PRODUCT MONOGRAPH

PrPEGASYS RBV®

PEGASYS®
peginterferon alfa-2a injection

Pre-filled syringes: 180 mcg/0.5 mL
Single-use Vials: 180 mcg/1 mL
ProClick® Autoinjector: 180 mcg/0.5 mL

Biological Response Modifier

and

COPEGUS®
ribavirin tablets, 200 mg

Antiviral Agent

Professed Standard

Hoffmann-La Roche Limited
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Mississauga, Ontario, Canada
L5N 5M8

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Date of Authorization:
November 18, 2015

Submission Control No: 180199

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PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Information as set forth in this label only applies to PEGASYS RBV.

Route of Administration	Dosage Form / Strength	Clinically Relevant Non-medicinal Ingredients
Subcutaneous	Solution in vial: 180 mcg/1.0 mL	Benzyl alcohol *For a complete listing see Dosage Forms, Composition and Packaging section.*
Subcutaneous	Solution in pre-filled syringe: 180 mcg/0.5 mL Solution in ProClick® autoinjector: 180 mcg/0.5 mL	Benzyl alcohol *For a complete listing see Dosage Forms, Composition and Packaging section.*
Oral	Tablet/200 mg	None *For a complete listing see Dosage Forms, Composition and Packaging section.*

DESCRIPTION

PEGASYS RBV (peginterferon alfa-2a and ribavirin) is a combination of PEGASYS (peginterferon alfa-2a) and COPEGUS (ribavirin) tablets.

PEGASYS: Peginterferon alfa-2a is a covalent conjugate of recombinant alfa-2a interferon (approximate molecular weight [MW] 20 kD) with a single branched bis-monomethoxy polyethylene glycol (PEG) chain (approximate MW 40 kD). Interferon alfa-2a is produced biosynthetically using recombinant DNA technology, and is the product of a cloned human leukocyte interferon gene inserted into and expressed in *E. coli*.

COPEGUS: Ribavirin, a synthetic nucleoside analog, has shown *in vitro* activity against some

RNA and DNA viruses, as well as immunomodulatory activity.

INDICATIONS AND CLINICAL USE

PEGASYS RBV (peginterferon alfa-2a and ribavirin) is indicated as part of a combination regimen with other hepatitis C virus (HCV) antiviral drugs that have been authorized for combination use in Canada, or alone for the treatment of Chronic Hepatitis C in:

- Adult patients without cirrhosis
- Adult patients with compensated cirrhosis,

including HCV/HIV co-infection patients with stable HIV disease with or without antiretroviral therapy.

For HCV genotype specific treatment, see DOSAGE AND ADMINISTRATION.

Treatment with PEGASYS RBV should be initiated and monitored by a physician experienced in the management of Chronic Hepatitis C.

For information on the use of PEGASYS RBV in combination with other HCV antiviral drugs authorized for use in Canada, refer to their Product Monographs.

Geriatrics (> 65 years of age): 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.

Pediatrics (< 18 years of age): PEGASYS RBV is not authorized for use in children and adolescents under the age of 18 years (see WARNINGS AND PRECAUTIONS: Special Populations, Pediatrics).

CONTRAINDICATIONS

When using in combination with other HCV antiviral drugs authorized for use in Canada, refer to their Product Monographs.

PEGASYS RBV (peginterferon alfa-2a and ribavirin) is contraindicated in:

- Women who are pregnant or by men whose female partners are pregnant. PEGASYS RBV should not be initiated until a report of a negative pregnancy test has been obtained immediately prior to initiation of therapy. Women of childbearing potential and their male partners must not receive PEGASYS RBV therapy unless they are using effective contraception (two reliable forms, one for each partner) during treatment with PEGASYS RBV and for the 6-month post-therapy period.
- Patients who are hypersensitive to alpha interferons, *E. coli*-derived products, polyethylene glycol, ribavirin and/or any ingredient in the formulation or component of PEGASYS or

COPEGUS (see DOSAGE FORMS, COMPOSITION AND PACKAGING).

- Patients with autoimmune hepatitis and patients with decompensated cirrhosis.
- HIV-HCV patients with cirrhosis and a base-line Child-Pugh score ≥ 6, except if only the high score (≥ 6) is induced by drugs known to cause indirect hyperbilirubinemia and without evidence of clinical hepatic decompensation. (See WARNINGS AND PRECAUTIONS: Hepatic/Biliary/Pancreas and DOSAGE AND ADMINISTRATION: Special Populations).
- Patients with a history of autoimmune disease.
- Patients with hemoglobinopathies (e.g. thalassemia, sickle-cell anemia).
- Neonates and infants because the PEGASYS component contains benzyl alcohol. There have been rare reports of death in neonates and infants associated with excessive exposure to benzyl alcohol. The amount of benzyl alcohol at which toxicity or adverse effects may occur in neonates or infants is not known.
- Patients who have a pre-existing severe psychiatric condition or a history of a severe psychiatric disorder, who have pre-existing thyroid abnormalities for which thyroid function cannot be maintained in the normal range by medication, and in women who are breast feeding.

WARNINGS AND PRECAUTIONS

Serious Warnings and Precautions

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

General

When using in combination with other HCV antiviral drugs authorized for use in Canada, refer to their Product Monographs.

Ribavirins, including the COPEGUS component of PEGASYS RBV (peginterferon alfa-2a and ribavirin) may cause birth defects and/or death of the exposed fetus. COPEGUS (ribavirin) must not be used by women who are pregnant or by men whose female partners are pregnant.

In order to improve traceability of biological medicinal products, the trade name of the administered product should be clearly recorded (or stated) in the patient file.

Treatment with PEGASYS RBV should be administered under the guidance of a qualified

physician and may lead to moderate to severe adverse experiences requiring dose reduction, temporary dose cessation or discontinuation of therapy.

Based on results of clinical trials, the use of ribavirin as monotherapy is not effective and COPEGUS must not be used alone.

The safety and efficacy of PEGASYS RBV have not been established in patients who have failed other alpha interferon treatments.

Patients should be informed regarding the potential benefits and risks attendant to the use of PEGASYS RBV. If home use is determined to be desirable by the physician, instructions on appropriate use should be given, including review of the contents of the Consumer Information, which does not disclose all possible adverse effects of PEGASYS RBV (see PART III: CONSUMER INFORMATION).

If home use is prescribed, patients should be thoroughly instructed in the importance of proper disposal of, and cautioned against, reuse of any needles and syringes.

Patients should be cautioned not to change to other pegylated interferons or switch to other alpha interferons without a medical consultation; changing from one interferon to another may require dosage change or adjustment.

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

Cardiovascular

Because cardiac disease may be worsened by ribavirin-induced anemia, patients with a history of significant or unstable cardiac disease in the previous six months should not use the COPEGUS component of PEGASYS RBV. Cardiovascular events such as hypertension, supraventricular arrhythmias, congestive heart failure, chest pain and myocardial infarction have been associated with interferon therapies, including PEGASYS. Therefore, PEGASYS RBV should be administered with caution to patients with pre-existing cardiac disease. Patients should be assessed before initiation of therapy and should be appropriately monitored during therapy. It is recommended that patients who have pre existing cardiac abnormalities have an electrocardiogram prior to initiation of PEGASYS RBV treatment and during the course of treatment. PEGASYS RBV should not be used in patients with pre existing severe, unstable or uncontrolled cardiac disease; if there is any deterioration of cardiovascular status, PEGASYS RBV therapy should be suspended or discontinued (see WARNINGS AND PRECAUTIONS: Hematologic).

Cerebrovascular

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.

Dental and Periodontal Disorders

Dental and periodontal disorders, which may lead to loss of teeth, have been reported in patients receiving PEGASYS RBV. In addition, dry mouth could have a damaging effect on teeth and mucous membranes of the mouth during long-term treatment with PEGASYS RBV. Patients should brush their teeth thoroughly twice daily and have regular dental examinations. In addition some patients may experience vomiting. If this reaction occurs, they should be advised to rinse out their mouth thoroughly afterwards.

Endocrine and Metabolism

Endocrine

As with other interferons, PEGASYS may cause or aggravate hypothyroidism and hyperthyroidism. Hypoglycemia, hyperglycemia, and diabetes mellitus have been observed in patients treated with PEGASYS RBV. Patients with these conditions at baseline who cannot be effectively controlled by medication should not be started on PEGASYS RBV therapy. Patients who develop these conditions during treatment and cannot be controlled with medication should not continue PEGASYS RBV therapy.

Gastrointestinal

Colitis

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

Growth and Development (Pediatric Patients)

During the course of PEGASYS plus ribavirin therapy lasting up to 48 weeks in patients aged 5 to 17 years, weight loss and growth inhibition were common (see ADVERSE REACTIONS). At 2 years post-treatment, 16% of pediatric patients were more than 15 percentiles below their baseline weight curve and 11% were more than 15 percentiles below their baseline height curve. The available longer term data on subjects who were followed up to 6 years post-treatment is too limited to determine the risk of reduced adult height in some patients. Safety and effectiveness have not been established in patients below the age of 18 (see INDICATIONS AND CLINICAL USE and Special Populations, Pediatrics).

Hematologic

Alpha interferons, including PEGASYS, may suppress bone marrow function which may result in severe cytopenias. Very rarely alpha interferons may be associated with pancytopenia including aplastic anemia. On the other hand, the primary toxicity of the COPEGUS component is hemolytic anemia (hemoglobin < 100 g/L), which was observed in approximately 13% of PEGASYS RBV treated patients in clinical trials. The anemia associated with COPEGUS occurs within 1 to 2 weeks of initiation of therapy. Because the initial acute drop in hemoglobin may be significant, it is advised that complete blood counts (CBC) should be obtained pre-treatment and at week 2 and week 4 of therapy, or more frequently if clinically indicated. Patients should then be followed as clinically appropriate.

Extreme caution should be exercised when administering PEGASYS RBV in combination with other potentially myelosuppressive agents (see WARNINGS AND PRECAUTIONS: Monitoring and Laboratory Tests).

PEGASYS RBV should be used with caution in patients with baseline absolute neutrophil counts (ANC) < 1.5 x 10^9/L, with baseline platelets < 90 x 10^9/L or baseline hemoglobin < 100 g/L. PEGASYS RBV should be discontinued, at least temporarily, in patients who develop severe decreases in ANC (< 0.5 x 10^9/L) and/or platelet (< 25 x 10^9/L) counts (see DOSAGE AND ADMINISTRATION: Dose Adjustments).

If there is any deterioration of hemoglobin blood concentration, COPEGUS should be suspended or discontinued (see DOSAGE AND ADMINISTRATION: Dose Adjustments). Although ribavirin has no direct cardiovascular effects, the anemia associated with PEGASYS RBV combination therapy may result in deterioration of cardiac function and/or exacerbation of the symptoms of cardiovascular disease. If there is any deterioration of cardiovascular status, COPEGUS therapy should be suspended or discontinued (see WARNINGS AND PRECAUTIONS: Cardiovascular and DOSAGE AND ADMINISTRATION).

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 ribavirin and azathioprine. This myelotoxicity was reversible within 4 to 6 weeks upon withdrawal of HCV antiviral therapy and concomitant azathioprine and did not recur upon reintroduction of either treatment alone (see DRUG INTERACTIONS).

Hepatic/Biliary/Pancreas

Hepatic

In patients who develop evidence of hepatic decompensation during treatment, PEGASYS RBV treatment should be discontinued. HIV-HCV co-infected patients with advanced cirrhosis receiving concomitant HAART may be at an increased risk of hepatic decompensation and possibly death when treated with ribavirin in combination with alpha interferons, including PEGASYS RBV. During treatment, co-infected patients should be closely monitored for signs and symptoms of hepatic decompensation (including ascites, encephalopathy, variceal bleeding, impaired hepatic synthetic function; (e.g. Child-Pugh score ≥ 6). The Child-Pugh scoring may be affected by factors related to treatment (i.e. indirect hyperbilirubinemia, decreased albumin) and not necessarily attributable to hepatic decompensation. Treatment with PEGASYS should be discontinued immediately in patients with hepatic decompensation (see DOSAGE AND ADMINISTRATION).

As with other alpha interferons, increases in ALT levels above baseline have been observed in patients treated with PEGASYS RBV, including those patients who exhibit a virological response. When the increase in ALT levels is progressive despite dose reduction or is accompanied by increased bilirubin, therapy should be discontinued (see DOSAGE AND ADMINISTRATION).

Pancreatitis

Pancreatitis, sometimes fatal, has occurred during alpha interferon treatment. PEGASYS RBV

treatment should be suspended if symptoms or signs suggestive of pancreatitis are observed. PEGASYS RBV should be discontinued in patients diagnosed with pancreatitis.

HBV

The safety and efficacy of PEGASYS RBV treatment has not been established for patients with hepatitis B virus (HBV).

Hydration

Adequate hydration must be maintained in patients undergoing therapy with PEGASYS RBV, since hypotension related to fluid depletion has been seen in some patients treated with alpha interferons. Fluid replacement may be necessary.

Hypersensitivity

Serious, acute hypersensitivity reactions (e.g. urticaria, angioedema, bronchoconstriction, anaphylaxis) have been rarely observed during alpha interferon therapy and cutaneous eruptions (Stevens Johnson syndrome, toxic epidermal necrolysis) have been very rarely reported. If such a reaction develops during treatment with PEGASYS RBV, treatment should be discontinued and appropriate medical therapy should be instituted immediately. Transient rashes do not necessitate interruption of treatment.

Immune

Exacerbation of autoimmune disease including myositis, hepatitis, immune thrombocytopenic purpura (ITP), rheumatoid arthritis, interstitial nephritis, thyroiditis and systemic lupus erythematosus has been reported in patients receiving alpha interferon therapy; PEGASYS RBV is contraindicated in patients with a history of autoimmune disease. In case of appearance of psoriatic lesions and sarcoidosis, discontinuation of therapy should be considered.

Infections

While fever may be associated with the flu-like syndrome reported commonly during interferon therapy, other causes of persistent fever must be ruled out, particularly in patients with neutropenia. Serious infections (bacterial, viral, fungal) 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.

Ophthalmologic

As with other interferons, retinopathy including retinal hemorrhages, cotton wool spots, papilledema, retinal artery or vein obstruction and serous retinal detachment, have been reported in rare instances after treatment with PEGASYS RBV. As with other interferons, decrease or loss of vision, macular edema and optic neuritis may be induced or aggravated by PEGASYS RBV treatment. All patients should receive an eye examination at baseline. Patients with preexisting ophthalmologic disorders (e.g. diabetic or hypertensive retinopathy) should receive periodic ophthalmologic exams during PEGASYS RBV treatment. Any patient complaining of loss of visual acuity or visual field must have a prompt and complete eye examination. PEGASYS RBV treatment should be discontinued in patients who develop new or worsening ophthalmologic disorders.

Psychiatric

Severe psychiatric adverse reactions may manifest in patients receiving therapy with interferons, including PEGASYS. Depression, suicidal ideation, and suicidal attempt may occur in patients with and without previous psychiatric illness. Other CNS effects including aggressive behavior, confusion and other alterations of mental status have been observed with alpha interferons. PEGASYS RBV should be used with extreme caution in patients who report a history of depression and physicians should monitor all patients (adults and pediatrics) for evidence of depression. Physicians should inform patients of the possible development of depression prior to initiation of PEGASYS RBV therapy, and patients should report any sign or symptom of depression immediately. If severe symptoms persist, therapy should be stopped and psychiatric intervention sought (see ADVERSE REACTIONS and DOSAGE AND ADMINISTRATION: Dose Adjustments). Safety and effectiveness have not been established in patients below the age of 18 (see INDICATIONS AND CLINICAL USE and Special Populations, Pediatrics).

Patients with Substance Use/Abuse
HCV infected patients having a co-occurring substance use disorder (alcohol, cannabis, etc.) are at an increased risk of developing psychiatric disorders or exacerbation of already existing psychiatric disorders when treated with alfa interferon. If treatment with alfa interferon is judged necessary in these patients, the presence of psychiatric co-morbidities and the potential for other substance use should be carefully assessed and adequately managed before initiating therapy. If necessary, an inter-disciplinary approach including a mental health care provider or addiction specialist should be considered to evaluate, treat and follow the patient. Patients should be closely monitored during therapy and even after treatment discontinuation. Early intervention for re-emergence or development of psychiatric disorders and substance use is recommended.

Renal
PEGASYS RBV therapy should not be initiated in patients with renal impairment, whether or not on hemodialysis, or continued if renal impairment occurs while on treatment, unless it is considered to be essential. It is recommended that renal function be evaluated in all patients prior to initiation of PEGASYS RBV therapy, preferably by estimating the patient's creatinine clearance. PEGASYS RBV should not be administered to patients with serum creatinine > 177 μmol/L or with creatinine clearance < 0.83 mL/sec as substantial increases in ribavirin plasma concentrations are seen at the recommended dosing regimen. There are insufficient data on the safety and efficacy in such patients to support recommendations for dose adjustments. Therefore, PEGASYS RBV must be administered with extreme caution and corrective action including drug discontinuation must be considered if adverse events develop (see DOSAGE AND ADMINISTRATION: Dose Adjustments and ACTION AND CLINICAL PHARMACOLOGY: Pharmacokinetics of PEGASYS RBV in Special Populations).

Respiratory
As with other alpha interferons, pulmonary symptoms, including dyspnea, pulmonary infiltrates, pneumonia, pneumonitis, including fatality, and pulmonary hypertension have been reported during therapy with PEGASYS RBV. Any patient developing fever, cough, and dyspnea or other respiratory symptoms must have a chest X-ray taken. If there is evidence of persistent or unexplained pulmonary infiltrates or pulmonary function impairment, treatment should be discontinued. PEGASYS RBV should not be administered to patients with chronic obstructive pulmonary disease (COPD).

Sexual Function/Reproduction

Reproduction

Ribavirin accumulates intracellularly and is cleared from the body very slowly. It is not known whether ribavirin contained in sperm will exert a potential teratogenic effect upon fertilization of the ova. Therefore, men must be instructed to use a condom to minimize delivery of ribavirin to their female partners. Male patients and their female partners of childbearing age must practice effective contraception (two reliable forms, one for each partner) during ribavirin therapy and for 6 months (based on the half-life of ribavirin of 12 days when the drug is administered at multiple doses) after treatment has stopped (see Pharmacokinetics of COPEGUS).

Evaluation of experimental animal studies showed reproductive toxicity. Significant teratogenic and/or embryocidal potential have been demonstrated for ribavirin in all animal species in which adequate studies have been conducted, occurring at doses well below the recommended human dose. 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 ribavirin dose. Survival of fetuses and offspring was reduced.

Peginterferon alfa-2a has not been studied for its teratogenic effect. Treatment with interferon alfa-2a resulted in a statistically significant increase in abortifacient activity in rhesus monkeys; no teratogenic effects were seen in the offspring delivered at term (see Special Populations: Pregnant Women).

Transplantation

Organ Transplant Recipients: The safety and efficacy of PEGASYS RBV treatment have not been established in patients with liver or other transplantations. As with other alpha interferons, liver and renal graft rejections have been reported on PEGASYS, alone or in combination with COPEGUS.

Special Populations

Pregnant Women: Ribavirins, including the COPEGUS component of PEGASYS RBV may cause birth defects and/or death of the exposed fetus. COPEGUS must not be used by women who are pregnant or by men whose female partners are pregnant.

PEGASYS RBV therapy must not be initiated until a report of a negative pregnancy test has been obtained immediately prior to initiation of therapy. Females of childbearing potential and males with female partners receiving PEGASYS RBV must be advised of the teratogenic/ embryocidal risks and must be instructed to use two forms of effective contraception (two reliable forms, one for each partner) during treatment and for 6 months after treatment has concluded. Routine monthly pregnancy tests must be performed during this time (see CONTRAINDICATIONS). Patients should be advised to notify the physician immediately in the event of a pregnancy. If pregnancy does occur during treatment or within six months from stopping treatment, the patient must be advised of the significant teratogenic risk of ribavirin to the fetus (see Sexual Function/Reproduction: Reproduction).

As with other alpha interferons, women of childbearing potential receiving PEGASYS therapy should be advised to use effective contraception during therapy (see Sexual Function/ Reproduction: Reproduction).

Nursing Women: It is not known whether the components of PEGASYS RBV are 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 PEGASYS RBV, nursing must be discontinued prior to the start of PEGASYS RBV therapy.

Pediatrics (< 18 years of age): Safety and effectiveness of PEGASYS RBV have not been established in patients below the age of 18. Therefore, PEGASYS RBV is not recommended for use in children and adolescents under the age of 18 years (see also INDICATIONS AND CLINICAL USE and WARNINGS AND PRECAUTIONS: Growth and Development (Pediatric Patients)).

Geriatrics (> 65 years of age): 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.

Monitoring and Laboratory Tests

Before beginning PEGASYS RBV combination therapy, standard hematological and biochemical profiles should be obtained for all patients. After initiation of therapy, hematological tests should be performed at 2 and 4 weeks and biochemical tests should be performed at 4 weeks. Additional testing should be performed periodically during therapy.

