January 2008

IMPORTANT DRUG WARNING

Dear Healthcare Professional:

Roche would like to advise you of a recent update to the PEGASYS® (Peginterferon alfa-2a) and COPEGUS® (Ribavirin, USP) package inserts. The revision to the product labels is a result of information about adverse events reported during postmarketing clinical use of PEGASYS and COPEGUS.

The WARNINGS section of the PEGASYS injectable solution and COPEGUS tablet labels has been updated. The information on Infections has been updated and expanded to include viral and fungal infections, along with bacterial infections. New language on serious skin reactions has been added to the Hypersensitivity section. A new class label section on Cerebrovascular Disorders has been added. The new language for these three WARNINGS is as follows:

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, 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.

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.

Hypersensitivity

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 rarely reported in patients receiving PEGASYS with and without ribavirin. Patients developing signs or symptoms or severe skin reactions must discontinue therapy. (see ADVERSE REACTIONS: Postmarketing Experience).

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

Important Safety Information:

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 Therapy should be withdrawn in patients with persistently severe or worsening signs or symptoms of these conditions.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

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

PEGASYS is contraindicated in patients with hypersensitivity to PEGASYS or any of its components, autoimmune hepatitis, and hepatic decompensation (Child-Pugh score greater than 6; class B and C) in cirrhotic CHC monoinfected patients before or during treatment. PEGASYS is also contraindicated in hepatic decompensation with Child-Pugh score greater than or equal to 6 in cirrhotic CHC patients coinfected with HIV before or during treatment. PEGASYS is also contraindicated in neonates and infants because i t contains benzyl alcohol. Benzyl alcohol is associated with an increased incidence of neurological and other complications in neonates and infants, which are sometimes fatal. PEGASYS and COPEGUS therapy is additionally contraindicated in patients with a hypersensitivity to COPEGUS or any of its components, in women who are pregnant, men whose female partners are pregnant, and patients with hemoglobinopathies (eg, thalassemia major, sickle-cell anemia).

Exacerbations of hepatitis during hepatitis B therapy are not uncommon and are characterized by transient and potentially severe increases in serum ALT. 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.

COPEGUS THERAPY SHOULD NOT BE STARTED UNLESS A REPORT OF A NEGATIVE PREGNANCY TEST HAS BEEN OBTAINED IMMEDIATELY PRIOR TO INITIATION OF THERAPY. Women of childbearing potential and men must use two forms of effective contraception during treatment and during the 6 months after treatment has concluded. Routine monthly pregnancy tests must be performed during this time. If pregnancy should occur during treatment or during 6 months post-therapy, the patient must be advised of the significant teratogenic risk of COPEGUS therapy to the fetus. Healthcare providers and patients are strongly encouraged to immediately report any pregnancy in a patient or partner of a patient during treatment or during 6 months after treatment cessation to the Ribavirin Pregnancy Registry at 1-800-593-2214.

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 coinfected 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. During treatment, patients' clinical status and hepatic function should be closely monitored, and PEGASYS treatment should be immediately discontinued if decompensation (Child-Pugh score ≥6) is observed. Ischemic and hemorrhagic cerebrovascular events have been observed in patients treated with interferon alpha-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 alpha-based therapies and these events is difficult to establish.

The most common adverse events reported for PEGASYS and COPEGUS combination therapy observed in clinical trials were fatigue/asthenia (65%), headache (43%), pyrexia (41%), myalgia (40%), irritability/anxiety/ nervousness (33%), insomnia (30%), alopecia (28%), neutropenia (27%), nausea/vomiting (25%), rigors (25%), anorexia (24%), injection-site reaction (23%), arthralgia (22%), depression (20%), pruritus (19%) and dermatitis (16%). The adverse event profile of coinfected patients treated with PEGASYS and COPEGUS was generally similar to that shown for monoinfected patients. Events occurring more frequently in coinfected patients were neutropenia (40%), anemia (14%), thrombocytopenia (8%), weight decrease (16%) and mood alteration (9%). In clinical trials of 48-week treatment duration, the adverse event profile of PEGASYS in chronic hepatitis B was similar to that seen in chronic hepatitis C PEGASYS monotherapy use, except for exacerbations of hepatitis. The most common adverse events reported for PEGASYS, observed in clinical studies, were pyrexia (54%), headache (27%), myalgia (26%), fatigue (24%), alopecia (18%) and anorexia (16%).

