriate [*see Dosage and Administration (2.4) and Use in Specific Populations (8.7)*].

12.4 Microbiology

Mechanism of Action

The biological activity of PEGASYS is derived from its recombinant human interferon α -2a moiety. Peginterferon α -2a binds to the human type 1 interferon receptor leading to receptor dimerization. Receptor dimerization activates multiple intracellular signal transduction pathways initially mediated by the JAK/STAT pathway. Given the diversity of cell types that respond to interferon α -2a, and the multiplicity of potential intracellular responses to interferon receptor activation, peginterferon α -2a is expected to have pleiotropic biological effects in the body.

Antiviral Activity in Cell Culture

In the stable HCV cell culture model system (HCV replicon), ribavirin inhibited autonomous HCV RNA replication with an effective concentration (EC₅₀) value of 11-21 μ M. In the same model, PEG-IFN α -2a also inhibited HCV RNA replication, with an EC₅₀ value of 0.1-3 ng/mL. The combination of PEG-IFN α -2a and ribavirin was more effective at inhibiting HCV RNA replication than either agent alone.

Resistance

Different HCV genotypes display considerable clinical variability in their response to PEG-IFN- α and ribavirin therapy. Viral genetic determinants associated with the variable response have not been definitively identified.

Cross-resistance

Cross-resistance between IFN- α and ribavirin has not been observed.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis

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 in *in vitro* and *in vivo* assays, and therefore, potential carcinogenic risk to humans cannot be excluded. In a p53 (+/-) mouse carcinogenicity study at doses up to 100 mg/kg/day ribavirin was not oncogenic. Ribavirin was also not oncogenic in a rat 2-year carcinogenicity study at doses 60 mg/kg/day. On a body surface area basis, these doses were 0.5 and 0.6 times the maximum recommended daily human dose of ribavirin respectively [*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 subcutaneous injections of 600 mcg/kg/dose (7200 mcg/m²/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 17 β -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 mcg/kg (1200 mcg/m²) 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 10⁶ IU/kg/day.

Use with Ribavirin: Ribavirin has shown reversible toxicity in animal studies of male fertility [*see COPEGUS Package Insert*].

14 CLINICAL STUDIES

14.1 Chronic Hepatitis C Studies 1, 2, and 3: PEGASYS Monotherapy

The safety and effectiveness of PEGASYS for the treatment of hepatitis C virus infection were assessed in three randomized, open-label, active-controlled clinical studies. All subjects were adults, had compensated liver disease, detectable hepatitis C virus (HCV), liver biopsy diagnosis of chronic hepatitis, and were previously untreated with interferon. All subjects received therapy by subcutaneous injection for 48 weeks, and were followed for an additional 24 weeks to assess the durability of response. In studies 1 and 2, approximately 20% of subjects had cirrhosis or bridging fibrosis. Study 3 enrolled subjects with a histological diagnosis of cirrhosis (78%) or bridging fibrosis (22%).

In Study 1 (n=630), subjects received either ROFERON-A (interferon alfa-2a) 3 MIU three times a week, PEGASYS 135 mcg once weekly or PEGASYS 180 mcg once weekly. In Study 2 (n=526), subjects received either ROFERON-A 6 MIU three times a week for 12 weeks followed by 3 MIU three times a week for 36

weeks or PEGASYS 180 mcg once weekly. In Study 3 (n=269), subjects received ROFERON-A 3 MIU three times a week, PEGASYS 90 mcg once weekly or PEGASYS 180 mcg once each week.

In all three studies, treatment with PEGASYS 180 mcg resulted in significantly more subjects who experienced a sustained response (defined as undetectable HCV RNA [less than 50 IU/mL] using the COBAS AMPLICOR[®] HCV Test, version 2 and normalization of ALT on or after study week 68) compared to treatment with ROFERON-A. In Study 1, response to PEGASYS 135 mcg was not different from response to 180 mcg. In Study 3, response to PEGASYS 90 mcg was intermediate between PEGASYS 180 mcg and ROFERON-A.

Table 11 Sustained Response to Monotherapy Treatment

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

*Percent difference between PEGASYS and ROFERON-A treatment.

[†]An induction dose of 6 million international units (MIU) three times a week for the first 12 weeks followed by 3 million international units three times a week for 36 weeks given subcutaneously.