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

- Platelet count $\geq 90 \times 10^9$/L (75×10^9/L in patients with cirrhosis or transition to cirrhosis)
- ANC $\geq 1.5 \times 10^9$/L
- Serum creatinine concentration < 1.5 x upper limit of normal
- TSH and T4 within normal limits or adequately controlled thyroid function.
- HIV-HCV co-infection: CD4+ ≥ 200/µl or CD4+ ≥ 100/µl - < 200/µl and HIV-1 RNA < 5000 copies/mL using Amplicor HIV-1 Monitor Test, v 1.5.

PEGASYS RBV treatment was associated with decreases in both total white blood cell (WBC) count and ANC, usually starting within the first 2 weeks of treatment (see ADVERSE REACTIONS). In clinical studies, progressive decreases thereafter were infrequent. PEGASYS dose reduction is recommended when ANC decreases to levels below 0.75×10^9/L (see DOSAGE AND ADMINISTRATION: Dose Adjustments). For patients with ANC values below 0.5×10^9/L treatment should be suspended until ANC values return to more than 1.0×10^9/L. In clinical trials with PEGASYS RBV, the decrease in ANC was reversible upon dose reduction of PEGASYS or cessation of therapy.

PEGASYS RBV treatment was associated with decreases in platelet count, which returned to pre-treatment (baseline) levels during the post-treatment observation period (see ADVERSE REACTIONS). PEGASYS dose reduction is recommended when platelet count decreases to

levels below 50 x 10^9/L, and discontinuation of therapy is recommended when platelet count decreases to levels below 25 x 10^9/L (see DOSAGE AND ADMINISTRATION: Dose Adjustments).

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

Pregnancy Tests: Monthly pregnancy testing must be done during PEGASYS RBV combination therapy and for 6 months after discontinuing therapy in female patients and female partners of male patients.

Thyroid Changes: The occurrence of thyroid function abnormalities or the worsening of pre-existing thyroid disorders has been reported with the use of alpha interferon therapies, including PEGASYS RBV. Discontinuation of therapy should be considered in patients whose thyroid abnormalities cannot be adequately treated.

ADVERSE REACTIONS

The adverse reactions observed with other alpha interferons and ribavirin may be expected with PEGASYS (peginterferon alfa-2a) and PEGASYS RBV (peginterferon alfa-2a and ribavirin).

When using in combination with other HCV antiviral drugs authorized for use in Canada, refer to their Product Monographs.

Adverse Drug Reaction Overview

The frequency and severity of the most commonly reported adverse reactions are similar in patients treated with PEGASYS RBV combination therapy and interferon alfa-2b plus ribavirin. Flu like illness (rigors, pyrexia, myalgia), depression, insomnia, irritability, and alopecia were reported less frequently with PEGASYS RBV than with interferon alfa-2b plus ribavirin (> 5% difference between treatment groups). The most frequently reported adverse reactions with PEGASYS RBV combination therapy were mostly mild to moderate in severity and were manageable without the need for discontinuation of therapy.

Clinical Trial Adverse Drug Reactions

Chronic Hepatitis C Mono-infection

In mono-infected clinical trials, the incidence of withdrawal from treatment for all patients due to adverse events and laboratory abnormalities was 9% for PEGASYS monotherapy and 13% for PEGASYS RBV combination therapy. Respectively, only 1% or 3% of patients required discontinuation of either PEGASYS or PEGASYS RBV combination therapy due to laboratory abnormalities. Treatment-limiting events including serious and severe adverse events and adverse events and laboratory abnormalities leading to premature withdrawal or requiring dose

modification with the combination treatment occurred with the lowest frequency in patients receiving 24 weeks of treatment and the 800 mg dose of COPEGUS.

HIV-HCV Co-infection
In HIV-HCV co-infected patients, the clinical adverse events reported on PEGASYS, PEGASYS RBV and interferon alfa-2a plus ribavirin were similar to that observed in HCV mono-infected patients.

In the co-infection study, the incidence of withdrawal from treatment for clinical adverse events, laboratory abnormalities or AIDS-defining events was 16% for PEGASYS monotherapy and 15% for both PEGASYS RBV and interferon alfa-2a plus ribavirin given for 48 weeks. Respectively, 4%, 3% or 1% of patients required discontinuation of PEGASYS or PEGASYS RBV or interferon alfa-2a plus ribavirin for laboratory abnormalities. In PEGASYS RBV combination therapy, the PEGASYS dose modification occurred in 39%, and the COPEGUS dose modification occurred in 37%, of the co-infected patients. In interferon alfa-2a plus ribavirin therapy, the interferon alfa-2a dose modification occurred in 16%, and the COPEGUS dose modification occurred in 28%, of the co-infected patients. In PEGASYS monotherapy, PEGASYS dose modification occurred in 38% of the co-infected patients. Serious adverse events were reported in 21%, 17% and 15% of those receiving PEGASYS monotherapy, PEGASYS RBV or interferon alfa-2a plus ribavirin, respectively.

Limited safety data (N= 31) is available in co-infected patients with CD4+ cell counts <200/µl treated with PEGASYS and PEGASYS RBV. PEGASYS containing treatment was associated with an on-treatment reduction in absolute CD4+ cell count without a reduction in CD4+ cell percentage. CD4+ cell count indices returned to baseline values during the follow-up period of the study. PEGASYS containing treatment had no apparent negative impact on the control of HIV viremia during therapy or follow-up.

Because clinical trials are conducted under very specific conditions the adverse drug reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse drug reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates.

Table 1a Adverse Reactions (≥ 5% of Incidence in Any Treatment Group).

	HCV			HIV-HCV	
Body System	**Interferon alfa-2b 3MIU + 1000 or 1200 mg ribavirin 48 weeks**	**PEGASYS 180 mcg + 1000 or 1200 mg ribavirin 48 weeks**	**PEGASYS 180 mcg + 800 mg ribavirin 24 weeks**	**INF alfa-2a 3MIU + ribavirin 800 mg 48 weeks**	**PEGASYS 180 mcg + 800 mg ribavirin 48 weeks**
	N=443[a] **%**	**N=887[b]** **%**	**N=207[c]** **%**	**N=285[d]** **%**	**N=288[d]** **%**
Endocrine Disorders					
Hypothyroidism	5	4	2	1	<1
Gastrointestinal					
Nausea	28	28	29	19	24
Diarrhea	10	14	15	10	16

	HCV			HIV-HCV	
Body System	**Interferon alfa-2b 3MIU + 1000 or 1200 mg ribavirin 48 weeks**	**PEGASYS 180 mcg + 1000 or 1200 mg ribavirin 48 weeks**	**PEGASYS 180 mcg + 800 mg ribavirin 24 weeks**	**INF alfa-2a 3MIU + ribavirin 800 mg 48 weeks**	**PEGASYS 180 mcg + 800 mg ribavirin 48 weeks**
	N=443[a]	**N=887[b]**	**N=207[c]**	**N=285[d]**	**N=288[d]**
	%	**%**	**%**	**%**	**%**
Abdominal pain	9	10	9	7	7
Dry mouth	7	6	8	2	5
Nausea and vomiting	6	7	8	8	8
Dyspepsia	5	6	2	6	4
General					
Fatigue	53	49	45	36	40
Pyrexia	54	39	37	32	41
Rigors	34	25	30	17	16
Injection site reaction	16	21	28	8	10
Asthenia	16	15	18	23	26
Pain	9	10	9	4	6
Malaise	3	4	3	7	6
Metabolic and Nutritional					
Anorexia	26	27	20	25	23
Weight decrease	10	7	2	13	16
Appetite decrease	-	-	-	9	7
Musculoskeletal, Connective Tissue and Bone					
Myalgia	49	38	42	27	32
Arthralgia	23	22	20	13	16
Back pain	5	5	3	3	3
Neurological					
Headache	49	47	48	34	35
Insomnia	37	32	30	23	19
Dizziness (excluding vertigo)	14	15	13	9	7
Concentration impairment	13	10	8	2	2
Memory impairment	5	5	4	<1	1
Psychiatric					
Depression	28	21	17	20	22
Irritability	27	24	28	17	15
Anxiety	12	8	8	7	8
Mood alteration	6	6	8	2	<1
Emotional disorders	4	5	5	1	<1
Libido decreased	3	3	5	1	2
Nervousness	5	3	-	1	1
Respiratory, Thoracic and Mediastinal					
Dyspnea	14	13	11	3	7
Cough	7	13	8	2	3
Dyspnea (exertional)	7	4	3	2	3
Skin and Subcutaneous Tissue					
Alopecia	33	24	25	5	10
Pruritus	18	21	25	3	4
Dermatitis	13	16	15	<1	1
Dry Skin	13	12	13	4	4
Rash	5	9	7	5	5
Sweating increased	5	5	2	2	5

	HCV			HIV-HCV	
Body System	**Interferon alfa-2b 3MIU + 1000 or 1200 mg ribavirin 48 weeks**	**PEGASYS 180 mcg + 1000 or 1200 mg ribavirin 48 weeks**	**PEGASYS 180 mcg + 800 mg ribavirin 24 weeks**	**INF alfa-2a 3MIU + ribavirin 800 mg 48 weeks**	**PEGASYS 180 mcg + 800 mg ribavirin 48 weeks**
	N=443[a] %	**N=887[b] %**	**N=207[c] %**	**N=285[d] %**	**N=288[d] %**

[a] Data from study 1
[b] Pooled data from studies 1 and 2
[c] Data from study 2
[d] Data from study 3

Table 1b Adverse reactions reported in ≥ 1% to **< 5% on PEGASYS RBV combination or PEGASYS monotherapy in patients in clinical trials were:**

	Any Treatment Group	HIV-HCV Only
Body system	**Common ≥ 1% to < 5%**	**Other adverse reactions ≥ 1% to ≤ 3%**
Blood and lymphatic system disorders	lymphadenopathy, thrombocytopenia	
Cardiac disorders	palpitations,oedema peripheral, tachycardia	
Ear and labyrinth disorders	vertigo, earache, tinnitus	
Endocrine disorders	hyperthyroidism	
Eye disorders	vision blurred, eye inflammation, xerophthalmia, eye pain	
Gastrointestinal disorders	mouth ulceration, flatulence, gingival bleeding, stomatitis, constipation, dysphagia, glossitis	cheilitis
General disorders and administration site conditions	lethargy, chest pain, hot flushes, thirst, influenza-like illness	
Infections and infestations	herpes simplex, URI infection, bronchitis, oral candidiasis	influenza, pneumonia
Injury and poisoning	substance abuse	
Metabolism and nutrition disorders	dehydration	hyperlactacidemia /lactic acidosis
Musculoskeletal, connective tissue and bone disorders	muscle cramps, neck pain, musculoskeletal pain, bone pain, arthritis, muscle weakness	
Nervous system disorders	taste disturbance, weakness, paraesthesia, hypoaesthesia, tremor , migraine, somnolence, hyperaesthesia, nightmares, syncope	
Psychiatric disorders	aggression, suicidal ideation, confusional state	affect lability, apathy
Renal and urinary disorders		chromaturia
Reproductive system and breast disorders	impotence	
Respiratory, thoracic and mediastinal disorders	sore throat, pharyngolaryngeal pain, epistaxis, nasopharyngitis, sinus congestion, rhinitis, nasal congestion	
Skin and subcutaneous tissue disorders	eczema, night sweats, psoriasis, photosensitivity reaction, urticaria, skin disorder	acquired lipodystrophy
Vascular disorders	flushing, hypertension	

As with other alpha interferon therapies, uncommon to rare cases (< 1%) of the following *serious* adverse events have been reported in patients receiving PEGASYS RBV combination or PEGASYS monotherapy during clinical trials:

Blood and the lymphatic system disorders: thrombotic thrombocytopenic purpura (TTP)
Cardiac disorders: arrhythmia, atrial fibrillation, pericarditis
Eye disorders: corneal ulcer
Gastrointestinal disorders: peptic ulcer, gastrointestinal bleeding, pancreatitis, abdominal distention
Immune system disorders: autoimmune phenomena (e.g. ITP, thyroiditis, psoriasis, rheumatoid arthritis, SLE), sarcoidosis
Infections and Infestations: skin infection, otitis externa, endocarditis
Hepato-biliary: hepatic dysfunction, fatty liver, cholangitis, malignant hepatic neoplasm
Nervous system disorders: myositis, peripheral neuropathy*, coma
Psychiatric disorders: suicide, panic attack, psychotic disorder, hallucination
Respiratory, thoracic and mediastinal disorders: interstitial pneumonitis with fatal outcome, pulmonary embolism
Vascular disorders: cerebral hemorrhage

Rarely, alpha interferon including PEGASYS RBV or PEGASYS monotherapy may be associated with pancytopenia, and very rarely, aplastic anemia has been reported.

Uncommon to very rare cases of hearing impairment (deafness) have been reported.

* In protocol NR15961 (HIV-HCV) the frequency was reported as 2% in the PEGASYS monotherapy arm.

Chronic Hepatitis C Pediatric Patients
In a clinical study, pediatric subjects treated with PEGASYS plus ribavirin 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 curve percentiles for weight (64^{th} mean percentile at baseline, 60^{th} mean percentile at 2 years post-treatment) and height (54^{th} mean percentile at baseline, 56^{th} mean percentile at 2 years post-treatment). At the end of treatment, 43% (23 of 53) of subjects experienced a weight percentile decrease of more than 15 percentiles, and 25% (13 of 53) experienced a height percentile decrease of more than 15 percentiles on the normative growth curves. At 2 years post-treatment, 16% (6 of 38) of subjects were more than 15 percentiles below their baseline weight curve and 11% (4 of 38) were more than 15 percentiles below their baseline height curve.

55% (21 of 38) of subjects who completed the original study enrolled in the long-term follow up extending up to 6 years post-treatment. The study demonstrated that the post-treatment recovery in growth at 2 years post-treatment was maintained to 6 years post-treatment. Of the 4 subjects who were more than 15 percentiles below their baseline height curve at 2 years post-treatment, 2 entered the long-term follow-up study. They either returned to baseline comparable height percentiles at 6 years post-treatment (n=1) or a non-treatment related causative factor has been

identified (n=1). The available longer term data on subjects who were followed up to 6 years post-treatment is limited to determine the risk of reduced adult height in some patients. Safety and effectiveness have not been established in patients below the age of 18 (see INDICATIONS AND CLINICAL USE and Special Populations, Pediatrics).

Abnormal Hematologic and Clinical Chemistry Findings

Hematology
As with other interferon therapies, treatment with PEGASYS monotherapy and PEGASYS RBV combination therapy was associated with decreases in hematological values, which generally improved with dosage modification and returned to pretreatment levels within 4 to 8 weeks upon cessation of therapy (see WARNINGS AND PRECAUTIONS and DOSAGE AND ADMINISTRATION).

Although hematological toxicities of neutropenia, thrombocytopenia and anemia occurred more frequently in HIV-HCV patients, the majority could be managed by dose modification and the use of growth factors and infrequently required premature discontinuation of treatment.

Hemoglobin: Treatment with PEGASYS monotherapy for HCV was associated with small gradual decrease in hemoglobin and hematocrit. Less than 1% of all patients treated with PEGASYS, including those with cirrhosis, required dose modification for anemia (< 100 g/L). No patients receiving interferon alfa-2a required anemia-related dose modifications, due to drops in hemoglobin levels. Anemia due to hemolysis is the most significant toxicity of ribavirin therapy. Anemia (hemoglobin < 100 g/L) was observed in 13% of PEGASYS RBV combination-treated patients in HCV clinical trials. The maximum drop in hemoglobin occurred during the first 8 weeks of initiation of ribavirin therapy (see DOSAGE AND ADMINISTRATION: Dose Adjustments).

Approximately 10% of patients on PEGASYS RBV combination therapy required COPEGUS dose modification for anemia. Patients receiving 800 mg of COPEGUS for 24 weeks had the lowest frequency of decrease in hemoglobin levels to < 100 g/L; hemoglobin levels did not fall to < 85 g/L in any of these patients.

Anemia (hemoglobin < 100g/L) was reported in 8% and 14% of HIV-HCV co-infected patients treated with PEGASYS monotherapy or PEGASYS RBV combination therapy, respectively.

White Blood Cells: Treatment with PEGASYS for HCV was associated with decreases in values for both total WBC and ANC. Approximately 4% and 5% of patients on PEGASYS monotherapy or PEGASYS RBV combination therapy, respectively, had transient decreases in ANC to levels below 0.5×10^9/L at some time during therapy.

In HIV-HCV co-infected patients, 13% and 11% of those receiving PEGASYS monotherapy and PEGASYS RBV combination therapy, respectively, had decreases in ANC levels below 0.5×10^9/L.

Platelet Count: Treatment with PEGASYS was associated with decreases in values for platelet counts. In HCV clinical trials, approximately 5% of patients had decreases in platelet counts to

levels below 50 x 10^9/L. Most of these patients were cirrhotic at baseline and/or entered the study with a baseline platelet count as low as 75 x 10^9/L.

Table 2

	Interferon alfa-2b 3MIU + 1000 or 1200 mg ribavirin 48 wk	**Peginterferon alfa-2a 180 mcg + 1000 or 1200 mg ribavirin 48 wk**	**Peginterferon alfa-2a 180 mcg + 800 mg ribavirin 24 weeks**
	N=443[a] %	N=887[b] %	N=207[c] %
Hemoglobin level (< 100 g/L)	10.8	13	3.4
ANC (< 0.5 x 10^9/L)	1.1	5	3.4
Platelet counts (< 50 x 10^9/L)	0.2	5	3.9

[a] Data from study 1
[b] Pooled data from studies 1 and 2
[c] Data from study 2

In HIV-HCV patients, 10% and 8% of those receiving PEGASYS monotherapy and PEGASYS RBV combination therapy, respectively, had decreases in platelets below 50 x 10^9/L.

Clinical Chemistry

Thyroid Function: PEGASYS treatments was associated with clinically significant abnormalities in thyroid laboratory values requiring clinical intervention (see WARNINGS AND PRECAUTIONS: Monitoring and Laboratory Tests). The frequencies observed with PEGASYS treatments were similar to those observed with other interferons.

Triglycerides: Triglyceride levels are found to be elevated in patients receiving alpha interferon therapy, including PEGASYS.

For a full listing of PEGASYS monotherapy adverse reactions, please refer to the current PEGASYS product monograph.

Post-marketing

During the post-marketing period, erythema multiforme, Stevens-Johnson Syndrome, toxic epidermal necrolysis, pure red cell aplasia (PRCA) and homicidal ideation have been reported very rarely with PEGASYS RBV combination therapy.

Dehydration has been reported rarely with PEGASYS RBV combination therapy.

As with other alpha interferons, serous retinal detachment has been reported with PEGASYS RBV combination therapy.

As with other alpha interferons, liver and renal graft rejections have been reported on PEGASYS, alone or in combination with COPEGUS.

Adverse reactions reported in a post-marketing setting are: tongue pigmentation and seizures.

DRUG INTERACTIONS

Overview

When using in combination with other HCV antiviral drugs authorized for use in Canada, refer to their Product Monographs.

PEGASYS RBV (peginterferon alfa-2a and ribavirin)

No pharmacokinetic interactions between PEGASYS (peginterferon alfa-2a) and COPEGUS (ribavirin) have been observed in HCV clinical trials in which PEGASYS was used in combination with ribavirin.

PEGASYS: Treatment with 180 mcg PEGASYS once weekly for 4 weeks had no effect on the pharmacokinetic profiles of tolbutamide (CYP 2C9), mephenytoin (CYP 2C19), debrisoquine (CYP 2D6), and dapsone (CYP 3A4) in healthy male subjects.

COPEGUS: Results of *in vitro* studies using both human and rat liver microsome preparations indicated no cytochrome P450 enzyme mediated metabolism of ribavirin. Ribavirin does not inhibit cytochrome P450 enzymes. There is no evidence from toxicity studies that ribavirin induces liver enzymes. Therefore, there is a minimal potential for P450 enzyme- based interactions.

The bioavailability of ribavirin 600 mg was decreased by co-administration with an antacid containing magnesium, aluminium and methicone; AUCtf decreased 14%. It is possible that the decreased bioavailability in this study was due to delayed transit of ribavirin or modified pH. This interaction is not considered to be clinically relevant.

Any potential for interactions may persist for up to 2 months (5 half-lives for ribavirin) after cessation of ribavirin therapy due to the long half-life.