Serious adverse events in hepatitis B and hepatitis C trials included neuropsychiatric disorders (homicidal ideation, suicidal ideation, suicide attempt, suicide, psychotic disorder and hallucinations), serious and severe bacterial infections (sepsis), bone marrow toxicity (cytopenia and rarely, aplastic anemia), cardiovascular disorders (hypertension, supraventricular arrhythmias and myocardial infarction), hypersensitivity (including anaphylaxis), endocrine disorders (including thyroid disorders and diabetes mellitus), autoimmune disorders (including idiopathic thrombocytopenic purpura, thrombotic thrombocytopenic purpura, psoriasis, lupus, rheumatoid arthritis and interstitial nephritis), pulmonary disorders (dyspnea, pneumonia, bronchiolitis obliterans, interstitial pneumonitis and sarcoidosis), colitis (ulcerative and hemorrhagic/ischemic colitis), pancreatitis, and ophthalmologic disorders (decrease or loss of vision, retinopathy including macular edema and retinal thrombosis/hemorrhages, optic neuritis and papilledema). Adverse reactions reported during post-approval use of PEGASYS therapy, with and without ribavirin, include hearing impairment, hearing loss, serious skin reactions, including erythema multiforme major, and infections (bacterial, viral and fungal).

The ADVERSE REACTIONS section of the label has also been updated to add the following two events to the list of Serious Adverse Events (SAEs) occurring in <1% of patients: psychotic disorder and hallucination.

Other minor changes have been made to the package insert to update the half-life (CLINICAL PHARMACOLOGY/Pharmacokinetics section) and the cross-references between the ADVERSE REACTIONS and WARNINGS sections of the label.

The COPEGUS package insert has been updated in the Hypersensitivity and ADVERSE REACTIONS sections with the same new language detailed above.

In addition, the following statement has been added to the PEGASYS Medication Guide, in the section: **What is the most important information I should know about PEGASYS therapy?** The same language has been added to the COPEGUS Medication Guide under the subheading **What are the possible side effects of COPEGUS?**

> **Skin rash can occur in patients taking PEGASYS. In some patients a rash can be serious. If you develop a rash with fever, blisters, or sores in your mouth, nose or eyes or conjunctivitis (red or inflamed eyes, like "pink eye"), stop using PEGASYS and call your doctor right away.**

We encourage you to become familiar with these label revisions. If you have any questions or require additional information concerning PEGASYS and/or COPEGUS, please contact the Roche Pharmaceuticals Service Center at 1-800-526-6367. Updated package inserts are enclosed for your information. In addition, healthcare professionals can access the revised PEGASYS and COPEGUS complete Prescribing Information at http://www.rocheusa.com/products.

Roche will continue to monitor the safety of PEGASYS and COPEGUS through established reporting mechanisms and notify regulatory authorities of any serious adverse events for evaluation. We will continue to provide you with the most current product information for PEGASYS and COPEGUS moving forward. You can assist us in monitoring the safety of PEGASYS and COPEGUS by reporting adverse reactions to us at 1-800-526-6367, by FAX at 1-800-532-3931, or to the FDA at www.fda.gov/medwatch, or by mail to MedWatch, HF-2, Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20851.

PEGASYS, (Peginterferon alfa-2a), alone or in combination with COPEGUS, is indicated for the treatment of adults with chronic hepatitis C virus infection who have compensated liver disease and have not been previously treated with interferon alpha. Patients in whom efficacy was demonstrated included patients with compensated liver disease and histological evidence of cirrhosis (Child-Pugh class A) and patients with HIV disease that is clinically stable (e.g., antiretroviral therapy not required or receiving stable antiretroviral therapy).