[‡] Defined as undetectable HCV RNA [less than 50 IU/mL] using the COBAS AMPLICOR[®] HCV Test, version 2 and normalization of ALT on or after study week 68

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

Of the subjects who did not demonstrate either undetectable HCV RNA or at least a 2log₁₀ drop in HCV RNA titer from baseline by 12 weeks of PEGASYS 180 mcg therapy, 2% (3/156) achieved a sustained virologic response [see *Dosage and Administration (2.2)*].

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

14.2 Chronic Hepatitis C Studies 4, 5, and 6: PEGASYS/COPEGUS Combination Therapy

Adult Patients

The safety and effectiveness of PEGASYS in combination with COPEGUS for the treatment of hepatitis C virus infection were assessed in two randomized controlled clinical trials. All subjects were adults, had compensated liver disease, detectable hepatitis C virus, liver biopsy diagnosis of chronic hepatitis, and were previously untreated with interferon. Approximately 20% of subjects in both studies had compensated cirrhosis (Child-Pugh class A). Subjects coinfecting with HIV were excluded from these studies.

In Study 4, subjects were randomized to receive either PEGASYS 180 mcg subcutaneous once weekly with an oral placebo, PEGASYS 180 mcg once weekly with COPEGUS 1000 mg by mouth (body weight less than 75 kg) or 1200 mg by mouth (body weight greater than or equal to 75 kg) or Rebetrin[®] (interferon alfa-2b 3 MIU subcutaneous three times a week plus ribavirin 1000 mg or 1200 mg by mouth). All subjects received 48 weeks of therapy followed by 24 weeks of treatment-free follow-up. COPEGUS or placebo treatment assignment was blinded. Sustained virological response was defined as undetectable (less than 50 IU/mL) HCV RNA on or after study week 68. PEGASYS in combination with COPEGUS resulted in a higher SVR compared

to PEGASYS alone or interferon alfa-2b and ribavirin (**Table 12**). In all treatment arms, subjects with viral genotype 1, regardless of viral load, had a lower response rate.

Table 12 Sustained Virologic Response to Combination Therapy (Study 4)

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

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

In Study 5 (see **Table 13**), all subjects received PEGASYS 180 mcg subcutaneous once weekly and were randomized to treatment for either 24 or 48 weeks and to a COPEGUS dose of either 800 mg or 1000 mg/1200 mg (for body weight less than 75 kg/greater than or equal to 75 kg). Assignment to the four treatment arms was stratified by viral genotype and baseline HCV viral titer. Subjects with genotype 1 and high viral titer (defined as greater than 2×10^6 HCV RNA copies/mL serum) were preferentially assigned to treatment for 48 weeks.

HCV Genotypes

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

HCV 2 and 3 – Irrespective of baseline viral titer, treatment for 24 weeks with PEGASYS and 800 mg of COPEGUS resulted in a similar SVR compared to longer treatment (48 weeks) and/or 1000 mg or 1200 mg of COPEGUS (see **Table 13**).

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

Table 13 Sustained Virologic Response as a Function of Genotype (Study 5)

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

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

Other Treatment Response Predictors

Treatment response rates are lower in subjects with poor prognostic factors receiving pegylated interferon alpha therapy. In studies 4 and 5, treatment response rates were lower in subjects older than 40 years (50% vs. 66%), in subjects with cirrhosis (47% vs. 59%), in subjects weighing over 85 kg (49% vs. 60%), and in subjects with genotype 1 with high vs. low viral load (43% vs. 56%). African-American subjects had lower response rates compared to Caucasians.

Paired liver biopsies were performed on approximately 20% of subjects in studies 4 and 5. Modest reductions in inflammation compared to baseline were seen in all treatment groups.

In studies 4 and 5, lack of early virologic response by 12 weeks (defined as HCV RNA undetectable or greater than 2log₁₀ lower than baseline) was grounds for discontinuation of treatment. Of subjects who lacked an early viral response by 12 weeks and completed a recommended course of therapy despite a protocol-defined option to discontinue therapy, 5/39 (13%) achieved an SVR. Of subjects who lacked an early viral response by 24 weeks, 19 completed a full course of therapy and none achieved an SVR.