Drug-Drug Interactions

Table 3 Established or Potential Drug-Drug Interactions

Proper name	Ref	Effect	Clinical comment

Proper name	Ref	Effect	Clinical comment
Peginterferon alfa-2a and Methadone	CT	In a pharmacokinetic study of 24 HCV patients concomitantly receiving methadone maintenance therapy (median dose 95mg; range 30 mg to 150 mg), treatment with PEGASYS 180µg sc once weekly for 4 weeks was associated with mean methadone levels that were 10% to 15% higher than at baseline.	The clinical significance of this finding is unknown; nonetheless, patients should be monitored for the signs and symptoms of methadone toxicity.
Peginterferon alfa-2a and Theophylline	T	PEGASYS is a modest inhibitor of cytochrome P450 1A2: a 25% increase in theophylline's AUC was observed in the same study. Comparable effects on the pharmacokinetics of theophylline have been seen after treatment with standard alpha interferons. Alpha interferons have been shown to affect the oxidative metabolism of some drugs by reducing the activity of hepatic microsomal cytochrome P450 enzymes.	Theophylline serum concentrations should be monitored and appropriate dose adjustments of theophylline made for patients taking theophylline and PEGASYS concomitantly.
Ribavirin and Didanosine	CT	Ribavirin potentiated the antiretroviral effect of didanosine (ddI) *in vitro* and in animals by increasing the formation of the active triphosphate anabolite (ddATP). This observation also raised the possibility that concomitant administration of ribavirin and ddI might increase the risk of adverse reactions related to ddI (such as peripheral neuropathy, pancreatitis, and hepatic steatosis with lactic acidosis). While the clinical significance of these findings is unknown, one study of concomitant ribavirin and ddI in patients with HIV disease did not result in further reductions in viraemia or an increase in adverse reactions. Plasma pharmacokinetics of ddI were not significantly affected by concomitant ribavirin in this study, although intracellular ddATP was not measured. Exposure to didanosine or its active metabolite (dideoxyadenosine 5'-triphosphate) is increased when didanosine is co-administered with ribavirin.	Co-administration of ribavirin and didanosine is not recommended. Reports of fatal hepatic failure, as well as, peripheral neuropathy, pancreatitis, and symptomatic hyperlactatemia/lactic acidosis have been reported.

Proper name	Ref	Effect	Clinical comment
Ribavirin and Lamivudine, Stavudine, Zidovudine.	T	Ribavirin was shown *in-vitro* to inhibit phosphorylation of zidovudine and stavudine. The clinical significance of these findings is unknown. However, these *in-vitro* findings raise the possibility that concurrent use of ribavirin with either zidovudine or stavudine might lead to increased HIV plasma viremia.	Therefore, it is recommended that plasma HIV RNA levels be closely monitored in patients treated with ribavirin concurrently with either of these two agents. If HIV RNA levels increase, the use of ribavirin concomitantly with reverse transcriptase inhibitors must be reviewed.
	CT	No evidence of drug interaction was observed in 47 HIV-HCV co-infected patients who completed a 12 week pharmacokinetic substudy to examine the effect of ribavirin on the intracellular phosphorylation of some nucleoside reverse transcriptase inhibitors (lamivudine, zidovudine, or stavudine).	Plasma exposure of ribavirin did not appear to be affected by concomitant administration of NRTIs.

Legend: C = Case Study; CT = Clinical Trial; T = Theoretical

Peginterferon alfa-2a and telbivudine

A non-Roche sponsored pilot clinical trial in Hepatitis B investigating the combination of telbivudine 600 mg daily, with pegylated interferon alfa -2a, 180 micrograms once weekly by subcutaneous administration, indicated that this combination is associated with an increased risk for developing **serious peripheral neuropathy** at a rate of 10%. An increased risk can not be ruled out for combination treatment with other interferon products (pegylated or standard). The benefit of telbivudine in combination with interferon alfa (pegylated or standard) is not currently established in patients. It is not recommended that telbivudine be given in combination with PEGASYS.

Azathioprine:

Ribavirin, by having an inhibitory effect on inosine monophosphate dehydrogenase, may interfere with azathioprine metabolism possibly leading to an accumulation of 6-methylthioinosine monophosphate (6-MTIMP), which has been associated with myelotoxicity in patients treated with azathioprine.

In individual cases where the benefit of administering ribavirin concomitantly with azathioprine warrants the potential risk, it is recommended that close hematologic monitoring be done during concomitant azathioprine use to identify signs of myelotoxicity, at which time treatment with these drugs should be stopped (see WARNINGS AND PRECAUTIONS, Hematologic).

Drug-Herb Interactions

Pulmonary symptoms have been reported more frequently when sho-saiko-to, a Chinese herbal medicine, also known as Xiao-Chai-Hu was given with interferon alfa-2a. This herb should not be taken by patients receiving interferon.

Drug-Laboratory Interactions

Interactions with laboratory tests have not been established.

DOSAGE AND ADMINISTRATION

When using PEGASYS RBV in combination with other HCV antiviral drugs authorized for use in Canada, refer to their Product Monographs for specific dosage and administration instructions pertaining to those products.

Dosing Considerations

Substitution by any other biological medicinal product requires the consent of the prescribing physician.

Treatment should be individualized to the patient depending on baseline disease characteristics, response to therapy, and tolerability of the regimen.

Because the autoinjector is designed to deliver the full content, the autoinjector should only be used for patients who need the full dose. If the required dose is not available in an autoinjector, pre-filled syringes or vials should be used to administer the required dose.

Recommended Dose and Dosage Adjustments

Recommended Dose

Chronic Hepatitis C Mono-infection

Table 4a PEGASYS RBV (peginterferon alfa-2a and ribavirin) Dosing Recommendations

Genotype	PEGASYS Dose	COPEGUS Dose (Take with food)	Duration
Genotype 1, 4	180 mcg	< 75 kg = 1000 mg ≥ 75 kg = 1200 mg	48 weeks 48 weeks
Genotype 2, 3	180 mcg	800 mg (regardless of weight)	24 weeks

PEGASYS (peginterferon alfa-2a)

The recommended dose of PEGASYS is 180 mcg administered subcutaneously in the abdomen or thigh once-weekly for 48 weeks for Genotype 1, 4 patients and for 24 weeks for Genotype 2, 3 patients.

The recommended duration of PEGASYS RBV treatment for patients previously untreated with interferon alfa-2a is 24 to 48 weeks. The duration of treatment should be individualized to the patient depending on baseline disease characteristics, response to therapy, and tolerability of the regimen.

A treatment duration of 24 weeks is recommended for Genotype 2, 3 patients and a treatment duration of 48 weeks is recommended for Genotype 1, 4 patients.

COPEGUS (ribavirin)
The daily dose of COPEGUS is 1000 mg to 1200 mg for 48 weeks for Genotype 1, 4 patients and 800 mg for 24 weeks for Genotype 2, 3 patients administered orally in two divided doses. The dose should be individualized to the patient depending on baseline disease characteristics (eg, genotype as indicated), response to therapy, and tolerability of the regimen (see Table 4a). In the pivotal clinical trials, patients were instructed to take COPEGUS with food; therefore, patients are advised to take COPEGUS with food.

HIV-HCV Co-infection

Table 4b PEGASYS RBV Dosing Recommendations

Genotype	PEGASYS Dose	COPEGUS Dose (Take with food)	Duration
Genotype 1, 2, 3, 4	180 mcg	800 mg (regardless of weight)	48 weeks

The recommended dosage of PEGASYS in combination with 800 mg daily COPEGUS (ribavirin) is 180 mcg once weekly subcutaneously for 48 weeks, regardless of genotype. The safety and efficacy of combination therapy with COPEGUS doses greater than 800 mg daily or a duration of therapy less than 48 weeks has not been studied.

Early Predictability of Response
After 12 weeks of treatment, virologic response should be assessed. Treatment discontinuation should be considered in any HCV (including HIV-HCV) patient who has not achieved viral clearance or an HCV-RNA reduction from baseline of at least 99% by week 12 (see CLINICAL TRIALS).

Dose Adjustments

PEGASYS:
General: When dose modification is required for moderate to severe adverse reactions (clinical and/or laboratory), initial dose reduction to 135 mcg is generally adequate. However, in some cases, dose reduction to 90 mcg is necessary. Following improvement of the adverse reaction, dose increases to or toward the original dose may be considered (see WARNINGS AND PRECAUTIONS and ADVERSE REACTIONS).

Hematological: Dose reduction to 135 mcg PEGASYS is recommended if the ANC is less than 0.75×10^9/L. For patients with ANC values below 0.5×10^9/L, treatment should be suspended until ANC values return to over 1.0×10^9/L. Therapy should initially be reinstituted at 90 mcg PEGASYS, and the ANC monitored.

Dose reduction to 90 mcg PEGASYS is recommended if the platelet count is less than 50×10^9/L. Cessation of therapy is recommended when platelet count decreases to levels below 25×10^9/L.

COPEGUS:

Table 5 COPEGUS Dosage Modification Guidelines for Management of Treatment Emergent Anemia

Laboratory Values	Reduce COPEGUS dose to 600 mg/day* only if:	Discontinue COPEGUS if**:
Hemoglobin: Patients with no cardiac disease	< 100 g/L	< 85 g/L
Hemoglobin: Patients with History of Stable cardiac disease	> 20 g/L decrease in hemoglobin during any 4 week period during treatment (permanent dose reduction)	< 120 g/L after 4 weeks of dose reduction

* Patients whose dose of COPEGUS is reduced to 600 mg daily receive one 200 mg tablet in the morning and two 200 mg tablets in the evening.

** If the abnormality is reversed, COPEGUS may be restarted at 600 mg daily, and further increased to 800 mg daily at the discretion of the treating physician. However, a return to higher doses is not recommended.

In case of intolerance to COPEGUS, PEGASYS monotherapy may be continued.

Liver Function:
PEGASYS: Fluctuations in abnormalities of liver function tests are common in patients with chronic hepatitis. However, as with other alpha interferons, increases in ALT levels above baseline have been observed in patients treated with PEGASYS, including patients with a virological response.

The dose should be reduced initially to 90 mcg in the presence of progressive ALT increases above baseline values. When increase in ALT levels is progressive despite dose reduction, or is accompanied by increased bilirubin or evidence of hepatic decompensation, therapy should be discontinued.

Depression:
PEGASYS RBV should be used with extreme caution in patients who report a history of depression and physicians should monitor all patients for evidence of depression. For mild depression, no dose adjustment is necessary. For moderate depression, an initial dose reduction to 135 mcg is recommended; however, dose reduction to 90 mcg may be needed. Patients should be closely monitored. The frequency and nature of the monitoring should be based on the clinical judgment of the physician. If severe symptoms persist, therapy should be stopped and psychiatric intervention sought (see WARNINGS AND PRECAUTIONS).

Special Populations

Geriatric Use:
PEGASYS: No special dosage modification is required for geriatric patients with normal renal function, based upon pharmacokinetic, pharmacodynamic, tolerability, and safety data from clinical trials.

COPEGUS: There does not appear to be a significant age-related effect on the pharmacokinetics of ribavirin. However, as in younger patients, renal function must be determined prior to administration of COPEGUS.

Hepatic Impairment:

PEGASYS RBV has been shown to be effective and safe in patients with compensated cirrhosis (e.g. Child-Pugh A). PEGASYS RBV has not been studied in patients with decompensated liver disease (e.g. Child-Pugh B/C or bleeding esophageal varices) (see CONTRAINDICATIONS and WARNINGS AND PRECAUTIONS).

The Child-Pugh classification divides patients into groups A, B, and C, or "Mild", "Moderate" and "Severe" corresponding to scores of 5-6, 7-9 and 10-15, respectively.

Table 6 Modified Assessment

Assessment	Degree of abnormality	Score
Encephalopathy	None Grade 1-2 Grade 3-4*	1 2 3
Ascites	Absent Slight Moderate	1 2 3
S-Bilirubin (mg/dL) SI unit = μmol/l)	<2 2-3 >3 <34 34-51 >51	1 2 3 1 2 3
S-Albumin (g/L)	>35 35-28 <28	1 2 3
INR	<1.7 1.7-2.3 >2.3	1 2 3

Grading according to Trey, Burns and Saunders (1966)

COPEGUS: No pharmacokinetic interaction appears between ribavirin and hepatic function. Therefore, no dose adjustment of COPEGUS is required in patients with hepatic impairment.

Renal Impairment:
PEGASYS: No dose adjustments in the recommended starting dose of PEGASYS 180 mcg once weekly is required in patients with creatinine clearance > 0.33 mL/sec. In patients with impaired renal function, signs and symptoms of interferon toxicity should be closely monitored.

In subjects with end-stage renal disease requiring hemodialysis, a starting dose of 135 mcg should be used. Regardless of the starting dose or degree of renal impairment, patients should be monitored and appropriate dose reductions of PEGASYS during the course of therapy should be made in the event of adverse reactions.

COPEGUS: The pharmacokinetics of ribavirin are altered in patients with renal dysfunction due to reduction of apparent clearance in these patients. Therefore, it is recommended that renal function be evaluated in all patients prior to initiation of COPEGUS, preferably by estimating the patient's creatinine clearance. Substantial increases in ribavirin plasma concentrations are seen at the recommended dosing regimen in patients with serum creatinine > 177 μmol/L or with

creatinine clearance < 0.83 mL/sec. There are insufficient data on the safety and efficacy in these patients and therefore, drug discontinuation, must be considered if adverse events develop (see WARNINGS AND PRECAUTIONS and ACTION AND PHARMACOLOGY: Pharmacokinetics of PEGASYS RBV in Special Populations).

Missed Dose

PEGASYS: If the PEGASYS dose is missed and remembered within 2 days of the scheduled dose, the PEGASYS dose should be administered as soon as possible. The next scheduled PEGASYS dose should be given on the usual day. If more than 2 days have elapsed, the dosage schedule should be based on the clinical judgement of the physician.

COPEGUS: If a COPEGUS dose is missed but remembered within the same day, it should be taken as soon as possible. If an entire day has passed, the next dose should be taken based on the clinical judgement of the physician. Two doses should not be taken at the same time.

Administration

PEGASYS is administered subcutaneously in the abdomen or thigh once-weekly (see DOSAGE AND ADMINISTRATION, Recommended Dose). Visually inspect the solution prior to administration. Do not use if discoloured or if particles are present.

COPEGUS is administered orally in two divided doses. In the pivotal clinical trials, patients were instructed to take COPEGUS with food; therefore, patients are advised to take COPEGUS with food (see DOSAGE AND ADMINISTRATION, Recommended Dose).

OVERDOSAGE

PEGASYS RBV (peginterferon alfa-2a and ribavirin)

There is limited experience with overdosage with PEGASYS (peginterferon alfa-2a). 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.

No cases of overdose with COPEGUS (ribavirin) have been reported in clinical trials. Absorption of ribavirin is generally complete after one hour. Hypocalcemia and hypomagnesemia have been observed in persons administered dosages greater than four times the maximal recommended dosages. In many of these cases ribavirin was administered intravenously. Treatment of overdose with ribavirin should consist of general supportive measures including monitoring of vital signs and observation of clinical status of the patient. There is no specific antidote for overdose with ribavirin. Ribavirin concentration is essentially unchanged by hemodialysis.

For management of a suspected drug overdose, contact your regional Poison Control Centre.

ACTION AND CLINICAL PHARMACOLOGY

PEGASYS RBV (peginterferon alfa-2a and ribavirin)

Mechanism of Action

PEGASYS: Peginterferon alfa-2a possesses the *in vitro* antiviral and antiproliferative activities of interferon alfa-2a. Interferons bind to specific receptors on the cell surface initiating a complex intracellular signalling pathway and rapid activation of gene transcription. Interferon-stimulated genes modulate many biological effects including the inhibition of viral replication in infected cells, inhibition of cell proliferation, and immunomodulation. The clinical relevance of these *in vitro* activities is not known.

COPEGUS: The mechanism by which ribavirin in combination with peginterferon alfa-2a exerts its effects against hepatitis C virus (HCV) is unknown, although it is likely to involve both direct antiviral and immunomodulatory activities. More than additive inhibition of HCV subgenomic RNA replication in human liver cells has been seen in combination with PEGASYS.

Pharmacodynamics of PEGASYS

HCV RNA levels decline in a biphasic manner in responding patients with hepatitis C with and without compensated cirrhosis who have received treatment with 180 mcg PEGASYS. The first phase of decline occurs within 24 to 36 hours after the first dose of PEGASYS and the second phase of decline occurs over the next 4 to 16 weeks in patients who achieve a sustained response. Treatment with 180 mcg PEGASYS per week enhances the virion clearance and improves the virological end of treatment responses compared to treatment with interferon alfa-2a.

PEGASYS stimulates the production of effector proteins such as serum neopterin and 2', 5'-oligoadenylate synthetase (2', 5'-OAS) raises body temperature and causes reversible decreases in leukocyte and platelet counts. The stimulation of 2', 5'- OAS is maximal after single doses of 135 to 180 mcg PEGASYS and stays maximal throughout the one week dosing interval. The magnitude and duration of 2',5'-OAS activity induced by PEGASYS were reduced in subjects older than 62 years and in subjects with significant renal impairment (creatinine clearances of 0.33 to 0.67 mL/sec) compared to that seen in healthy subjects. The correlation between the *in vitro* and *in vivo* pharmacology and pharmacodynamic and clinical effects is unknown.

Pharmacokinetics

PEGASYS: The structure of the PEG moiety directly affects the clinical pharmacology of PEGASYS. Specifically, the size, branching and location of attachment of the 40 kD PEG moiety contribute to defining the absorption, distribution and elimination characteristics of PEGASYS. The pharmacokinetics of PEGASYS were studied in healthy volunteers and hepatitis C virus (HCV)-infected patients.

Absorption: The absorption of PEGASYS is sustained with peak serum concentrations reached 72 to 96 hours after dosing. Serum concentrations are measurable within 3 to 6 hours of a single dose. Dose proportional increases in AUC and Cmax are seen in patients that received once weekly doses of PEGASYS.

The absolute bioavailability of PEGASYS following sc administration in the abdomen is 84% and is similar to that seen with interferon alfa-2a.

Distribution: The volume of distribution at steady-state (V_{ss}) of 6 to 14 liters after intravenous dosing suggests that the drug is found mainly in the bloodstream and extracellular fluid.

Metabolism: The metabolic profile of PEGASYS is not fully characterized.

Excretion: The systemic clearance of PEGASYS is about 100 mL/h, which is 100-fold lower than that of interferon alfa-2a. After an intravenous dose, the terminal half-life of PEGASYS in healthy subjects is about 60 hours compared to 3 to 4 hours for standard interferon. The terminal half-life after subcutaneous administration in patients is longer with a mean value of 160 hours (84 to 353 hours). The terminal half-life after subcutaneous dosing may be reflecting the sustained absorption of PEGASYS and not the elimination of the drug.

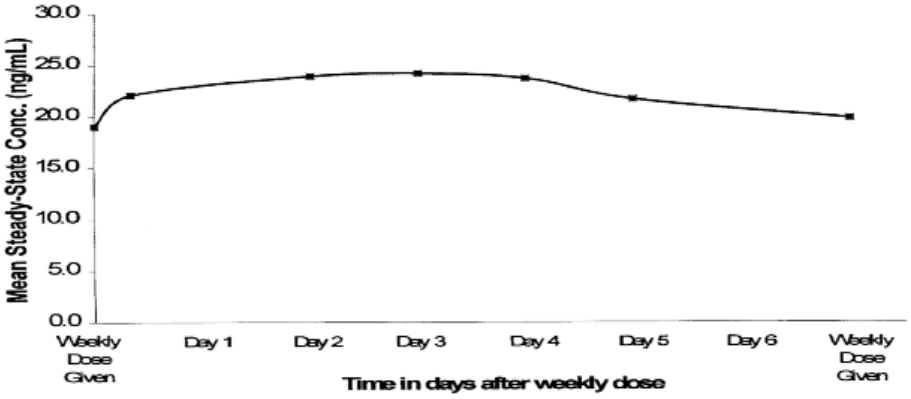
The kidneys eliminate less than 10% of a dose as the intact peginterferon alfa-2a. The rest is broken down metabolically.

Steady state serum levels are reached within 5 to 8 weeks of once-weekly dosing. Once steady state has been achieved, there is no accumulation of peginterferon alfa-2a. The peak to trough ratio after 48 weeks of treatment is about 1.5 to 2.0. Peginterferon alfa-2a serum concentrations are sustained throughout the 1 week dosing interval (168 hours) [Table **7** and Figure 1].