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

Important Safety Information:

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

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

PEGASYS is contraindicated in patients with hypersensitivity to PEGASYS or any of its components, autoimmune hepatitis, and hepatic decompensation (Child-Pugh score greater than 6; class B and C) in cirrhotic CHC monoinfected patients before or during treatment. PEGASYS is also contraindicated in hepatic decompensation with Child-Pugh score greater than or equal to 6 in cirrhotic CHC patients coinfected with HIV before or during treatment. PEGASYS is also contraindicated in neonates and infants because i t contains benzyl alcohol. Benzyl alcohol is associated with an increased incidence of neurological and other complications in neonates and infants, which are sometimes fatal. PEGASYS and COPEGUS therapy is additionally contraindicated in patients with a hypersensitivity to COPEGUS or any of its components, in women who are pregnant, men whose female partners are pregnant, and patients with hemoglobinopathies (eg, thalassemia major, sickle-cell anemia).

Exacerbations of hepatitis during hepatitis B therapy are not uncommon and are characterized by transient and potentially severe increases in serum ALT. 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.

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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 coinfected 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. During treatment, patients' clinical status and hepatic function should be closely monitored, and PEGASYS treatment should be immediately discontinued if decompensation (Child-Pugh score ≥6) is observed. Ischemic and hemorrhagic cerebrovascular events have been observed in patients treated with interferon alpha-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 alpha-based therapies and these events is difficult to establish.

The most common adverse events reported for PEGASYS and COPEGUS combination therapy observed in clinical trials were fatigue/asthenia (65%), headache (43%), pyrexia (41%), myalgia (40%), irritability/anxiety/ nervousness (33%), insomnia (30%), alopecia (28%), neutropenia (27%), nausea/vomiting (25%), rigors (25%), anorexia (24%), injection-site reaction (23%), arthralgia (22%), depression (20%), pruritus (19%) and dermatitis (16%). The adverse event profile of coinfected patients treated with PEGASYS and COPEGUS was generally similar to that shown for monoinfected patients. Events occurring more frequently in coinfected patients were neutropenia (40%), anemia (14%), thrombocytopenia (8%), weight decrease (16%) and mood alteration (9%). In clinical trials of 48-week treatment duration, the adverse event profile of PEGASYS in chronic hepatitis B was similar to that seen in chronic hepatitis C PEGASYS monotherapy use, except for exacerbations of hepatitis. The most common adverse events reported for PEGASYS, observed in clinical studies, were pyrexia (54%), headache (27%), myalgia (26%), fatigue (24%), alopecia (18%) and anorexia (16%).

Serious adverse events in hepatitis B and hepatitis C trials included neuropsychiatric disorders (homicidal ideation, suicidal ideation, suicide attempt, suicide, psychotic disorder and hallucinations), serious and severe bacterial infections (sepsis), bone marrow toxicity (cytopenia and rarely, aplastic anemia), cardiovascular disorders (hypertension, supraventricular arrhythmias and myocardial infarction), hypersensitivity (including anaphylaxis), endocrine disorders (including thyroid disorders and diabetes mellitus), autoimmune disorders (including idiopathic thrombocytopenic purpura, thrombotic thrombocytopenic purpura, psoriasis, lupus, rheumatoid arthritis and interstitial nephritis), pulmonary disorders (dyspnea, pneumonia, bronchiolitis obliterans, interstitial pneumonitis and sarcoidosis), colitis (ulcerative and hemorrhagic/ischemic colitis), pancreatitis, and ophthalmologic disorders (decrease or loss of vision, retinopathy including macular edema and retinal thrombosis/hemorrhages, optic neuritis and papilledema). Adverse reactions reported during post-approval use of PEGASYS therapy, with and without ribavirin, include hearing impairment, hearing loss, serious skin reactions, including erythema multiforme major, and infections (bacterial, viral and fungal).

COPEGUS in combination with PEGASYS is indicated for the treatment of adults with chronic hepatitis C virus infection who have compensated liver disease and have not been previously treated with interferon alpha. Patients in whom efficacy was demonstrated included patients with compensated liver disease and histological evidence of cirrhosis (Child-Pugh class A) and patients with HIV disease that is clinically stable (e.g., antiretroviral therapy not required or receiving stable antiretroviral therapy).

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Sincerely,

Lars E. Birgerson, M.D., Ph.D.
Vice President
Medical Affairs

18-004-167-673-0108

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