Pediatric Patients

Previously untreated pediatric subjects 5 through 17 years of age (55% less than 12 years old) with chronic hepatitis C, compensated liver disease and detectable HCV RNA were treated with COPEGUS approximately 15 mg/kg/day plus PEGASYS 180 mcg/1.73 m² x body surface area once weekly for 48 weeks. All subjects were followed for 24 weeks post-treatment. Sustained virological response (SVR) was defined as undetectable (less than 50 IU/mL) HCV RNA on or after study week 68. A total of 114 subjects were randomized to receive either combination treatment of COPEGUS plus PEGASYS or PEGASYS monotherapy; subjects failing PEGASYS monotherapy at 24 weeks or later could receive open-label COPEGUS plus PEGASYS. The initial randomized arms were balanced for demographic factors; 55 subjects received initial combination treatment of COPEGUS plus PEGASYS and 59 received PEGASYS plus placebo; in the overall intent-to-treat population, 45% were female, 80% were Caucasian, and 81% were infected with HCV genotype 1. The SVR results are summarized in **Table 14**.

Table 14 Sustained Virologic Response (NV17424 - Study 6)

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

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

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

***Includes HCV genotypes 2, 3 and others

14.3 Chronic Hepatitis C and Coinfection with HIV (CHC/HIV) Study 7: PEGASYS Monotherapy and PEGASYS/COPEGUS Combination Therapy

In Study 7, subjects with CHC/HIV were randomized to receive either PEGASYS 180 mcg subcutaneous once weekly plus an oral placebo, PEGASYS 180 mcg once weekly plus COPEGUS 800 mg by mouth daily or ROFERON-A (interferon alfa-2a), 3 MIU subcutaneous three times a week plus COPEGUS 800 mg by mouth daily. All subjects received 48 weeks of therapy and sustained virologic response (SVR) was assessed at 24 weeks of treatment-free follow-up. COPEGUS or placebo treatment assignment was blinded in the PEGASYS treatment arms. All subjects were adults, had compensated liver disease, detectable hepatitis C virus, liver biopsy diagnosis of chronic hepatitis C, and were previously untreated with interferon. Subjects also had CD4+ cell count greater than or equal to 200 cells/mm³ or CD4+ cell count greater than or equal to 100 cells/mm³ but less than 200 cells/mm³ and HIV-1 RNA less than 5,000 cells/mm³, and stable status of HIV. Approximately 15% of subjects in the study had cirrhosis. Results are shown in **Table 15**.

Table 15 Sustained Virologic Response in Subjects with Chronic Hepatitis C Coinfected with HIV (Study 7)

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

Treatment response rates are lower in CHC/HIV subjects with poor prognostic factors (including HCV genotype 1, HCV RNA greater than 800,000 IU/mL, and cirrhosis) receiving pegylated interferon alpha therapy. Geographic region is not a prognostic factor for response. However, poor prognostic factors occur more frequently in the US population than in the non-US population.

Of the subjects who did not demonstrate either undetectable HCV RNA or at least a 2log₁₀ reduction from baseline in HCV RNA titer by 12 weeks of PEGASYS and COPEGUS combination therapy, 2% (2/85) achieved an SVR.

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

14.4 Chronic Hepatitis B Studies 8 and 9: PEGASYS Monotherapy

The safety and effectiveness of PEGASYS for the treatment of chronic hepatitis B were assessed in controlled clinical trials in HBeAg positive (Study 8) and HBeAg negative (Study 9) subjects with chronic hepatitis B.

Subjects were randomized to PEGASYS 180 mcg subcutaneous once weekly, PEGASYS 180 mcg subcutaneous once weekly combined with lamivudine 100 mg once daily by mouth or lamivudine 100 mg once daily by mouth. All subjects received 48 weeks of their assigned therapy followed by 24 weeks of treatment-free follow-up. Assignment to receipt of PEGASYS or no PEGASYS was not masked.

All subjects were adults with compensated liver disease, had chronic hepatitis B virus (HBV) infection, and evidence of HBV replication (serum HBV greater than 500,000 copies/mL for Study 8 and greater than 100,000 copies/mL for Study 8) as measured by PCR (COBAS AMPLICOR[®] HBV Assay). All subjects had serum alanine aminotransferase (ALT) between 1 and 10 times the upper limit of normal (ULN) and liver biopsy findings compatible with the diagnosis of chronic hepatitis.

The results observed in the PEGASYS and lamivudine monotherapy groups are shown in **Table 16**.