Table 7 Pharmacokinetic Parameters of PEGASYS after single and multiple dose of 180 mcg

PEGASYS Pharmacokinetic Parameter	Healthy Subjects 180 mcg sc (N=50)	CHC Patients 180 mcg sc (N=16)	
	Single Dose Mean±SD [Range]	Single Dose Mean±SD [Range]	Week 48 Dose Mean±SD [Range]
C_{max} (ng/mL)	14±5 [6-26]	15±4 [7-23]	26±9 [10-40]
T_{max} (h)	92±27 [48-168]	80±28 [23-119]	45±36 [0-97]
$AUC_{1\text{-}168h}$ (ng·h/mL)	1725±586 [524-3013]	1820±586 [846-2609]	3334±994 [1265-4824]
Clearance/F (mL/h)	94±56 [34-337]	83±50 [33-186]	60±25 [37-142]
Week 48 trough concentration (ng/mL)	Not applicable	Not applicable	16±6 [4-28]
Peak to trough ratio for week 48	Not applicable	Not applicable	1.7±0.4 [1.1-2.5]
Accumulation ($AUC_{Week\ 48}/AUC_{Single\ Dose}$)	Not applicable	Not applicable	2.3±1.0 [1.1-4.0]

Figure 1 Mean steady-state PEGASYS concentrations in patients with CHC following 180 mcg peginterferon alfa-2a in combination therapy



COPEGUS:

Absorption: Orally administrated ribavirin is absorbed rapidly, reaching maximal plasma concentrations between 1 and 2 hours. The $AUC_{0\text{-}192h}$ and C_{max} following a single oral dose of 600-mg of ribavirin ranged from 14 to 20 mg·h/mL and from 650 to 770 ng/mL, respectively. Intersubject variability was high, with values of approximately 30% for $AUC_{0\text{-}192h}$ and 40% for C_{max}. Absorption is extensive with about 10% to 15% of a radiolabelled dose excreted in the feces. However, the absolute bioavailability is between 33% to 65%, probably due to high first-pass metabolism. Ribavirin is absorbed from the gastrointestinal tract via an active sodium dependent nucleoside transport process. Since this process is saturable, less than proportional increases in C_{max} were observed for doses above 800 mg. However, the exposure as measured by $AUC_{0\text{-}192h}$ was proportional up to a 2400-mg dose.

Bioavailability of a single oral dose of ribavirin was increased by co-administration with a high-fat meal. The absorption was slowed (T_{max} was doubled) and the $AUC_{0\text{-}192h}$ and C_{max} increased by 42% and 66%, respectively, when the ribavirin film-coated tablet was taken with a high-fat meal compared with fasting conditions.

Distribution: Ribavirin partitions into all cells rapidly and extensively and a very large steady-state volume of distribution of about 850 liters after intravenous dosing. This distribution is facilitated by the sodium independent *es* nucleoside transporter that is present in all types of cells and thus ribavirin accumulates in erythrocytes, ova and spermatozoa. Ribavirin sequesters in erythrocytes extensively with a ratio of 60:1 between whole blood and plasma concentrations. Ribavirin does not bind to plasma proteins.

Metabolism: Ribavirin is metabolized via two major pathways:

- A reversible phosphorylation in nucleated cells forming mono-, di-, and tri-phosphate metabolites and
- Deribosylation and amide hydrolysis forming the triazole carboxylic acid metabolite. The triazole carboxylic acid and triazole carboxamide were the principal metabolites. The

cytochrome P450 enzyme system is not involved in the metabolism of ribavirin.

Excretion: Both renal excretion and metabolism are major routes of elimination of ribavirin in humans and animals. Total body clearance after intravenous dosing was about 20 L/h to 25 L/h, with about 30% accounted for by renal clearance. In humans, about 61% of the radioactivity of a 600-mg oral dose was eliminated in the urine within 336 hours, of which unchanged ribavirin accounted for 17%.

Due to extensive distribution, the terminal half-life of a single oral or intravenous dose is about 120 to 170 hours. This half-life is further prolonged to 270 to 300 hours following multiple doses. Extensive accumulation of ribavirin is seen after multiple dosing (BID) such that the AUC at steady state was sixfold higher than that of a single dose.

Pharmacokinetics Analysis of PEGASYS RBV

No pharmacokinetic interactions between PEGASYS and COPEGUS have been observed in clinical trials in which PEGASYS is used in combination with COPEGUS. Results from a pharmacokinetic substudy of a pivotal phase III trial demonstrated no pharmacokinetic interaction between peginterferon alfa-2a and ribavirin.

Special Populations and Conditions

Pediatrics (<18 years of age):

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

COPEGUS: Pharmacokinetic evaluations in pediatric patients have not been performed.

Geriatrics:

PEGASYS: In subjects older than 62 years, the AUC was modestly increased (1663 vs 1295 ng·h/mL, older than 62 years vs younger, respectively), but peak concentrations (9.1 vs 10.3 ng/mL) were similar in the two age groups (see DOSAGE AND ADMINISTRATION).

COPEGUS: Specific pharmacokinetic evaluations for elderly patients have not been performed. However, in a published population pharmacokinetic study, age was not a key factor in the kinetics of ribavirin; renal function is the determining factor.

Gender:

PEGASYS: The pharmacokinetics of PEGASYS after single subcutaneous injections were comparable between male and female healthy subjects.

COPEGUS: No clinically significant differences in the pharmacokinetics of ribavirin were observed between male and female subjects in a population pharmacokinetic analysis of 3600 sparsely collected serum concentration data from 138 patients.

Race:

PEGASYS: In a pharmacokinetic study in 40 CHC patients, no ethnicity-based differences in PEGASYS pharmacokinetic parameters were observed between Black (n=13) and Caucasian

(n=15) patients or Hispanic (n=12) and Caucasian patients.

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

Hepatic Insufficency:
PEGASYS: The pharmacokinetics of PEGASYS were similar between healthy subjects and patients with hepatitis C. Comparable pharmacokinetic profiles were seen in cirrhotic patients with compensated liver disease and patients without cirrhosis.

COPEGUS: Single-dose pharmacokinetics of ribavirin in patients with mild, moderate or severe hepatic dysfunction are similar to those of normal controls.

Renal Insufficency:
PEGASYS: Renal impairment is associated with decreased total apparent clearance and prolonged half-life. In subjects with a creatinine clearance between 0.33 and 0.67 mL/sec, the average total apparent clearance is reduced by approximately 30% compared with subjects with normal renal function following single doses of PEGASYS. Adverse events and laboratory abnormalities that occurred during the study were those expected following interferon administration and occurred with only slightly greater frequency in subjects with renal impairment (see WARNINGS AND PRECAUTIONS).

In subjects with end-stage renal disease undergoing hemodialysis, there is a 25% to 45% reduction in the clearance of peginterferon alfa-2a and doses of 135 mcg provide exposure similar to those observed in subjects with normal renal function receiving 180 mcg doses. Regardless of the starting dose or degree of renal impairment, patients should be monitored and appropriate dose reductions of PEGASYS during the course of therapy should be made in the event of adverse reactions (see WARNINGS AND PRECAUTIONS and DOSAGE AND ADMINISTRATION: Dose Adjustments).

COPEGUS: Single-dose ribavirin pharmacokinetics were altered (increased AUC_{tf} and C_{max}) in patients with renal dysfunction compared with control subjects whose creatinine clearance was greater than 1.50 mL/sec. The oral clearance of ribavirin is substantially reduced in patients with serum creatinine > 177 μmol/L or creatinine clearance < 0.83 mL/sec. There are insufficient data on the safety and efficacy of ribavirin in these patients and therefore, COPEGUS must be administered with extreme caution and corrective action including drug discontinuation must be considered if adverse events develop (see WARNINGS AND PRECAUTIONS and DOSAGE AND ADMINISTRATION: Dose Adjustments). Plasma concentrations of ribavirin are essentially unchanged by hemodialysis.

Genetic Polymorphism: Different HCV genotypes display considerable clinical variability in their response to PEGASYS and COPEGUS. Viral genetic determinants associated with the variable response have not been definitively identified.

STORAGE AND STABILITY

Stability and Storage Recommendations:
Store PEGASYS RBV (peginterferon alfa-2a and ribavirin) packages in the refrigerator at 2-8°C. Protect from light. Do not freeze or shake. Do not use PEGASYS RBV beyond the date of expiry.

If package components are separated: Store PEGASYS vials, autoinjectors or pre-filled syringes in the refrigerator at 2-8°C. Protect from light. Do not freeze or shake. Do not use PEGASYS beyond the date of expiry.

Parenteral drug products such as PEGASYS should be inspected visually for particulate matter and discolouration before administration. Do not use PEGASYS if it contains particulate matter or it appears discoloured. Store COPEGUS below 30°C or under refrigeration. Keep bottle tightly closed.

SPECIAL HANDLING INSTRUCTIONS

PEGASYS RBV (peginterferon alfa-2a and ribavirin)

Disposal of syringes/sharps:
The following points should be strictly adhered to regarding the use and disposal of syringes and other medicinal sharps:

- Needles and syringes should never be reused.
- Place all used needles, autoinjectors and syringes into a sharps container (puncture-proof disposable container).
- Keep this container out of the reach of children.
- Placing used sharps containers in the household waste should be avoided.
- Dispose of the full container according to local requirements or as instructed by your healthcare provider

For home use, a puncture resistant container for the disposal of used syringes, autoinjectors and needles should be supplied to the patients.

Disposal of unused/expired medicines:
The release of pharmaceuticals in the environment should be minimized. Medicines should not be disposed of via wastewater and disposal through household waste should be avoided. Use established “collection systems” if available in your location.

DOSAGE FORMS, COMPOSITION AND PACKAGING

Dosage forms:

PEGASYS (peginterferon alfa-2a) is a sterile, ready-to-use solution for subcutaneous injection. PEGASYS is supplied as 180 mcg/0.5 mL in single-use, graduated, clear glass pre-filled syringes and as 180 mcg/mL in single-use, clear glass vials. PEGASYS ProClick™ is supplied as 180 mcg/0.5 mL in single-use, disposable autoinjectors.

COPEGUS (ribavirin) is a light pink to pink, flat, oval, film-coated tablet with RIB and 200 engraved on one side and ROCHE on the other side. Each tablet contains 200 mg ribavirin for oral administration.

Composition:
PEGASYS Pre-filled Syringe: Each 0.5 mL contains 180 mcg of peginterferon alfa-2a (expressed as the amount of interferon alfa-2a), 4.0 mg sodium chloride, 0.025 mg polysorbate 80, 5.0 mg benzyl alcohol, 1.3085 mg sodium acetate trihydrate, 0.0231 mg acetic acid and water for injection, at pH 6 ± 0.2.

PEGASYS Vial: Each 1 mL vial contains 180 mcg of peginterferon alfa-2a (expressed as the amount of interferon alfa-2a), 8.0 mg sodium chloride, 0.05 mg polysorbate 80, 10.0 mg benzyl alcohol, 2.617 mg sodium acetate trihydrate, 0.0462 mg acetic acid and water for injection, at pH 6 ± 0.2.

PEGASYS ProClick® Autoinjector: Each 0.5 mL contains 180 mcg of peginterferon alfa-2a (expressed as the amount of interferon alfa-2a), 4.0 mg sodium chloride, 0.025 mg polysorbate 80, 5.0 mg benzyl alcohol, 1.3085 mg sodium acetate trihydrate, 0.0231 mg acetic acid and water for injection, at pH 6 ± 0.2.

The ready to use autoinjector includes a post-injection needle shield that was designed to help prevent needle-stick injuries and keeps the needle non-visible.

COPEGUS Tablets: Each COPEGUS tablet contains 200 mg ribavirin. Non-medicinal ingredients are: pregelatinized starch, sodium starch glycolate, microcrystalline cellulose, maize starch, magnesium stearate, ethyl cellulose, hydroxypropyl methylcellulose, titanium dioxide, talc, iron oxide yellow, iron oxide red, and triacetin.

Packaging:
PEGASYS RBV (peginterferon alfa-2a and ribavirin) is available in the following packaging configurations that provide sufficient peginterferon alfa-2a and ribavirin for 1 and 4 weeks of therapy:

PEGASYS RBV - PEGASYS Pre-filled syringes (PFS) and COPEGUS

1 carton containing	1 PFS of PEGASYS 180 mcg/0.5 mL and 1 injection needle* (27 gauge x ½ inch) 1 bottle of COPEGUS containing 28 tablets
1 carton containing	1 PFS of PEGASYS 180 mcg/0.5 mL and 1 injection needle* (27 gauge x ½ inch) 1 bottle of COPEGUS containing 35 tablets

1 carton containing	1 PFS of PEGASYS 180 mcg/0.5 mL and 1 injection needle* (27 gauge x ½ inch) 1 bottle of COPEGUS containing 42 tablets
1 carton containing	4 PFS of PEGASYS 180 mcg/0.5 mL and 4 injection needles* (27 gauge x ½ inch) 1 bottle of COPEGUS containing 112 tablets
1 carton containing	4 PFS of PEGASYS 180 mcg/0.5 mL and 4 injection needles* (27 gauge x ½ inch) 1 bottle of COPEGUS containing 140 tablets
1 carton containing	4 PFS of PEGASYS 180 mcg/0.5 mL and 4 injection needles* (27 gauge x ½ inch) 1 bottle of COPEGUS containing 168 tablets
1 carton containing	4 PFS of PEGASYS 180 mcg/0.5 mL and 4 injection needles* (27 gauge x ½ inch) 1 bottle of COPEGUS containing 168 tablets + 1 bottle of COPEGUS containing 28 tablets

* Injection needle manufactured by Terumo Europe N. V., Interleuvenlaan 40 Leuven, ZZ, Belgium 3001

PEGASYS RBV - PEGASYS vials and COPEGUS

1 carton containing	1 vial of PEGASYS 180 mcg/mL 1 bottle of COPEGUS containing 28 tablets
1 carton containing	1 vial of PEGASYS 180 mcg/mL 1 bottle of COPEGUS containing 35 tablets
1 carton containing	1 vial of PEGASYS 180 mcg/mL 1 bottle of COPEGUS containing 42 tablets
1 carton containing	4 vials of PEGASYS 180 mcg/mL 1 bottle of COPEGUS containing 112 tablets
1 carton containing	4 vials of PEGASYS 180 mcg/mL 1 bottle of COPEGUS containing 140 tablets
1 carton containing	4 vials of PEGASYS 180 mcg/mL 1 bottle of COPEGUS containing 168 tablets

PEGASYS RBV - PEGASYS ProClick® Autoinjector and COPEGUS

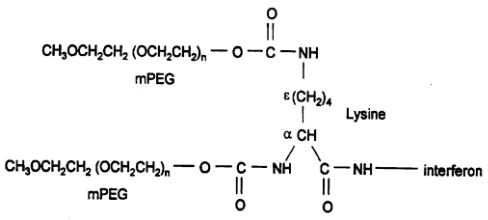
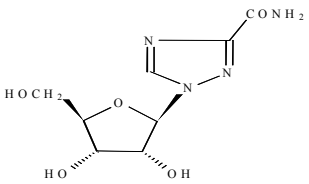
1 carton containing	1 PEGASYS ProClick® Autoinjector 180 mcg/0.5 mL 1 bottle of COPEGUS containing 28 tablets
1 carton containing	1 PEGASYS ProClick® Autoinjector 180 mcg/0.5 mL 1 bottle of COPEGUS containing 35 tablets
1 carton containing	1 PEGASYS ProClick® Autoinjector 180 mcg/0.5 mL

	1 bottle of COPEGUS containing 42 tablets
1 carton containing	4 PEGASYS ProClick® Autoinjector 180 mcg/0.5 mL 1 bottle of COPEGUS containing 112 tablets
1 carton containing	4 PEGASYS ProClick® Autoinjector 180 mcg/0.5 mL 1 bottle of COPEGUS containing 140 tablets
1 carton containing	4 PEGASYS ProClick® Autoinjector 180 mcg/0.5 mL 1 bottle of COPEGUS containing 168 tablets
1 carton containing	4 PEGASYS ProClick® Autoinjector 180 mcg/0.5 mL 1 bottle of COPEGUS containing 168 tablets + 1 bottle of COPEGUS containing 28 tablets

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

Drug Substance

Proper Name	Peginterferon alfa-2a (INN)	Ribavirin
Chemical Name	Bis-(N-monomethoxypolyethyleneglycol-urethanyl) lysyl interferon alfa-2a.	1-β-D-Ribofuranosyl-1H-1,2,4-triazole-3-carboxamide
Molecular formula and molecular mass	Peginterferon alfa-2a is made by conjugating a single branched polyethylene glycol chain (PEG), of approximate molecular weight of 40,000 dalton, to interferon alfa-2a (20,000 dalton) via a stable amide bond. Interferon alfa-2a is a monomeric protein containing 165 amino acids with a molecular formula $C_{860}H_{1349}N_{227}O_{255}S_9$.	244.2 $C_8H_{12}N_4O_5$
Structural Formula		
Physicochemical properties:	Colourless to light yellow solution	White to off-white powder
Other Properties	–	Ribavirin is freely soluble in water and exhibits lower solubility in organic solvents. The pKa of ribavirin is 12.25; the pH of a 2.0% w/v aqueous solution of ribavirin is approximately 6.3. Ribavirin melts between 166-168°C. The partition coefficient (1-octanol/water): log P=-2.24.

CLINICAL TRIALS

For information on clinical studies with PEGASYS RBV (peginterferon alfa-2a and ribavirin) in combination with other HCV antiviral drugs authorized for use in Canada, refer to their Product Monographs.

Chronic Hepatitis C Mono-infection

The safety and effectiveness of PEGASYS RBV (peginterferon alfa-2a and ribavirin) 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, elevated serum ALT activity and were previously untreated with interferon. Approximately 20% of patients in both studies had compensated cirrhosis.

Table 8 Summary of patient demographics for clinical trials for the treatment of Chronic Hepatitis C mono-infection

Study #	Trial Design	Dosage, route of administration and duration	Number	Gender	Mean age (Range)	% HCV Genotype 1
Study 1	Randomized, multicentre, partially blinded, active-controlled and placebo-controlled study.	PEGASYS 180 mcg sc once weekly with placebo, oral for 48 weeks of therapy followed by 24 weeks of treatment-free follow-up.	224	Male/Female (151/73)	42.4 years (19 – 64)	65%
		PEGASYS 180 mcg sc once weekly with COPEGUS 1000 mg, oral (body weight <75 kg) or 1200 mg (body weight ≥ 75 kg) for 48 weeks of therapy followed by 24 weeks of treatment-free follow-up.	453	Male/Female (324/129)	42.8 years (19 – 76)	66%
		Interferon alfa-2b plus ribavirin (active control), oral for 48 weeks of therapy followed by 24 weeks of treatment-free follow-up.	444	Male/Female (325/119)	42.3 years (20 – 71)	64%
Study 2	Randomized, multicentre, double blind study	PEGASYS 180 mcg sc qw with COPEGUS 800 mg for 24 weeks, followed by 24 weeks of treatment-free follow-up.	207	Male/Female (140/67)	41.2 years (18 – 66)	49%
		PEGASYS 180 mcg sc qw with COPEGUS 1000 mg (body weight <75 kg) or 1200 mg (body weight ≥ 75 kg) for 24 weeks, followed by 24 weeks of treatment-free follow-up.	280	Male/Female (185/95)	42.0 years (19 – 76)	42%
		PEGASYS 180 mcg sc qw with COPEGUS 800 mg for 48 weeks followed by 24 weeks of treatment-free follow-up.	361	Male/Female (226/135)	42.6 years (19 – 74)	69%
		PEGASYS 180 mcg sc qw with COPEGUS 1000 mg (body weight <75 kg) or 1200 mg (body weight ≥ 75 kg) for 48 weeks followed by 24 weeks of treatment-free follow-up.	436	Male/Female (287/149)	43.0 years (20 – 73)	62%

Study 1

Study 1 was a randomized, multicentre, partially blinded, active-controlled and placebo-controlled study that was designed to demonstrate the superiority (efficacy and safety) of PEGASYS RBV (a pegylated interferon plus ribavirin) combination therapy over interferon alfa-2b (a non-pegylated interferon) and ribavirin and PEGASYS monotherapy. Patients were randomized to receive either PEGASYS 180 mcg sc once weekly (qw) with placebo, PEGASYS 180 mcg sc qw with COPEGUS 1000 mg (body weight <75 kg) or 1200 mg (body weight ≥ 75 kg) or interferon alfa-2b plus ribavirin (active control) for 48 weeks of therapy followed by 24 weeks of treatment-free follow-up. COPEGUS or placebo treatment assignment was blinded. The study enrolled 1149 patients of which 28 never received treatment; the 1121 patients receiving treatment were 71% male, 84% Caucasian, 13% with cirrhosis or developing cirrhosis, and 65% genotype 1.

The sustained virological response (SVR) to treatment presented in Table 9, is defined as an undetectable HCV RNA (COBAS AMPLICOR™ HCV Test, version 2.0) value at the end of the treatment-free follow-up period in patients who received at least one dose of study medication.

The SVR of PEGASYS RBV combination therapy for 48 weeks was statistically significantly higher than the SVR of interferon alfa-2b and ribavirin (overall and by genotype). The SVR for patients with cirrhosis or developing cirrhosis treated with PEGASYS 180 mcg and COPEGUS 1000 mg or 1200 mg for 48 weeks was 41 % (n=23/56) (compared to 33% (n=18/54) for interferon alfa-2b 3 MIU and ribavirin 1000 - 1200 mg). Improvement over interferon alfa-2b and ribavirin was seen in patients with either high or low viral load (see Table 9). The SVR of the PEGASYS 180 mcg arm was essentially the same as that seen in clinical studies evaluating monotherapy.

Table 9 Response to Treatment

	Study 1					
	Interferon alfa-2b + ribavirin (I + R) 1000 mg or 1200 mg 48 Weeks		**PEGASYS + Placebo (P) 48 Weeks**		**PEGASYS + COPEGUS (P + C) 1000 mg or 1200 mg 48 Weeks**	
	N	**SVR**	**N**	**SVR**	**N**	**SVR**
Sustained Virological Response All patients [a]	444	198 (45%)	224	65 (29%)	453	245 (54%)
Genotype 1 Patients [b]	285	103 (36%)	145	29 (20%)	298	134 (45%)
Low viral load[1]	94	41 (44%)	44	16 (36%)	115	61 (53%)
High viral load[2]	189	62 (33%)	101	13 (13%)	182	73 (40%)
Genotype non-1 Patients [c]	159	95 (60%)	79	36 (46%)	155	111 (72%)
Low viral load[1]	56	38 (68%)	25	15 (60%)	44	33 (75%)
High viral load[2]	103	57 (55%)	54	21 (39%)	111	78 (70%)

[a] Cochran-Mantel-Haenszel test - P+C vs I + R (p= 0.003); P + C vs P (p=0.001); I + R vs P (p=0.001)
[b] Cochran-Mantel-Haenszel test - P+C vs I + R (p= 0.031); P + C vs P (p=0.001); I + R vs P (p=0.001)
c Cochran-Mantel-Haenszel test - P+C vs I + R (p= 0.036); P + C vs P (p=0.001); I + R vs P (p=0.001)
[1]Low viral load ≤ 800,000 IU/mL; [2]High viral load > 800,000 IU/mL

An administrative amendment was made to the protocol for Study 1 to obtain follow-up data on 125 patients whose last HCV RNA PCR measurement was undetectable or indeterminate (i.e. detectable by the COBAS AMPLICOR™ HCV Test, version 2.0 but not by the COBAS AMPLICOR HCV Monitor™ Test, version 2.0) at week 60 or 72 and who did not have two (2) consecutive measurements at week 60 or later (including those who were lost to follow-up while responding virologically). Follow-up data were collected for 68 of the 125 patients. The last single HCV RNA measurement was undetectable on or after week 68 in 264/453 patients treated with PEGASYS RBV, SVR of 58 %. The corresponding SVRs for the interferon alfa and ribavirin and PEGASYS monotherapy treatment arms were 214/444 (48%) and 67/224 (30%), respectively.

Sustained biochemical response at week 72 was highest among patients receiving PEGASYS RBV (50%) and statistically superior to the sustained biochemical response observed with interferon alfa-2b and ribavirin (43%, p=0.02) and PEGASYS monotherapy (32%, p=0.001). The difference in biochemical response between the patients treated with interferon alfa-2b and ribavirin and patients who received PEGASYS monotherapy was also statistically significant (p=0.004).

Paired biopsies were obtained in a subset of patients (17%) to evaluate the histological benefit of PEGASYS therapy. At the end of follow-up, 80% of patients who had a paired biopsy and were treated with PEGASYS RBV combination therapy had a histological response versus 76% of patients treated with interferon alfa-2b and ribavirin and 72% of patients treated with PEGASYS monotherapy. Sustained virological response was associated with histological response in most patients. Among patients with a sustained virological response and paired biopsies, 89% (100 of 112 patients) had a histological response. Histological response was defined as ≥ 2 point decrease in total HAI score at end of follow-up as compared with pretreatment.

Published Literature

In the publication of Study 1, by Fried et al., the comparison between PEGASYS 180 mcg + COPEGUS (1000 mg or 1200 mg) and interferon alfa-2b 3 MIU and ribavirin (1000 mg or 1200 mg) was reported with the following SVRs. Overall SVR in patients treated for 48 weeks was 56% for PEGASYS + COPEGUS versus interferon alfa-2b 3 MIU + ribavirin (44%, p<0.001). Genotype 1 patients receiving PEGASYS + COPEGUS (46% vs 36%, p=0.01); Genotype 1 with low viral load (56% vs 43%, p=NA); Genotype 1 with high viral load (41% vs 33%, p=NA); Genotype 2 and 3 (achieved an SVR of 76% vs 61%, p=0.005); Genotype 2 or 3 with low viral load (81% vs 65%, p=NA) and Genotype 2 or 3 patients with high viral load (74% vs 58%, p=NA).

Study 2

Study 2 was a randomized, multicentre, double-blind study that was prospectively designed to evaluate the duration of PEGASYS RBV treatment (24 weeks vs 48 weeks of treatment) and COPEGUS dose (800 mg fixed dose vs 1000 or 1200 mg by body weight) in patients randomized by HCV genotype and viral load. Patients were randomized to receive either PEGASYS 180 mcg sc qw with COPEGUS 800 mg for 24 weeks, PEGASYS 180 mcg sc qw with COPEGUS 1000 mg (body weight <75 kg) or 1200 mg (body weight ≥ 75 kg) for 24 weeks, PEGASYS 180 mcg sc qw with COPEGUS 800 mg for 48 weeks or PEGASYS 180 mcg

sc qw with COPEGUS 1000 mg (body weight <75 kg) or 1200 mg (body weight ≥ 75 kg) for 48 weeks followed by 24 weeks of treatment-free follow-up. The study enrolled 1311 patients of which 27 never received treatment; the 1284 treated patients were 65% male, 89% Caucasian, 25% with cirrhosis or developing cirrhosis, and genotype 1 varied by treatment group (42% to 69%).

The SVR to treatment presented in Table 10 is defined as an undetectable HCV RNA (COBAS AMPLICOR™ HCV Test, version 2.0) value at the end of the treatment-free follow-up period at or beyond week 44 (24 week treatment groups) or week 68 (48 week treatment groups).

Table 10 Rates of Response to Treatment Based on Genotype and Viral Load

	24 Weeks Treatment				48 Weeks Treatment			
	PEGASYS + COPEGUS 800 mg		PEGASYS + COPEGUS 1000 mg or 1200 mg		PEGASYS + COPEGUS 800 mg		PEGASYS + COPEGUS 1000 mg or 1200 mg	
	N	SVR	N	SVR	N	SVR	N	SVR
All patients	207	n/a	280	n/a	361	n/a	436	265 (61%)
Genotype 1	101	29 (29%)	118	48 (41%)	250	99 (40%)	271	138 (51%)
Low viral load	51	21 (41%)	71	36 (51%)	60	32 (53%)	85	52 (61%)
High viral load	50	8 (16%)	47	12 (26%)	190	67 (35%)	186	86 (46%)
Genotype non-1	106	83 (78%)	162	127 (78%)	111	81 (73%)	165	127 (77%)
Low viral load	39	28 (72%)	61	47 (77%)	41	32 (78%)	57	44 (77%)
High viral load	67	55 (82%)	101	80 (79%)	70	49 (70%)	108	83 (77%)

The SVR in genotype 1 patients, irrespective of low or high viral load, was highest in the group treated for 48 weeks with 1000 mg or 1200 mg of COPEGUS in patients with and without cirrhosis. The SVR in genotype 1 cirrhosis or developing cirrhosis patients who were treated with PEGASYS 180 mcg and COPEGUS 1000 mg or 1200 mg for 48 weeks was 41% (n=32/78). The SVR for all patients treated with PEGASYS 180 mcg and COPEGUS 1000 mg or 1200 mg for 48 weeks was 61 % (n=265/436). The SVR for patients with cirrhosis or developing cirrhosis was 50 % (n=58/115).

The study results demonstrated that treatment for 24 weeks with PEGASYS RBV combination therapy in patients infected with genotype non-1 (predominantly genotypes 2 and 3), was as efficacious as treatment for 48 weeks in patients infected with genotype non-1, either with low or high viral load. In genotype non-1 genotypes 2 and 3 patients, the 800 mg dose of COPEGUS was as effective as the 1000 mg or 1200 mg dose of COPEGUS. In the small number of patients evaluated with genotype 4 across all treatment groups (n=36), the SVR was highest in the group of patients treated for 48 weeks with 1000 mg or 1200 mg of COPEGUS (n=9/11, 82%). The SVR (73%) in genotype 2 and 3 patients with cirrhosis or developing cirrhosis treated for 48 weeks with PEGASYS 180 mcg and 1000 mg or 1200 mg of COPEGUS was similar to the SVR (70%) for 24 weeks of treatment with PEGASYS 180 mcg and 800 mg of COPEGUS.

Paired biopsies were obtained in a subset of patients (20%). Percentages of patients with a histological response were similar in all four treatment groups and ranged from 72% to 78%. The total HAI score with fibrosis decreased in all four treatment groups, and the median change ranged from -3.5 to -4. There were nine patients whose HAI score worsened. None of these

patients were sustained virological responders.

There was a good correlation between SVR and histological response; 79% to 97% of patients with a SVR also had a histological response across all treatment groups.

Published Literature
In publication of Study 2, by Hadziyannis et al., the overall SVR in patients treated for 48 weeks with PEGASYS 180 mcg and COPEGUS (1000 or 1200 mg) was 63%. In this arm, results were further reported as follows: Genotype 1 patients had an SVR of 52%, Genotype 1 with low viral load had an SVR of 65%, and those with high viral load had an SVR of 47%. In another arm of the study, Genotype 2 and 3 patients were treated for 24 weeks with PEGASYS 180 mcg and COPEGUS 800 mg. This arm reported SVRs in 84% of patients. Low viral load patients achieved an SVR of 85%, and high viral load achieved an SVR of 84%.

Predictability of Response
Patients who do not demonstrate an early virological response (defined as achieving undetectable levels of HCV RNA or at least a 99% reduction in viral titer from baseline by the end of 12 weeks of treatment) to PEGASYS RBV combination therapy are unlikely to achieve a SVR at week 72 with continuation of treatment. Among patients treated with PEGASYS 180 mcg and COPEGUS 1000 mg or 1200 mg combination therapy in the studies 1 and 2, 108 of the 113 patients with a lack of an early virological response did not achieve a SVR at week 72. The results of this analysis indicate a 96% negative predictability by week 12. For difficult to treat patients (genotype 1, high viral load) on PEGASYS RBV combination therapy, all patients without an early virological response did not achieve a SVR at week 72, indicating a 100% negative predictability by week 12. Consideration should be given to discontinuing therapy if virological results by week 12 do not indicate a response to therapy.

Among patients achieving an early virological response, the rate of sustained virological response was as high as 75% in those who maintained the full dosing schedule (at least 80% of the planned treatment).

Anti-Interferon Antibodies
A total of 14 out of 294 patients (4.8%) treated with 180 mcg PEGASYS and 1000-1200 mg COPEGUS developed neutralizing anti-interferon antibodies. The development of neutralizing anti-interferon antibodies does not preclude achieving a sustained virological response. Nine (9) of the 14 patients who developed neutralizing anti-interferon antibodies had a sustained virological response.

HIV-HCV Co-Infection

Study 3

In the co-infection clinical trial, study 3, 859 HIV-HCV co-infected patients were randomized and treated with PEGASYS, PEGASYS RBV or interferon alfa-2a 3 MIU three times weekly and ribavirin 800 mg/day for 48 weeks followed by a 24 week treatment free follow-up. The sustained virologic responses for the three treatment groups are summarized for all patients and by genotype in Table 12.

Table 11 Summary of patient demographics for clinical trials in HCV-HIV co-infection

Study #	Trial Design	Dosage, route of administration and duration	Number	Gender	Mean age (Range)	% HCV Genotype 1
Study 3	randomized, multicentre, partially blinded, active-controlled and placebo-controlled study and drug interaction nested trial between PEG-IFN alfa-2a and protease inhibitors.	PEGASYS 180 mcg/week and placebo for 8 weeks followed by a 24 week treatment free follow-up.	286	Male/Female (234/52)	40.0 years (22 – 66)	61%
		PEGASYS 180 mcg/week and COPEGUS 800 mg/day for 48 weeks followed by a 24 week treatment free follow-up.	288	**Male/Female (232/57)**	39.7 years (20 – 64)	61%
		Interferon alfa-2a 3 MIU three times weekly and ribavirin 800 mg/day for 48 weeks followed by a 24 week treatment free follow-up.	285	**Male/Female (231/54)**	40.1 years (18 – 74)	60%

Table 12 Sustained Virologic Response in HIV-HCV Co-infected Patients

	PEGASYS 180mcg + Placebo 48 weeks	PEGASYS 180mcg + COPEGUS 800 mg 48 weeks	Interferon alfa-2a 3MIU + COPEGUS 800 mg 48 weeks
All patients	20% (58/286)*	40% (116/289)*	12% (33/285)*
Genotype 1	14% (24/175)	29% (51/176)	7% (12/171)
Genotype 2/3	36% (32/90)	62% (59/95)	20% (18/89)

*** PEGASYS 180mcg COPEGUS 800mg *vs.* Interferon alfa-2a 3MIU COPEGUS 800mg: Odds Ratio (95% CI) = 5.40 (3.42 to 8.54) p-value (stratified Cochran-Mantel-Haenszel test) = < 0.0001**

*** PEGASYS 180mcg COPEGUS 800mg *vs.* PEGASYS 180mcg: Odds Ratio (95% CI): 2.89 (1.93 to 4.32), p-value (stratified Cochran-Mantel-Haenszel test) = < 0.0001**

*** Interferon alfa-2a 3 MIU COPEGUS 800 mg vs. PEGASYS 180mcg: Odds Ratio (95% CI): 0.53 (0.33 to 0.85), p-value (stratified Cochran-Mantel-Haenszel test) = < 0.0084**

Predictability of Response

Patients who do not demonstrate an early virological response (defined as achieving undetectable levels of HCV RNA or at least a 99% reduction in viral titer from baseline by the end of 12 weeks of treatment) to PEGASYS RBV combination therapy are unlikely to achieve a SVR at week 72 with continuation of treatment. In co-infection clinical study 3, the negative predictive value that has been observed in HIV-HCV co-infected patients treated with PEGASYS RBV was

(98%). Positive predictive value of 45% and 70% were observed for genotype 1 and genotype 2/3 HIV-HCV co-infected patients receiving PEGASYS RBV combination therapy, respectively.

DETAILED PHARMACOLOGY

PEGASYS RBV (peginterferon alfa-2a and ribavirin)

Nonclinical Pharmacology:
Peginterferon alfa-2a: The preclinical studies have demonstrated that peginterferon alfa-2a (PEG-IFN) retains the ability to bind to the alpha interferon receptor, to activate interferon-induced signaling pathways, and to stimulate the expression of a known interferon-inducible human gene *in vitro*. PEG-IFN has also been shown to retain antiviral and antiproliferative properties typical of an alpha interferon. These *in vitro* data support the hypothesis that the biological activity of interferon alfa-2a (IFN) is retained following the pegylation process and is mediated by the IFN portion of the PEG-IFN molecule, acting via a classical alpha interferon pathway.

The *in vivo* studies demonstrate that PEG-IFN retains biological activity as shown by induction of 2,5-OAS activity in the monkey and by reduction of tumor xenograft growth and regression in the mouse. The comparison of once weekly administration of PEG-IFN with three times weekly administration of IFN in the mouse model demonstrates that the *in vivo* biological activity of PEG-IFN is enhanced compared with IFN.

Safety pharmacology studies were conducted to evaluate the effects of PEG-IFN on the cardiovascular, respiratory, renal, gastrointestinal and central nervous systems. Decreases in urine volume accompanied by decreases in urinary potassium levels were noted after sc administration of PEG-IFN to saline-loaded rats. In cynomolgus monkeys a slight tachycardia was observed following iv administration of PEG-IFN.

Studies designed to investigate the apparent neutropenia observed in clinical studies following PEG-IFN administration, and to show the effect of administration of G-CSF (filgrastim) on neutrophil counts, were conducted in female mice. Due to the species specificity of IFN, a pegylated form of hybrid human IFN (PEG-IFNαA/D), which is active on murine cells was used.

Treatment of female mice with PEG-IFNαA/D resulted in lymphopenia in the peripheral blood and to a lesser extent in the bone marrow. In addition, neutropenia, reticulocytopenia and thrombocytopenia were observed in the peripheral blood. Treatment with filgrastim on days 2 and 3 ameliorated the neutropenia caused by a single dose of PEG-IFNαA/D.

Ribavirin: Ribavirin, a synthetic nucleoside analog, has shown *in vitro* activity against some RNA and DNA viruses, as well as immunomodulatory activity. The mechanism by which ribavirin in combination with peginterferon alfa-2a exerts its effects against hepatitis C virus (HCV) is unknown, although it is likely to involve both direct antiviral and immunomodulatory activities. More than additive inhibition of HCV subgenomic RNA replication in human liver cells has been seen in combination with PEGASYS (peginterferon alfa-2a).

TOXICOLOGY

PEGASYS RBV (peginterferon alfa-2a and ribavirin)

Peginterferon alfa-2a (PEG-IFN)
The preclinical toxicology data demonstrate that the modification of the interferon alfa-2a (IFN) molecule by pegylation (PEG-IFN) does not induce additional or unexpected toxicity beyond that previously observed with interferons. The following were the main findings:

A 4-week toxicity study was performed in cynomologus monkeys using twice weekly sc dosing to give dose levels of 30, 375, and 1125 mcg/kg/week. Only mild effects were observed and these were limited to transient clinical pathology changes at the mid and high doses. Toxicological findings were limited to the following: slight transient hematological changes (i.e., decreased platelet and WBC counts) and slight transient clinical chemistry changes, including decreases in protein, calcium, and, in a few animals, elevated ALT and/or AST (1.4 to 2.3 times baseline) values. In a 13-week study of similar design, comparable results for the decreases in platelets, WBC and protein were seen at all three dose levels (30, 100 and 300 mcg/kg/week).

The toxicity profile of PEG-IFN was further characterized in a 4-week daily dose study employing sc doses of 15, 100, and 600 mcg/kg/day. Changes similar to those described above but with more pronounced effects were observed. In one female monkey receiving 600 mcg/kg/day, pronounced adverse effects, clinical signs, and clinical pathology changes (regenerative anemia, leukopenia, thrombocytopenia, and increases in liver function chemistry) were seen that required dosing to be discontinued. Upon resumption of dosing, these effects did not reappear. No histopathologic findings occurred in any multiple-dose toxicity study.

PEG-IFN is less immunogenic than IFN in mice. PEG-IFN and IFN were comparably immunogenic in monkeys. As a consequence of an immunogenic response to PEG-IFN by monkeys, which results in a marked reduction in serum exposure to PEG-IFN, a resolution of adverse effects was observed during the treatment period in all multiple-dose studies. The immunogenic response of monkeys to PEG-IFN was expected, as human interferons are known to be immunogenic in other animal species. Effects of treatment beyond 4 weeks could not be accurately assessed in the animal models as a result of their immunogenic response.

Despite the marked reduction in serum exposure with time, the exposure in animals (AUC, C_{max}) remained considerably higher than that seen in patients.

During all toxicity studies, a mild subcutaneous inflammatory reaction occurred at the injection sites of both PEG-IFN and placebo-control animals. No histopathological findings are observed in any of the multiple-dose toxicity studies, with the exception of subcutaneous inflammation at the injection sites.

Carcinogenesis: Peginterferon alfa-2a has not been tested for its carcinogenic potential.

Mutagenesis: Peginterferon alfa-2a was neither mutagenic nor clastogenic 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.

Impairment of Fertility: As with other alpha interferons, prolongation of the menstrual cycle accompanied by both a decrease and delay in the peak of 17ß-estradiol and progesterone levels have been observed following administration of peginterferon alfa-2a to female cynomolgus monkeys. A return to normal menstrual rhythm followed discontinuation of treatment. Similar effects in the monkey have previously been associated with the occurrence of spontaneous abortions in addition to impaired female fertility. Peginterferon alfa-2a has not been studied for its effect on male fertility. However, treatment with interferon alfa-2a did not affect fertility of male rhesus monkeys treated for 5 months at doses up to 25 x 10^6 IU/kg/day.

The toxicology studies performed with PEG-IFN are summarized in Tables 13 to 18.