Table 16 Percentage of Subjects with Serological, Virological, Biochemical, and Histological Response

	Study 8 HBeAg positive			Study 9 HBeAg negative		
	Lamivudine N = 272		PEGASYS N = 271	Lamivudine N = 181		PEGASYS N = 177
	EOT ¹	EOF ²	EOF ²	EOT ¹	EOF ²	EOF ²
HBeAg Seroconversion (%)	20	19	32	NA	NA	NA
HBV DNA Response (%) ³	62	22	32	85	29	43
ALT Normalization (%)	62	28	41	73	44	59
HBsAg Seroconversion (%)	0	0	3	1	0	3
	N = 184		N = 207	N = 125		N = 143
Histological Improvement (%) ⁴	ND	40	41	ND	41	48
Changes in Ishak fibrosis score compared to baseline (%):						
- Improved ⁵	ND	32	25	ND	31	32
- Unchanged		20	25		23	30
- Worsened ⁵		16	26		15	19

¹ End of Treatment (week 48)

² End of follow-up – 24 weeks post-treatment (week 72)

³ Less than 100,000 copies/mL for HBeAg positive and less than 20,000 copies/mL for HBeAg negative subjects

⁴ Greater than or equal to 2 point decrease in Ishak necro-inflammatory score from baseline with no worsening of the Ishak fibrosis score. Not all subjects provided both initial and end of follow-up biopsies (missing biopsy rates: 19% to 24% in the PEGASYS and 31% to 32% in the lamivudine arms)

⁵ Change of 1 point or more in Ishak fibrosis score

PEGASYS co-administered with lamivudine did not result in any additional sustained response when compared to PEGASYS monotherapy.

Conclusions regarding comparative efficacy of PEGASYS and lamivudine treatment based upon the end of follow-up results are limited by the different mechanisms of action of the two compounds. Most treatment effects of lamivudine are unlikely to persist 24 weeks after therapy is withdrawn.

16 HOW SUPPLIED/STORAGE AND HANDLING

Single Use Vial: Each PEGASYS (peginterferon alfa-2a) 180 mcg single use, clear glass vial provides 1 mL containing 180 mcg peginterferon alfa-2a for subcutaneous injection. Each package contains 1 vial (NDC 0004-0350-09).

Prefilled Syringes Monthly Convenience Pack: Four prefilled syringes of PEGASYS (peginterferon alfa-2a), 180 mcg single use, graduated, clear glass prefilled syringes, in a box with 4 needles and 4 alcohol swabs (NDC 0004-0352-39) or without alcohol swabs (NDC 0004-0357-30). Each syringe is a 0.5 mL (½ cc) volume syringe supplied with a 27-gauge, ½-inch needle with needle-stick protection device.

Storage and Handling

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

Disposal Instructions

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 FDA Approved Medication Guide*].

17 PATIENT COUNSELING INFORMATION

- “See FDA-approved patient labeling (Medication Guide and Instructions for Use)”

17.1 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.

Pregnancy

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 healthcare provider immediately in the event of a pregnancy [see *Contraindications (4) and Warnings and Precautions (5.1)*].

Women of childbearing potential and men must use two forms of effective contraception during treatment and during the 6 months after treatment has been stopped; routine monthly pregnancy tests must be performed during this time [see *Contraindications (4) and COPEGUS Package Insert*].

To monitor maternal and fetal outcomes of pregnant women exposed to COPEGUS, the Ribavirin Pregnancy Registry has been established. Patients should be encouraged to register by calling 1-800-593-2214.

Laboratory Evaluations and Hydration

Patients should be advised that laboratory evaluations are required before starting therapy and periodically thereafter [see *Warnings and Precautions (5.16)*]. Patients should be instructed to remain well hydrated, especially during the initial stages of treatment. Patients should be advised to take COPEGUS with food.

General Information

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

Patients should be informed that it is not known if therapy with PEGASYS will prevent transmission of HBV infection to others or prevent cirrhosis, liver failure or liver cancer that might result from HBV infection.

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

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

Patients should be advised to avoid drinking alcohol to reduce the chance of further injury to the liver.

Patients should not switch to another brand of interferon without consulting their healthcare provider.

Dosing Instructions

Patients should be advised to take their prescribed dose of PEGASYS on the same day and approximately same time each week. Patients should also be advised that if they miss a dose, but remember within 2 days, to take their missed dose as soon as they remember and then to take their next dose on the day they normally do. If they remember when more than 2 days have passed, patients should be advised to consult their healthcare provider.

Patients must be instructed on the use of aseptic techniques when administering PEGASYS. Appropriate training for preparation using the vial or syringe must be given by a healthcare provider, including a careful review of the PEGASYS Medication Guide and Medication Guide Appendix: Instructions for Preparing and Giving a Dose with a PEGASYS[®] Prefilled Syringe and Appendix: Instructions for Use PEGASYS[®] Solution for Injection Vial.