Table 13 Peginterferon alfa-2a: Summary of Acute (Single-Dose) Toxicity Studies

Title	Species/ Strain	No./ Sex/ Dose	Dose (μg/kg)	Duration of Observations/ Route of Administration	Maximum Non-Lethal Dose	Target Organs/ Systems of Toxicity
Acute Study	Monkeys/ Cynomolgus	one	6750	14 days after final dosing Subcutaneous	> 6750 μg/kg (technical limit dose)	Clinical signs: piloerection in the male and unsteady gait in the female. Clinical Pathology: transient mild anemia and decrease in WBC. Elevated ALT and decrease in protein and albumin. Mild subcutaneous hemorrhage at one injection site
Acute Study	Monkeys/ Cynomolgus	one	0, 15, 70, 300	14 days after final dosing Intravenous	> 300 μg/kg	Adverse effects were limited to bruising at the injection sites and transient elevation of AST in one monkey at the high dose

Table 14 Peginterferon alfa-2a: Summary of Multiple-Dose Toxicity and Toxicokinetic Studies in Monkeys: 4-Week Twice Weekly Subcutaneous Dosing Study

Species/ Strain & No. Animals	Dose (μg/kg dose)	Day Sampled	Dose sampled	Mean [Serum] (ng/mL)	Mean C_{max} ±SD (ng/mL)	Mean AUC_{0-72h} (ng·h/mL)	Treatment-Related Effects	Neutralizing Antibody Titer[b]
Monkeys Cynomolgus	15	1	1		98 ±21	6000	No toxicity was observed. Total antibodies to IFN were present in 1 female on day 15 and in all monkeys at the end of the study.	Median: 22.5
3/sex/group		15	4[a]	46				Range: 17.5-400
		26	8		184 ±320	9770		
	187.5	1	1		2050 ±263	130000	After 2 weeks of treatment, transient changes included: ↓mean protein (albumin, globulin fractions) and calcium level compared to pre-study. ↑ ALT in 2 males and AST in 1 male. No histopathologic findings were noted. Total antibodies to IFN were present in 1 male and 2 females on day 15 and in all monkeys at the end of the study.	Median: 60
		5	4[a]	1818				
		26	8		203 ±178	13200		Range: 30-400
	562.5	1	1		6565 ±1403	392000	Transient changes noted included: ↓ mean platelets prior to doses 3 and 5 in 1 male and 1 female; ↓ in WBC and neutrophil prior to dose 3; ↓mean protein and calcium prior to dose 5; ↑ ALT and AST in 1 male and 1 female, and ↑ absolute and relative liver and spleen weights. No histopathologic findings were noted. Total antibodies to IFN were present in all monkeys on day 15 and at the end of the study.	Median: 280
		15	4[a]	113				
		26	8		328 ±169	22400		Range: 60-560

[a] Samples 72 hours after dose 4 only.
[b] Samples 72 hours after last dose (dose 8). Neutralizing antibody titer is the reciprocal of the last dilution of serum that reduces the effective concentration of IFN alfa-2a from 10 U/mL to 1 U/mL.

Table 15 Peginterferon alfa-2a: Summary of Multiple-Dose Toxicity and Toxicokinetic Studies in Monkeys: 4-Week Daily Subcutaneous Study with 4-Week Recovery Period

Species/ Strain No. Animals	Dose (μg/kg/ day)	Dose sampled (day)	Mean[a] [Serum] (ng/mL)	Mean[b] C_{max} (ng/mL)	Mean[b] AUC_{0-24h} (ng·h/mL)	Treatment-Related Effects	Total Antibody Titer (IFN binding Units/mL)	Neutralizing Antibody Titer[b]
Monkeys Cynomolgus 5/sex/ group	15	1		133	1970	Transient changes that peaked at days 8 and/or 15 included: ↓ mean platelets that were significant only in males; ↓ WBC (neutrophils); ↓ reticulocytes. ↑ APTT in some males and females. No histopathologic findings were noted.	Day 16 (Treatment) 1 of 10 monkeys = 1110 Day 29 (Treatment)[c] Median: 1632 Range: 0 - 8196 Day 16 (Recovery) Median: 795 Range: 580 - 2391 Day 29 (Recovery) Median: 753 Range: 0 - 1125	Day 16 (Recovery) Median: 298 Range: 75 to 520 Day 29 (Recovery) Median: 210 Range: 130 to 480
		2	133	-	-			
		4	419	-	-			
		8		1070	23700			
		9	1072					
		11	948					
		16	270					
		18	331					
		23	50					
		25	46					
		29[c]	70					
	100	1		1250	18800	Transient changes that peaked at days 8 and/or 15 included: ↓ mean platelets that were significant only in males; ↓ WBC (neutrophils); ↓ reticulocytes; ↓ fibrinogen in males. ↑ APTT in some males and females. ↓ total protein. No histopathologic findings were noted.	Day 16 (Treatment) Median: 573 Range: 0 - 2228 Day 29 (Treatment)[c] Median: 3880 Range: 0 - 20475 Day 16 (Recovery) Median: 2657 Range: 608 - 4050 Day 29 (Recovery) Median: 2069 Range: 0 - 3833	Day 16 (Recovery) Median: 800 Range: 640 to 960 Day 29 (Recovery) Median: 1880 Range: 1200 to 2560
		2	1250	-	-			
		4	4776	-	-			
		8		9240	209000			
		9	8280					
		11	8693					
		16	778					
		18	390					
		23	251					
		25	169					
		29[c]	199					
	600	1		6670	102000	Transient changes that peaked at days 8 and/or 15 included: ↓ mean platelets that was significant only in males; ↓ WBC (neutrophils); ↓ reticulocytes; ↓ fibrinogen in males; significant ↑ APTT. There was ↑ RDW on days 22 and at end of treatment period. At most time points minimal ↓ HCT, HGB, and RBC were seen in males. ↓ total protein. ↓ calcium and BUN in females. No histo-pathologic findings were noted.	Day 16 (Treatment) Median: 3678 Range: 0 – 9736 Day 29 (Treatment)[c] Median: 14031 Range: 486-54694 Day 16 (Recovery) Median: 9397 Range: 2601-18225 Day 29 (Recovery) Median: 5931 Range: 1145-11328	Day 16 (Recovery) Median: 1840 Range: 400-4267 Day 29 (Recovery) Median: 880 Range: 760 to 8320
		2	6674					
		4	21445					
		8		48900	1120000			
		9	48270					
		11	37113					
		16	684					
		18	365					
		23	329					
		25	631					
		29[c]	572					

[a] Mean serum concentrations from samples obtained on specified days, prior to dosing.
[b] C_{max} and AUC_{0-24hr} were calculated for sample days 1 and 8 of the treatment period.
[c] Sampled 24 hours after the last dose (dose 28).
[d] The neutralizing antibody titer is the reciprocal of the last dilution of serum that reduces the effective concentration of IFN alfa-2a from 20 units/mL to 1 unit/mL.

Table 16 Peginterferon alfa-2a: Summary of Multiple-Dose Toxicity and Toxicokinetic Studies in Monkeys: 13-Week Twice Weekly Subcutaneous Study with 4-Week Recovery Period

Species/ Strain & No. Animals	Dose (µg/kg/dose)	Day Sampled	Dose sampled	Mean C_{max} (ng/mL)	Mean AUC_{0-96h} (ng·h/mL)	Treatment-Related Effects	Day Sampled	Median Total Antibody Titer[a] (IBU/mL)	Median Neutralizing Antibody Titer[a,b]
Monkeys Cynomol-gus 5/sex/ group	15	0 - 14 - 28 - 56 - 84	1 - 5 - 9 - 17 - 25	161 110 86 196 426	11837 3679 7642 15182 36947	Slight transient ↓ leukocytes, neutrophils, total protein & albumin. Slight hemorrhage and inflammation at injection sites	33 - 61 - 92 - 103 - 117	543 (154-972) 391 (0-783) 428 (0-823) 426 (225-528) 202 (144-323)	80 (40-320) 800 (0-800) 1600 (0-6400) 2400 (1600-3200) 6400 (1600-12800)
	50	0 - 14 - 28 - 56 - 84	1 - 5 - 9 - 17 - 25	515 425 114 455 819	40643 23508 9819 36135 69168	Slight transient ↓ platelets, leucocytes, neutrophils, total protein & albumin. Slight transient ↑fibrinogen. Slight hemorrhage and inflammation at injection sites	33 - 61 - 92 - 103 - 117	814 (367-1350) 692 (204-1070) 740 (223-1330) 535 (187-1270) 245 (0-980)	200 (80-800) 1600 (400-12800) 2400 (1600-12800) 6400 (3200-12800) 9600 (1600-12800)
	150	0 - 14 - 28 - 56 - 84	1 - 5 - 9 - 17 - 25	1445 423 228 1284 2545	117626 36424 17798 104849 226566	Slight transient ↓ platelets, leukocytes, neutrophils, prothrombin time, total protein & albumin. Slight transient ↑ APTT & fibrinogen. Slight transient ↑ ALT (2 animals), Slight hemorrhage and inflammation at injection sites	33 - 61 - 92 - 103 - 117	959 (702-1130) 919 (663-1270) 1270 (982-5010) 1010 664 (358-812)	180 (0-3200) 2400 (100-12800) 8000 (200-12800) 6400 (1600-12800) 12800 (3200-12800)

[a] Range of observed values appears in brackets
[b] The neutralizing antibody titers are reported as the reciprocal of the last dilution of antiserum that neutralizes IFN alfa-2a from 10 lab units/mL to 1 lab unit/mL.

Table 17 Summary of Pilot Study on the Effects of Peginterferon alfa-2a on Sex Steroid Hormones in Female Monkeys

Species/ Strain No. of Animal	Dose (μg/kg/dose) Regimen	Duration/ Route of Administration	Treatment-Related Effects
Cynomolgus Monkeys 2 females/ group	100, 300, 600 3 times/week Roferon-A (positive control): 25 MIU/kg, daily	Subcutaneous administration over 1 menstrual cycle or maximum of 6 weeks Roferon-A (positive control): intramuscular	Low Dose: no adverse effects Mid Dose: prolonged menstrual cycle (1 of 2), with delayed peak of 17β-estradiol and progesterone levels. High Dose: menstruation not observed (amenorrhea) in one of 2 females, with delayed peak of 17β-estradiol and progesterone levels. Interferon alfa-2a: prolonged menstrual cycle (2 of 2), with delayed peak of 17β-estradiol and progesterone levels.

Table 18 Summary of Study on the Effects of Peginterferon alfa-2a on Sex Steroid Hormones in Female Monkeys with a Recovery Period

Species/ Strain & No. Animals	Dose (μg/kg/ dose)	Duration/ Route/ Regimen	Dose sampled	Mean C_{max} ±SD (ng/mL)	Mean AUC_{0-48h}±SD (ng·h/mL)	Median Neutralizing Antibody Titer[b]	Treatment-Related Effects
Monkeys Cynomolgus 5 females/ group	Interferon alfa-2a: 25 MIU/kg/day	Daily IM administered over 1 menstrual cycle or maximum of 6 weeks. Recovery period of 1 menstrual cycle.				96 hr after last dose: Median: 2000 Range: 1000-32000 20 days after last dose: Median: 4000 Range: 1000-32000	Prolonged menstrual cycle (4 of 5 monkeys), with a decrease and a delay in the peak of 17β-estratidiol and progesterone levels. Changes were reversible. Mean cycle length[c]: Dosing period: 39.2 d Recovery period: 32.6 d
	100	3 time/week SC administration over 1 menstrual cycle or maximum of 6 weeks. Recovery period of 1 menstrual cycle.	1 4 7 Last Dose	1650±284 3540±743 1410±3020 2000±2280	53400±13800 159000±30200 43000±91100 98600±104000[a]	96 hr after last dose: Median: 1600 Range: 400-51200 20 days after last dose: Median: 3200 Range: 200-51200	Prolonged menstrual cycle (2 of 5 monkeys), with a decrease and a delay in the peak of 17β- estradiol and progesterone levels. Changes were reversible. Mean cycle length[c]: Dosing period: 41.0 d Recovery period: 31.2 d
	600	3 time/ week SC administration over 1 menstrual cycle or maximum of 6 weeks. Recovery period of 1 menstrual cycle.	1 4 7 Last Dose	8870±2560 24400±7910 197±178 2050±1230	298000±79700 1060000±318000 5410±3190 138000±105000[a]	96 hr after last dose: Median: 6400 Range: 3200-12800 20 days after last dose: Median: 12800 Range: 3200- 12800	Prolonged menstrual cycle (5 of 5 monkeys), with a decrease and a delay in the peak of 17β- estradiol and progesterone levels. Changes were reversible. Mean cycle length[c]: Dosing period: 61.8 d Recovery period: 28.8 d

[a] Last dose values represent from mean $AUC_{0-96\ h.}$
[b] The neutralizing antibody titers are reported as the reciprocal of the last dilution of antiserum that neutralizes IFN alfa-2a from 10 lab units/mL to 1 lab unit/mL.
[c] Mean cycle length (Vehicle control): Dosing period:27.8 d; Recovery period:28.0 d

Peginterferon alfa-2a and Ribavirin Combination

A four-week toxicity study with combination therapy was conducted in cynomologous monkeys. The findings from this study are summarized in Table 19. At a dose of 100 mg/kg/day of ribavirin alone, effects on the erythron indicative of a mild anemia were observed. These effects were slightly more severe in monkeys treated with 600 mcg/kg/dose of PEG-IFN alfa-2a twice weekly plus 100 mg/kg/day of ribavirin. These doses are 400 times the intended weekly clinical dose of PEG-IFN alfa-2a (180 mcg/week, 3 mcg/kg for a 60-kg person) and approximately six times the intended daily clinical dose of ribavirin (1000 mg/day for a 60-kg person or 16 mg/kg/day).

Animals treated with 50 mg/kg/day of ribavirin alone exhibited no effects on the erythron. Animals administered 600 mcg/kg of PEG-IFN alfa-2a twice weekly plus 50 mg/kg/day of ribavirin exhibited decreases in red blood cell (RBC) parameters.

Bone marrow cytology and microscopic evaluations showed erythroid hypoplasia for one of 10 animals treated with 600 mcg/kg of PEG-IFN alfa-2a twice weekly plus 50 mg/kg/day of ribavirin and for two of 10 animals treated with 600 mcg/kg of PEG-IFN alfa-2a twice weekly plus 100 mg/kg/day of ribavirin.

No new or unexpected toxicities were observed for animals treated with the combination therapy compared with animals treated with ribavirin or PEG-IFN alfa-2a alone.

Table 19 PEGASYS + Ribavirin: Summary of Multiple-Dose Toxicity and Toxicokinetic Studies in Monkeys - Twice Weekly Subcutaneous Dosing (PEGASYS) and Daily Oral (Gavage) Dosing (Ribavirin) Study

Species/ Strain and No. Animals	Dose (mg/kg/day)	Day of Sampling	Ro 20-9963 in Serum		Ro 20-9963 in Blood		Ro 25-8310 in Serum		SNF	Treatment-related Effect
			C_{max} (ng/mL)	AUC_{1-24} (ng hr/mL)	C_{max} (ng/mL)	AUC_{1-24} (ng hr/mL)	C_{max} (ng/mL)	AUC_{1-48} (ng hr/mL)	Nu/mL	
Cynomo-logus monkeys	50 – Rib	1 15 29	383 1510 1700	5800 2580 NA	2630 3320 25900	29700 60600 141000				Discolored urine, Slight ↓Body wt. & Food consumption, ↓cholesterol
(5/sex/ group-main study;#2 /sex/ group-TK)	100 – Rib	1 15 29	474 3120 2810	7060 51100 52200	1810 50100 38900	23400 565000 695000				Dehydrated appearance, Slight↓ Body wt. & Food consumption, ↓ erythrocytes, hemoglobin, hematocrit, ↑ reticulocytes, ↓cholesterol, erythroid hyperplasia - bone marrow cytology
	600 - PEG	38 54							80->640 320->640	Dehydrated appearance, Discolored urine, ↓ Feces, Slight ↓ Body wt. & Food consumption, slight transient ↓ erythrocytes, hemoglobin, hematocrit, ↑reticulocytes, ↓WBC, platelets, neutrophils, ↓ total protein, albumin, globulin, total bilirubin, calcium, phosphorus
	50 – Rib + 600 - PEG	1 15 29 38 54	214 1460 1470	4860 26500 23000	394 2910 51200	7790 54600 159000	10500 2830 307	297000 54700 9380	80->640 >640	Dehydrated appearance, Discolored urine, ↓ Feces, Slight↓ Body wt. & Food consumption, ↓ erythrocytes, hemoglobin, hematocrit, ↑ reticulocytes, ↓ WBC, platelets, neutrophils, ↓ total protein, albumin, globulin, total bilirubin, calcium, phosphorus, erythroid hyperplasia - bone marrow cytology, erythroid hypoplasia - bone marrow cytology and histopathology
	100 – Rib + 600 - PEG	1 15 29 38 54	931 2550 3710	14000 51800 59100	1250 56000 66000	24100 590000 415000	11100 33200 1180	360000 1030000 NA	40->640 >640	Dehydrated appearance, Discolored urine, ↓ Feces, Slight ↓ Body wt. & Food consumption, ↓ erythrocytes, hemoglobin, hematocrit, ↑ reticulocytes, ↓WBC, platelets, neutrophils, ↓ cholesterol, ↓ total protein, albumin, globulin, total bilirubin, calcium, phosphorus, erythroid hypoplasia - bone marrow cytology and histopathology

Rib = Ro 20-9963 (ribavirin), PEG = Ro 25-8310 (pegylated interferon alfa 2-a)
SNF = Serum Neutralization Factor, NA = not available due to the death of 1 female on Day 28.

Ribavirin
At all doses tested in the repeat-dose rodent studies, effects on the erythron (reduced RBC counts, hemoglobin, and/or hematocrit) were noted. At the higher doses tested, these effects were indicative of anemia. In dogs, slight effects on the erythron were noted only at the highest dose tested (20 mg/kg/day). The effects on the erythron were similar to those reported in the literature for monkeys and patients following administration of ribavirin.

Histopathology findings that correlated with the effects on the erythron included extramedullary splenic hematopoiesis in rodents and hypercellularity of the femur marrow in rats. Erythroid hypoplasia in the bone marrow was observed in decedent mice at 200 and 400 mg/kg/day in a 4-week study and in rats at the highest dose of 160 mg/kg/day in a 13-week study.

Decreased leucocyte and/or lymphocyte counts were observed at relatively high doses in rodents and at all tested doses (5 to 20 mg/kg/day) in dogs.

Consistent with the literature, lymphoid depletion was noted microscopically at most of the tested doses in the rodent studies.

Gastrointestinal effects (crypt cell necrosis and reduced number of epithelial cells) were noted in rodents that died prematurely. Similar findings and chronic inflammation and erosion were also noted for dogs treated at 10 and 20 mg/kg/day.

The majority of the effects noted in the repeat-dose studies with ribavirin were reversible upon treatment withdrawal.

The toxicity studies performed with ribavirin are summarized in Tables 20 to 24.

Table 20 Ribavirin: Summary of Multiple-Dose Toxicity and Toxicokinetic Studies in Mice: 4-Week Daily Oral (Gavage) Dosing Study

Species/ Strain & No. Animals	Dose (mg/kg/day)	Mean C_{max} (ng/mL)	Mean $AUC_{0\text{-}24hr}$ (ng·hr/mL)	Mean blood conc. [Mean RBC conc.] (ng/mL)*	Treatment-Related Effects
Mice CD-1 10/sex/ group-main study; 24/sex/dose level and 6/sex-controls; toxicokinetic animals	30	1148	11591	77.9 [77.3--mean of 4 animals]	↓ erythrocytes (males), ↓ alanine aminotransferases (males), ↑ splenic extramedullary hematopoiesis
	100	3394	35490	184 [171-1 animal only]	↓ erythrocytes, ↓ hemoglobin, ↓ hematocrit, ↑ platelets, ↓ alanine aminotransferases, ↑ splenic extramedullary hematopoiesis
	200	4585	71887	440 [563-1 animal only]	↑ mortality, ↓ erythrocytes, ↓ hemoglobin, ↓hematocrit, ↓ leukocytes ↓ lymphocytes, ↑platelets, ↓ alanine and aspartate aminotransferases, ↓ relative testes and epididymis weight,↑ absolute and relative spleen weight, ↑ splenic extramedullary hematopoiesis, the following noted in animals that died: crypt cell necrosis and regenerative hyperplasia in the small and large intestine; lymphoid depletion/necrosis in the thymus, spleen, and mesenteric lymph node; adrenal cortical hypertrophy, atrophy of salivary glands, congestion and hypocellularity in the bone marrow; and hypospermia in the epididymis
	400	19570	NA (males) 142513 (females)	NA	↑ mortality (all animals died); ↓ erythrocytes, ↓ hemoglobin, ↓ hematocrit, ↓ leukocytes, ↓ lymphocytes, ↑ platelets, ↓ alanine and aspartate aminotransferase, crypt cell necrosis and regenerative hyperplasia in the small and large intestine; lymphoid depletion/necrosis in the thymus, spleen, and mesenteric lymph node; adrenal cortical hypertrophy, atrophy of salivary glands, congestion and hypocellularity in the bone marrow; and hypospermia in the epididymis

NA = Not Available
Note: Samples from 30, 100 and 200 mg/kg/day groups were collected on dosing days 28 and 29 while samples from the 400 mg/kg/day group were collected on day 12.
*Ribavirin concentrations in whole blood samples and erythrocytes were determined from samples obtained 24 hours after the last dose (Study Day 29). Because animals in Group 5 died or were sacrificed on or before Day 12, ribavirin concentrations in whole blood were not obtained for Group 5 animals.

Table 21 Ribavirin: Summary of Multiple-Dose Toxicity and Toxicokinetic Studies in Rats: 13-Week Daily Oral (Gavage) Dosing Study

Species /Strain and No. Animals	Dose (mg/kg/day)	Day of Sampling	Serum		Mean blood conc. (ng/mL)	Mean RBC conc. (ng/mL)		Treatment-related Effect
			C_{max} (ng/mL)	AUC_{0-24} (ng·hr/mL)		Males	Females	
Wistar rats 12/sex/ group-main study; 15/sex/ group-toxicokinetics	10	1 28 91	112 145 132	1044 1969 1861	2 17 24	NR 15.5 27.2	19.7 6.4 17.7	↓ Hemoglobin and ↓ hematocrit
	40	1 28 91	363 539 538	5625 8681 8952	25 65 119	NR NR 54.7	NR 91.8 128	↓ Hemoglobin, ↓ hematocrit, thymic lymphoid depletion, ↓ thymic weights and skin lesions
	80	1 28 91	700 858 947	9930 13584 16842	65 157 244	NR NR 104	NR 14.8 130	↓ Body weight, ↓ body weight gain, ↓ food consumption, skin sores/scabs, ↓ erythrocytes, ↓ hemoglobin, ↓ hematocrit, ↑ platelet counts, ↓ cholesterol, ↑ inorganic phosphorus, ↓ thymic weights, skin lesions, and thymic lymphoid depletion
	160	1 28 91	1202 2022 2809	16963 35908 46350	151 636 936	17.8 388 487	45.8 172 1041	Mortality, hunched appearance, thin appearance, hypoactivity, sensitive to touch, vocalization, nasal discharge, few, liquid and no feces, pale eyes, audible, irregular and labored respiration, pale ears and body, skin sores/scabs, cold to touch (entire body), ↓ body weight, ↓ body weight gain, ↓ food consumption, ↓ erythrocytes, ↓ hemoglobin, ↓ hematocrit, ↑ reticulocyte counts, ↑ platelet counts, ↓ absolute lymphocyte counts, ↑ M/E ratio and erythroid hypoplasia (bone marrow cytology), ↑ prothrombin time, ↓ activated partial thromboplastin time, ↓ total protein, ↓ albumin, ↓ globulin, ↑ albumin-to-globulin ratio, ↓ cholesterol, ↓ triglycerides, ↑ aspartate aminotransferase, ↑ inorganic phosphorus, ↑ heart, lung and spleen weights, ↓ thymic weights, crusted areas of skin, skin lesions, thymic lymphoid depletion, depletion of thymus-dependent areas of spleen and mesenteric lymph nodes, ↓ number of erythroid and myeloid precursors in bone marrow, extramedullary hematopoiesis, ↑ foamy alveolar macrophages, hepatocellular degeneration and necrosis, hepatic pigment, and ↓ number of epithelial cells on the GI mucosa (unscheduled sacrifice-males)

NR=Not reported due to negative erythrocyte concentrations of Ro 20-9963.

Table 22 Ribavirin: Summary of Multiple-Dose Toxicity and Toxicokinetic Studies in Mice: 26-Week Daily Oral (Gavage) Dosing Study

Species/ Strain and No. Animals	Dose (mg/kg/day)	Day of Sampling	Serum		Treatment-Related Effects
			C_{max} (ng/mL)	$AUC_{0\text{-}24hr}$ (ng·hr/mL)	
P53 N5 hetero-zygous (+/-) mice (20/sex/group) - mainstudy; C57BL/6 mice (66/sex/group) -TK	10	1 183	1145 893	6305 6520	No treatment-related effects were observed
	50	1 183	2500 3180	21500 23150	↓ Hemoglobin, ↑ red cell distribution width, ↓ testes/epididymis weights (absolute and relative)
	100	1 183	3706 3810	29400 33800	↓ Hemoglobin, ↓ Hematocrit, ↑ red cell distribution width, ↓ testes/epididymis weights (absolute and relative), ↓ spleen weight (absolute and relative)

*An increased trend for mortality and an increased trend for splenic and thymic lymphoid depletion was observed in males.

Table 23 Ribavirin: Summary of Multiple-Dose Toxicity and Toxicokinetic Studies in Rats (26-Week Daily Oral (Gavage) Dosing Study)

Species/Strain and No. Animals	Dose (mg/kg/day)	Day of Sampling	Serum		Mean Blood	Mean RBC conc. (ng/mL)		
			C_{max} (ng/mL)	AUC_{0-24hr} (ng·hr/mL)	conc. (ng/mL)	Males	Females	Treatment-related Effects
Wistar rats 20/sex/ group-main study;	10	1 28 91 126 182	100 165 226 205 199	1162 2170 2259 2260 2264	8 18 21 23 21	10.2 3.4 5.3 10.9 1.68	10.7 8.5 22.7 16.2 9.5	↓ Hemoglobin, ↓ hematocrit, ↑ platelet counts and thymic lymphoid depletion
15/sex/ group-toxicokinetics	35	1 28 91 126 182	324 457 490 612 537	4054 6186 7149 8521 7925	30 60 72 89 69	6.7 21.6 33.9 47.2 18.0	4.9 11.8 NR 18.0 5.1	↑ Skin sores/scabs, ↓ hemoglobin, ↓ hematocrit, ↑ platelet counts, ↓ alanine aminotransferase activity, crusted regions of skin, skin ulceration (histologic), thymic lymphoid depletion, and hypercellularity of femur marrow
	70	1 28 91 126 182	663 887 1007 1297 1138	8744 6857 17244 21460 19152	67 141 205 265 197	9.4 49.4 74.2 81.7 30.0	1.7 57.0 41.9 103 71.8	Mortality, ↑ skin sores/scabs, ↑ audible respiration, ↓ body weight,↓ body weight gain, ↓ food consumption, ↓ erythrocyte counts, ↓ hemoglobin, ↓ hematocrit, ↑ platelet counts, ↑ absolute and relative reticulocyte counts, ↓ cholesterol, ↑ inorganic phosphorus, ↓ alanine aminotransferase activity, crusted regions of skin, skin ulceration (histologic), small thymus , ↓ thymus weights, thymic lymphoid depletion, hypercellularity of femur marrow, extramedullary hematopoiesis in spleen, and hepatic pigment deposition

NR= Not reported due to negative erythrocyte concentrations of Ro 20-9963.

Table 24 Ribavirin: Summary of Multiple-Dose Toxicity and Toxicokinetic Studies in Dogs: 26-Week Daily Oral (Gavage) Dosing Study

Species/Strain and No. Animals	Dose (mg/kg/day)	Day of Sampling	Serum		Mean Blood	Mean RBC conc. (ng/mL)		
			C_{max} (ng/mL)	AUC_{0-24hr} (ng•hr/mL)	conc. (ng/mL)	Males	Females	Treatment-related Effects
Beagle dogs 7/sex/ group	5	1	1495	8315	37.9	NR	NR	↓ Mean lymphocyte counts
		28	1180	9200	102.7	96.5	95.1	
		91	1555	9795	73.1	1.8	58.3	
		182	1605	10395	97.7	53.4	84.5	
	10	1	3170	17600	86.1	22.2	15.3	↓ Mean lymphocyte counts,
		28	2855	18550	142.5	61.0	81.9	dilatation/necrosis of intestinal crypts
		91	3405	19450	202.5	89.8	345	(duodenum)
		182	3700	23100	174.5	74.8	78.5	
	20	1	7175	35700	236.5	18.2	205	Fecal alterations, ↓ mean body weight (up to Week 4),
		28	6888	42600	386	250	286	↓ body weight gain (up to Week 4), ↓ food consumption
		91	7175	40450	273.5	NR	NR	(up to Week 4), ↓ mean lymphocyte counts, ↓ WBCs,
		182	6145	40050	358	121	152	↓ erythrocyte counts, ↓ hemoglobin, ↓ hematocrit, ↑ reticulocytes, ↓ alanine aminotransferase activity, ↓ total protein, ↑ pigment in the red pulp of the spleen, pigment deposition in Kupffer cells of the liver, ↑ dilatation/necrosis of intestinal crypts (duodenum), erosion of ileum,chronic inflammation of small intestine

NR= Not reported due to negative erythrocyte concentrations of Ro 20-9963.

Carcinogenesis: Results from a 6-month alternative (p53 (+/-) mouse) carcinogenicity study and a rat 2-year carcinogenicity study showed no treatment-related increase in the incidence or severity of any neoplastic lesion up to the maximum tolerated dose of 100 mg/kg/day (sixfold higher than the therapeutic dose) and 60 mg/kg/day, respectively. On a body surface area basis, these doses are approximately 0.5 and 0.6 times the maximum recommended human 24-hour dose of ribavirin. The 100 mg/kg/day dose level resulted in an $AUC_{0\text{-}24hr}$ of 34 mcg·hr/mL. The therapeutic $AUC_{0\text{-}12hr}$ for ribavirin was 26.4 mcg·hr/mL (calculated from samples collected after the morning dose of ribavirin), which was similar to the exposure at the highest dose tested in the mouse study, which resulted in no treatment-related neoplasia.

Mutagenesis: Ribavirin was tested negative in the Ames mutagenicity assay, positive in the in vitro mouse lymphoma assay, and negative in the in vivo micronucleus assay. See Table 25.

Table 25 Ribavirin: Summary of Mutagenicity and Genotoxicity Studies

Title	Assay System	Concentration/ Dose of Ribavirin Administered	Duration of Exposure	Genotoxic and Other Findings
Bacterial Cell Gene Mutation	Ames Test: standard plate incorporation method using strains TA98, 100, 1535 & 1537 of *Salmonella typhimurium,* and strain WP2uvrA of *Escherichia coli* with and without metabolic activation	3.33 to 5000 µg/plate *(Salmonella typhimurium)*; 10.00 to 5000 µg/plate *(Escherichia coli)*	2 days	No mutagenic activity observed with or without metabolic activation.
Mouse Lymphoma (*in vitro*)	Mouse lymphoma L5178Y cell line	7.85 to 2500 µg/ml	4-hour treatment period	Positive without activation; Weak positive with activation
In vivo mouse micronucleus	Polychromatic erythrocytes (PCEs) from CD-1 mouse bone marrow	500, 1000, 2000 mg/kg/day	3 days	↓ PCE:NCE ratio at all doses indicating cytotoxicity to bone marrow; no ↑ in micronucleated PCEs (negative)

Reproduction Studies

No reproductive toxicology studies have been performed using PEGASYS in combination with COPEGUS (ribavirin). The collective data indicate that PEG-IFN alfa-2a and ribavirin combination therapy is a reproductive toxicant and teratogen. Effects on reproductive parameters can be attributed to both PEG-IFN alfa-2a and ribavirin. These effects are expected to be fully reversible after treatment discontinuation. The teratogenic potential of the combination therapy is attributed to the known teratogenic potential of ribavirin.

Extensive data are available in the literature with regard to the teratogenic potential of ribavirin. These data indicate that ribavirin is teratogenic in all rodent species tested (mice, rats, and hamsters) following single or multiple dose administration. The dose of ribavirin that induced teratogenic effect was as low as 2.5 mg/kg. In non-rodent species (rabbits and baboons), a definitive assessment of the teratogenic potential of ribavirin could not be made due to the inadequate design of the published studies.

Results from a segment I study in rats (Table 26) for investigating the effect of ribavirin on fertility showed an increase in preimplantation loss and resorption rates in female animals from the mid-dose (30 mg/kg/day) and high-dose (100 mg/kg/day) groups. These results were consistent with ribavirin's inhibitory effects on rapidly proliferating cells and confirmed that ribavirin is embryotoxic.

Results from the segment I study also showed a marginal reduction in sperm counts in male animals receiving high ribavirin dose. The fertility of the untreated female animals, who mated with the ribavirin-treated male animals with reduced sperm counts, was not affected. The ribavirin-induced reduction in sperm counts is consistent with findings in literature, which reports decreased spermatid counts and sperm motility and increased abnormal sperm following oral administration of ribavirin to mice at 35, 75, and 150 mg/kg for up to 6 months. Additionally, histopathological changes, including degeneration of the seminiferous tubular epithelium primarily characterized by vacuolization, reduced thickness, and necrosis of germinal cells were also reported previously in animals treated with ribavirin at doses ≥35 mg/kg/day. Although no treatment-related findings of histopathology were noted in the segment I fertility study in rats, hypospermia in the epididymis was observed microscopically in male mice that died prematurely. These mice were treated with ribavirin doses of 200 and 400 mg/kg/day in a 4-week repeat-dose study. Published data showed that upon cessation of treatment, a complete recovery from the testicular toxicity was apparent within one to two spermatogenesis cycles. Similarly, reduced sperm counts were shown to be reversible after a 9-week recovery period in the segment I fertility study in rats.

Table 26 Ribavirin: Summary of Reproductive Toxicity Studies: Fertility Oral (Gavage) Dosing

Species/Strain and No. Animals	Dose (mg/kg/day)	Duration	Serum		Treatment-Related Effects
			C_{max} (ng/mL)	AUC_{0-24hr} (ng·hr/mL)	
Sprague-Dawley rats 20 females/group: main study; mated with untreated males 11 females/group: Toxicokinetics	10	4 weeks before mating, through gestation day 7	279 (day 0) 291 (day 27)	1420 (Day 0) 1970 (Day 27)	
	30	4 weeks before mating, through gestation day 7	484 (day 0) 439 (day 27)	4220 (Day 0) 4940 (Day 27)	↑ preimplantation loss; ↑ resorption rate
	100	4 weeks before mating, through gestation day 7	1230 (day 0) 1380 (day 27)	15200 (Day 0) 18300 (Day 27)	↓ maternal food consumption; ↑ pre-implantation loss; ↑ resorption rate; ↓ live litter size
Sprague-Dawley rats 20 females/group: main study; mated with untreated males **(recovery)**	10	4 weeks + 6 weeks of no treatment prior to mating			
	30	4 weeks + 6 weeks of no treatment prior to mating			
	100	4 weeks + 6 weeks of no treatment prior to mating			↓ body-weight gain during treatment; ↓ food consumption during treatment
Sprague-Dawley rats 20 males/group: main study; mated with untreated females 11 males/group: Toxicokinetics	10	9 weeks before and through mating	304 (day 0) 219 (day 62)	1700 (Day 0) 1970 (Day 62)	
	30	9 weeks before and through mating	954 (day 0) 839 (day 62)	6310 (Day 0) 6770 (Day 62)	↓ body-weight gain during treatment
	100	9 weeks before and through mating	2010 (day 0) 1470 (day 62)	17600 (Day 0) 18200 (Day 62)	↓ body-weight gain during treatment; ↓ food consumption during treatment; ↓ sperm count
Sprague-Dawley rats 20 males/group: main study; mated with untreated females **(recovery)**	10	11 weeks + 9 weeks of no treatment prior to mating			
	30	11 weeks + 9 weeks of no treatment prior to mating			
	100	11 weeks + 9 weeks of no treatment prior to mating			↓ body-weight gain during treatment; ↓ food consumption during treatment

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PART III: CONSUMER INFORMATION
PrPEGASYS RBV®
peginterferon alfa-2a and ribavirin

This leaflet is part III of a three-part "Product Monograph" published when PEGASYS RBV was approved for sale in Canada and is designed specifically for Consumers. This leaflet is a summary and will not tell you everything about PEGASYS RBV. Contact your doctor or pharmacist if you have any questions about the drug.

You have been prescribed PEGASYS (pronounced PEG-ah-sis) RBV by your doctor, a combination therapy of PEGASYS and COPEGUS (pronounced Co-PEG-UH-s), to treat your Hepatitis C infection. Reading this information can help you learn about PEGASYS RBV and how to make these medicines work best for you.

Before starting on this medication, please read this leaflet carefully and make sure that you have all supplies needed on hand. Please discuss the supplies you need with your doctor.

ABOUT THIS MEDICATION

What the medication is used for:
PEGASYS RBV (peginterferon alfa-2a and ribavirin) is used in combination with other hepatitis C virus (HCV) drugs that have been authorized for combination use in Canada, or alone for the treatment of chronic hepatitis C in:

- Adult patients without cirrhosis
- Adult patients with compensated cirrhosis,

including HCV/HIV co-infection patients with stable HIV disease with or without antiretroviral therapy.

PEGASYS RBV is not authorized for use in children and adolescents under the age of 18 years (see SIDE EFFECTS AND WHAT TO DO ABOUT THEM).

If your doctor has prescribed additional medication (that works by directly targeting Hepatitis C virus to reduce the amount of virus in your body), also read the leaflet for that medication.

What it does:
PEGASYS is a prescription medication belonging to the family of drugs called interferons. "Interferon" refers to a kind of protein normally made in a person's body. Interferons are a normal part of your body's defense system for fighting disease. Scientists can also make interferons outside of the body for use as medicines. Another name for PEGASYS is peginterferon alfa-2a. PEGASYS is a modified interferon that is different from the interferon made in a person's body. This modification helps the interferon (PEGASYS) stay in your body for a prolonged time and allows PEGASYS to be injected only once a week.

COPEGUS is an antiviral agent, also known as ribavirin, that fights infection, but is not used by itself to treat hepatitis C. It is used in combination with PEGASYS to treat chronic (lasting) hepatitis C in adults whose liver still works normally.

What is Hepatitis C:
Hepatitis C is a liver disease caused by the hepatitis C virus. Hepatitis C is spread by contact with blood of a person carrying the hepatitis C virus.

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

With PEGASYS RBV combination therapy, the hepatitis C virus can be decreased to a level so low that it cannot be measured by blood tests. The virus is decreased and cannot be measured in 5 - 8 out of every 10 people who take PEGASYS RBV therapy for approximately one year. After 3 months of therapy, a blood test can help your healthcare provider determine your likelihood of long-term response. It has not been shown in clinical trials that PEGASYS RBV combination therapy can cure hepatitis C (permanently eliminate the virus) or if it can prevent liver failure or liver cancer that is caused by hepatitis C infection. It is not known if treatment with PEGASYS RBV combination therapy will prevent an infected person from spreading the hepatitis C virus to another person. It is not known how COPEGUS and PEGASYS work together to fight hepatitis C virus infections.

Your healthcare provider will monitor the effects of your medicine on your body through blood tests. While you are using PEGASYS RBV combination therapy, it is very important to get the blood tests your doctor orders. This will help your doctor see how well the medicine is working for you.

If you have questions about your health condition or PEGASYS RBV, talk to your healthcare provider.

When it should not be used:

- **HARM TO UNBORN CHILDREN. The COPEGUS component of PEGASYS RBV therapy may cause birth defects and/or death of an unborn child. If you are female and are pregnant or plan to become pregnant or, if you are male and have a female partner who is pregnant or plans to become pregnant, you must not receive PEGASYS RBV combination therapy. Extreme care must be taken to avoid pregnancy during PEGASYS RBV therapy and for 6 months after completion of treatment in both female and male patients. Two forms of effective birth control (one for each partner) must be used during this time and for 6 months after stopping therapy.**

During this time, you must also have monthly pregnancy tests that show you are not pregnant. If pregnancy occurs, report the pregnancy to your doctor right away.

- **Anemia. PEGASYS RBV therapy may cause your red blood cell count to decrease (anemia). This can be dangerous, especially if you have heart or breathing problems. This may cause a worsening of heart (cardiovascular) or circulatory problems.**
- you ever had an allergic reaction to other alpha interferons, ribavirin or any component of PEGASYS or COPEGUS.
- you have autoimmune hepatitis (hepatitis caused by your immune system attacking your liver).
- you have unstable or advanced liver disease.
- you have an autoimmune disease (where the body's immune system attacks the body's own cells) such as psoriasis (a skin disease) or sarcoidosis.
- you are coinfected with HIV and you have unstable or advanced liver disease, as determined by your doctor.
- you have blood disorders, including anemia (low red blood cell count), thalassemia (Mediterranean anemia) and sickle-cell anemia.
- neonates and infants because the PEGASYS component contains benzyl alcohol. There have been rare reports of death in neonates and infants associated with excessive exposure to benzyl alcohol. The amount of benzyl alcohol at which toxicity or adverse effects may occur in neonates or infants is not known.
- you have a history of or current mental illness (such as depression or anxiety). PEGASYS RBV combination therapy may make them worse. Tell your doctor if you are being treated or had treatment in the past for any mental problems, including depression, thoughts of ending your life (suicidal thoughts) or a feeling of loss of contact with reality, such as hearing voices or seeing things that are not there (psychosis). Tell your doctor if you take any medicines for these problems.
- you have problems with your thyroid gland.
- you are breast feeding.

What the medicinal ingredient is:
peginterferon alfa-2a and ribavirin.

What the non-medicinal ingredients are:
PEGASYS: acetic acid, benzyl alcohol, polysorbate 80, sodium acetate trihydrate, sodium chloride and water for injection.

COPEGUS: ethyl cellulose, hydroxypropyl methylcellulose, iron oxide red, iron oxide yellow, magnesium stearate, maize starch, microcrystalline cellulose, pregelatinized starch, sodium starch glycolate, talc, titanium dioxide, triacetin.

What dosage forms it comes in:
PEGASYS:
Pre-filled Syringes: Each syringe contains 180 mcg of PEGASYS in a 0.5 mL volume.
Vials: Each vial contains 180 mcg of PEGASYS in a 1 mL volume.
ProClick® Autoinjector: Each autoinjector contains 180 mcg of PEGASYS in a 0.5 mL volume.

COPEGUS:
Bottles: Pink film-coated tablets containing 200 mg ribavirin.

WARNINGS AND PRECAUTIONS

Serious Warnings and Precautions

Interferons, including PEGASYS cause or aggravate fatal or life-threatening neuropsychiatric (mental illness), autoimmune (where the body's immune system attacks the body's own cells), ischemic (conditions in which blood flow, and thus oxygen, is restricted to a part of the body) and infectious disorders. If you have persistently severe or worsening signs or symptoms of these conditions you should contact your doctor. Your doctor will assess you and may discontinue you from therapy. In many cases, but not all cases, these disorders resolve after stopping interferon therapy.

BEFORE you use PEGASYS RBV talk to your doctor or pharmacist if:

- **you are pregnant or breast feeding or plan to become pregnant at any time while you are being treated or during 6 months after your treatment has ended.**
- you are a male patient with a female sexual partner who is pregnant or plans to become pregnant at any time while you are being treated or during 6 months after your treatment has ended.
- you have autoimmune hepatitis (hepatitis caused by your immune system attacking your liver).
- you have an autoimmune disease (where the body's immune system attacks the body's own cells) such as psoriasis (a skin disease) or sarcoidosis.
- you have unstable or advanced liver disease.
- you ever had an allergic reaction to other alpha interferons, ribavirin or any component of PEGASYS or COPEGUS.
- you are allergic to other medicines, including those not prescribed by your doctor.
- you have a history of or current mental illness (such as depression or anxiety). PEGASYS RBV combination therapy may make them worse. Tell your doctor if you are being treated or had treatment in the past for any mental problems, including depression, thoughts of ending your life (suicidal thoughts) or a feeling of loss of contact with reality, such as hearing voices or seeing things that are not there (psychosis). Tell your doctor if you take any medicines for these problems.
- you have a history of or current drug or alcohol addiction or abuse.
- you have high blood pressure or a history of heart disease or previous heart attack or high blood fat (such as elevated triglyceride or cholesterol levels).
- you have a history of cancer.

- you have kidney problems.
- you have blood disorders, including anemia (low red blood cell count), thalassemia (Mediterranean anemia) and sickle-cell anemia.
- you are taking any other medicines, vitamins or herbal supplements, including those not prescribed by your doctor. Your doctor should know if you are taking medicines called methadone, theophylline, didanosine, zidovudine, stavudine or azathioprine.
- you are taking the Chinese herbal medicine sho-saiko-to, also known as Xiao-Chai-Hu.
- you have had an organ transplant and are taking medicine that keeps your body from rejecting your transplant (suppresses your immune system).
- you have been infected with hepatitis B virus and/or human immunodeficiency virus (the virus that causes AIDS).
- you have diabetes (high blood sugar).
- you have problems with your thyroid gland.
- you have liver problems (other than hepatitis C).
- you have past interferon treatment for hepatitis C virus infection that did not work for you.
- you have lung (respiratory) problems, such as pneumonia, shortness of the breath, and Chronic Obstructive Pulmonary Disease (COPD).

This information will help your doctor and you decide whether you should use PEGASYS RBV combination therapy and what extra care may need to be taken while you are on these medicines. If you have any doubts about your health condition or about taking PEGASYS RBV, talk to your doctor.

INTERACTIONS WITH THIS MEDICATION

Drugs that may interact with PEGASYS RBV include: didanosine, lamivudine, methadone, sho-saiko-to/Xiao-Chai-Hu, stavudine, theophylline, zidovudine, azathioprine.

Tell your doctor or pharmacist if you are taking Sebivo® (telbivudine) for chronic hepatitis B because taking this medicine together with PEGASYS may increase your risk of developing peripheral neuropathy (numbness, weakness, tingling, and/or burning sensations, or pain in the arms and/or legs). The combined use of these medications is not recommended.

Pancytopenia (marked decreases in red and white blood cells and platelets) and bone marrow (tissue inside bones that makes blood cells) suppression have been seen when ribavirin is taken with azathioprine. This was reversible when these treatments were stopped.

PROPER USE OF THIS MEDICATION

Usual dose:

How should you take PEGASYS RBV combination therapy?

Your doctor has prescribed PEGASYS RBV combination therapy after carefully studying your case. Other people may not benefit from taking this medicine, even though their problems may seem similar to yours. Do not give your medicine to anyone else.

PEGASYS is given as an injection just under the skin, on the stomach or thighs. You may hear people call this type of injection a "subcutaneous" or "Sub Q" injection. This means that the injection goes into the layer of fat just under the skin. If you have any questions about how to take PEGASYS or have trouble giving yourself the injections, call your doctor immediately.

Your healthcare provider will tell you how much medicine to take and how often to take it. PEGASYS is a ready-to-use solution usually given as a single injection once per week. Make sure that you drink plenty of fluids while you are being treated with PEGASYS.

PEGASYS is supplied in three different ways: pre-filled syringes, autoinjectors, and vials. It is important that you follow the specific instructions for using the kind of PEGASYS that your doctor has prescribed. **Whether you give yourself the injection, or another person gives the injection to you, it is important to follow the instructions (see Appendix 1- How to use) in this information sheet.**

COPEGUS tablets should be taken each day in two doses with food (morning and evening). Your healthcare provider will determine the correct dose of COPEGUS tablets based on your weight and the genotype of the disease you have.

Do not take COPEGUS alone to treat hepatitis C virus infection. COPEGUS does not treat hepatitis C virus infections by itself. COPEGUS should be used in combination with PEGASYS to treat continuing (chronic) hepatitis C virus infections.

How long will you have to take PEGASYS RBV?

Your doctor will tell you how long you need to use PEGASYS RBV. Over time, your doctor may change your dose of PEGASYS RBV. For information on how to change your dose of PEGASYS, see the section called **"How do you use PEGASYS?"** Only change your dose of PEGASYS RBV if your doctor tells you to change it.

After 3 months of therapy, your doctor may ask you to have a blood test to determine how you are responding to your treatment.

What should you do if your doctor changes your dose of PEGASYS?

If your doctor changes your dose of PEGASYS, you will need to pull a different amount of medicine into the syringe from the vial. Your doctor will tell you which mark on the syringe to use. Do not change your dose of PEGASYS unless your doctor tells you to.

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

The autoinjector is designed to deliver the full content. If your required dose is not available in an autoinjector, pre-filled syringes or vials should be used.

Are all interferon and ribavirin combinations the same?
Once you start treatment with PEGASYS RBV combination therapy, do not switch to another brand of interferon and/or ribavirin without talking to your doctor. Other brands may not have the same effect on the treatment of your disease. Switching brands will also require a change in your dose.

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

In case of drug overdose, contact a health care practitioner, hospital emergency department or regional Poison Control Centre immediately, even if there are no symptoms.

Missed Dose:
If you miss a dose of PEGASYS and remember **within 2 days** of the scheduled dose, give yourself an injection of PEGASYS as soon as you remember. Take your next PEGASYS dose on the day you would usually take it. If **more than 2 days** have passed, ask your doctor what you should do.

If you miss a dose of COPEGUS tablets and remember **within the same day**, take the missed dose as soon as you remember. If **an entire day has passed**, ask your doctor what to do. Do not take two doses at the same time.

To get the most benefit from this medicine, it is important to take PEGASYS RBV combination therapy exactly as your doctor and healthcare providers tell you.

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

Unwanted effects are possible with all medicines. PEGASYS RBV combination therapy can cause some serious side effects. Before starting PEGASYS RBV combination, you should talk with your doctor about the possible benefits and possible side effects of treatment. Talk to your doctor or pharmacist if you are worried about side effects or find them very bothersome. There may be a way to relieve your symptoms. While taking PEGASYS RBV combination therapy, you will need to see your doctor regularly for medical examinations and blood tests to make sure your treatment is working and to check for side effects.

The most common side effects of interferon therapy, including PEGASYS RBV are:

- Flu-like symptoms such as unusual tiredness, fever, chills, muscle aches, joint pain, and headaches. Most people have mild to moderate flu-like symptoms, but these usually decrease after the first few weeks of treatment. Taking acetaminophen (e.g. Tylenol®) or ibuprofen (e.g. Advil®) before you take PEGASYS can help with these symptoms. Ask your pharmacist or doctor for a recommendation as to which pain reliever to take. You can also try taking PEGASYS at night. You may be able to sleep through the symptoms.

Other common side effects can occur with PEGASYS RBV, but are usually mild. These may include:

- Upset stomach, nausea, vomiting, loss of appetite, diarrhea, back pain, trouble sleeping, poor concentration, dizziness, decreased sexual desire, numbness or tingling, rash, dry itchy skin, hair thinning, redness and swelling at the injection site, problems with blood sugar, feeling tired and cough.

Dental and gum disorders, which may lead to loss of teeth, have been reported in patients receiving PEGASYS RBV. In addition, dry mouth could have a damaging effect on teeth and membranes of the mouth during long-term treatment with PEGASYS RBV. You should brush your teeth thoroughly twice daily and have regular dental examinations. In addition some patients may experience vomiting. If you have this reaction, be sure to rinse your mouth thoroughly afterwards.

The serious possible side effects of interferon therapy, including PEGASYS RBV are:

- Mood or behavioral problems including irritability (getting easily upset), depression (feeling low, feeling bad about yourself or feeling hopeless), and anxiety. Some patients may have aggressive behaviour (sometimes directed towards others) or develop thoughts about ending their lives (suicidal thoughts) and may attempt to do so. A few patients have ended their lives.
- Blood related disorders such as pancytopenia (marked decreases in red and white blood cells and platelets) and different forms of anemia
- A drop in the number of white blood cells causing a risk for infection, and drop in platelets resulting in bleeding if the numbers drop too low.
- Serious infections (bacterial, viral or fungal).
- Lung problems, such as difficulty breathing, pneumonia, or high blood pressure of the lungs (pulmonary hypertension)
- Eye problems that may cause blurred vision, a visual field deficit, or loss of vision.
- Autoimmune problems (where the body's own immune system begins to attack itself) including psoriasis or thyroid problems.

- Chest pain and very rarely heart attack.
- Stroke: some patients may have weakness, loss of coordination and numbness
- Nerve problems: some patients may have numbness, tingling or burning sensation in the arms or legs
- Effect on growth in children: In a clinical study, it was observed that 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, however some children may not reach the height that they were expected to have before treatment. (PEGASYS RBV is not authorized for use in children and adolescents under the age of 18 years.)

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM				
Symptom / effect		Talk with your doctor or pharmacist		Stop taking drug and call your doctor or pharmacist
		Only if severe	In all cases	
Less Common	Depressed or think of suicide		☑	
	Experience hallucinations, aggressiveness or confusion, or have trouble sleeping or concentrating		☑	
	Severe chest pain or irregular heart beat		☑	
	Trouble breathing or persistent cough		☑	
	Problems with your eyesight, a change in your vision (such as blurred vision, a visual field deficit or loss of vision) or hearing problem		☑	
	Unusual bleeding or bruising, including severe nosebleeds		☑	
	Psoriasis (skin disease) and it gets worse while taking medicine		☑	
	Serious skin rash, hives, swelling or itching		☑	
	High fever or chills or have pain when urinating		☑	
	Severe stomach pain or lower back pain		☑	
	Bloody diarrhea		☑	
	Woman and become pregnant		☑	
	Weakness, loss of coordination and numbness, tingling or burning sensation in the arms or legs		☑	

If you are concerned about these or any other unexpected effects while on PEGASYS RBV, talk to your doctor or pharmacist.

HOW TO STORE IT

PEGASYS RBV packages must be stored in the refrigerator at a temperature of 2-8°C. Do not freeze. Do not shake. Protect from light.

If the package components are separated: PEGASYS must be stored in the refrigerator at a temperature of 2-8°C. Do not freeze. Do not shake. Protect from light. COPEGUS should be stored below 30°C or in the refrigerator (2-8°C).

Keeping PEGASYS at temperatures outside the recommended range and shaking can destroy the medicine.

Do not use after expiry date stated on the label.
Keep this and all other medicines out of the reach of children.

Appendix 1 How to Use

What is the safe way to handle and dispose of PEGASYS?
If you use PEGASYS at home, you must throw away syringes, autoinjectors, and needles in a box that will not let the needles stick through it. This will help protect you and other people from accidental needle sticks. Being stuck by a needle not only hurts, but also can pass diseases on to other people.

You can get these special boxes, often called "puncture-resistant containers," from your doctor or pharmacist. Keep this box out of the reach of children. When the box is full, follow your healthcare provider's instructions for throwing it away. Placing used boxes in the household waste should be avoided.

For safety reasons, always throw away syringes and needles promptly and never reuse them.

How do you use PEGASYS?
Please ask your doctor what supplies you need for properly administering this drug.

Pre-filled Syringes:
The following instructions will help you learn how to use PEGASYS pre-filled syringes to inject yourself. It is important to follow these directions carefully. Talk to your healthcare provider if you have any concerns about how to use PEGASYS.

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

Getting ready
Wash your hands carefully before handling any of the items.

Collect the necessary items before beginning:

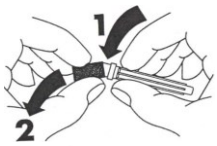
Included in the pack:
- a pre-filled syringe of PEGASYS
- an injection needle*

Not included in the pack:
- alcohol swabs
- small bandage or sterile gauze
- a puncture-resistant container for cleaning up when you are finished

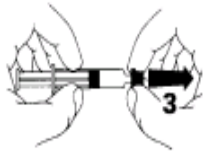
You may need to purchase these.

Preparing the syringe and needle for injection

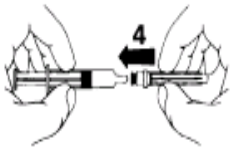
- Remove the protective cap that covers the back of the needle (1-2)



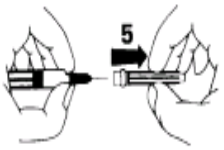
- Remove the rubber cap from the syringe (3). Do not touch the tip of the syringe.



- Place the needle firmly on the tip of the syringe (4).

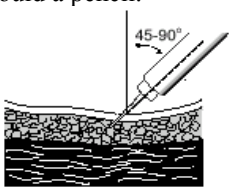


- Remove the needle guard from the syringe needle (5).



- To remove air bubbles from the syringe, hold the syringe with the needle pointing up. Tap the syringe gently to bring the bubbles to the top. Push the plunger up slowly to the correct dose. Replace the needle guard and place the syringe in a horizontal position until ready for use.
- Allow the solution to reach room temperature before injection or warm the syringe between your palms.
- Visually inspect the solution prior to administration. Do not use if it is discoloured (any colour besides colourless to light yellow) or if particles are present and report the lot number to your healthcare provider.
- You are now ready to inject the dose.

Injecting the solution
- Select the injection site in the abdomen or thigh (except your navel or waistline). Change your injection site each time.
- Clean and disinfect the skin where the injection is to be made with an alcohol swab.
- Wait for the area to dry.
- Remove the needle guard.
- With one hand, pinch a fold of loose skin. With your other hand hold the syringe as you would a pencil.
- Insert the needle all the way into the pinched skin at an angle of 45° to 90° (6).



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- Inject the solution by gently pushing the plunger all the way down.
- Pull the needle straight out of the skin.

Disposal of the injection materials
- Clean up after your injection.
- Place the syringe and needle in a puncture-resistant container immediately after use.
- Throw away full containers according to directions provided by your healthcare provider.

Vials:
The following instructions will help you learn how to use PEGASYS vials. Please read all of these directions before trying to take your medicine. It is important to follow these directions carefully. Talk to your healthcare provider if you have any concerns about how to use PEGASYS.

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

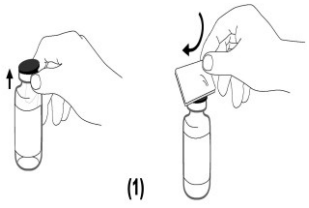
Getting ready
Wash your hands carefully before handling any of the items. Collect the necessary items before beginning:

Included in the pack:
- a vial of PEGASYS solution for injection.

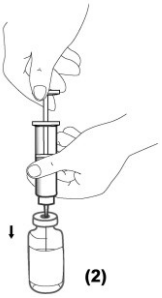
Not included in the pack:
- alcohol swabs
- 1 mL syringe and needle (recommended: 27 gauge x ½ inch) for subcutaneous administration
- small bandage or sterile gauze
- a puncture-resistant container for cleaning up when you are finished.
- You may need to purchase these.

Measuring the dose of PEGASYS

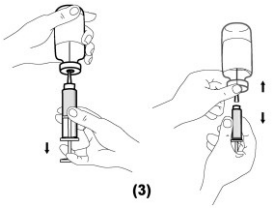
- Remove the protective cap from the PEGASYS vial (1).
- Clean the rubber top of the vial with an alcohol swab.

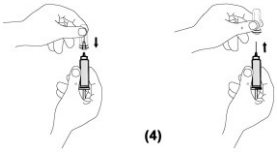


- Remove the needle and syringe from their packaging.
- Pull the syringe plunger back to the mark on the syringe barrel as instructed, this will pull air into the syringe barrel.
- Remove the needle guard without touching the needle and insert through the center of the stopper on the PEGASYS vial.
- Slowly inject all the air from the syringe into the air space above the solution. Do not inject air into the fluid (2).



- Hold the vial and syringe in one hand and turn the vial and the syringe upside down (3).
- With the syringe pointing up, make certain that the tip of the needle is in the PEGASYS solution. Your other hand will be free to move the plunger of the syringe.
- Slowly pull back on the plunger until the medicine is in the syringe up to the mark specified by your doctor.
- When you have pulled up the medicine to the right mark, pull the syringe needle out of the vial (4).

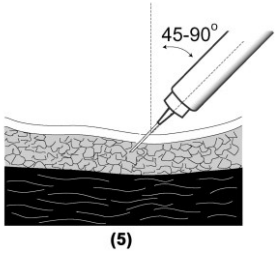




- Check for air bubbles in the syringe. If you see any bubbles, pull the plunger slightly back. To remove air bubbles from the syringe, hold the syringe with the needle pointing up. Tap the syringe gently to bring the bubbles to the top. Push the plunger up slowly to the correct dose. Replace the needle guard and place the syringe in a horizontal position until ready for use.
- Allow the solution to reach room temperature before injection or warm the syringe between your palms.
- Visually inspect the solution prior to administration. Do not use if it is discoloured (any colour besides colourless to light yellow) or if particles are present and report the lot number to your healthcare provider.
- You are now ready to inject the dose.

Injecting the solution
- Select the injection site in the abdomen or thigh (except your navel or waistline). Change your injection site each time.
- Clean and disinfect the skin where the injection is to be made with an alcohol swab.
- Wait for the area to dry.
- Remove the needle guard.
- With one hand, pinch a fold of loose skin. With your other hand hold the syringe as you would a pencil.

- Insert the needle all the way into the pinched skin at an angle of 45° to 90° (5).



(5)

- Inject the solution by gently pushing the plunger all the way down.
- Pull the needle straight out of the skin.

Disposal of the injection materials
- Clean up after your injection.
- Place the syringe and needle in a puncture-resistant container immediately after use.
- Throw away full containers according to directions provided by your healthcare provider.

ProClick® Autoinjector:

The following instructions will help you or your caregiver learn how to use PEGASYS ProClick™ autoinjector correctly. These instructions do not replace training from your healthcare provider. Your healthcare provider should show you how to prepare and use your autoinjector properly before you use it for the first time. Ask your healthcare provider any questions you may have. Do not attempt to administer an injection until you are sure you understand how to use the autoinjector.

The ready to use autoinjector includes a post-injection needle shield that was designed to help prevent needle-stick injuries and keeps the needle non-visible. The autoinjector is for single use only and is then to be discarded.

Do not:
- attempt to open the autoinjector or take it apart.
- expose to excessive forces or shock.
- use through clothing covering the skin.
- use if autoinjector appears to be damaged.
- use if medicine is cloudy, hazy, discoloured or has particles in it.
- shake the autoinjector.
- remove the blue cap if you are not ready to use it.
- re-use the autoinjector.
- push or pull the red needle-shield before, during or after use, as this is a safety device.

Getting ready:
Wash your hands carefully before handling any of the items.

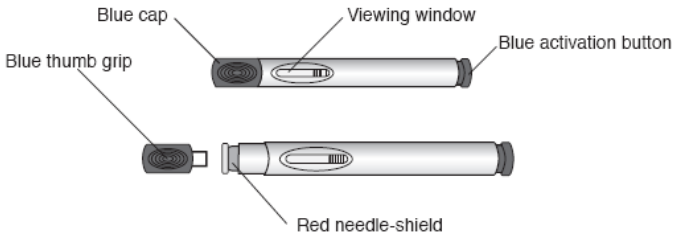
Collect the necessary items before beginning:

Included in the pack:
- a PEGASYS ProClick® autoinjector

Not included in the pack:
- alcohol swabs
- small bandage or sterile gauze
- a puncture-resistant container for cleaning up when you are finished

You may need to purchase these.

ProClick® Autoinjector parts:



How to proceed:

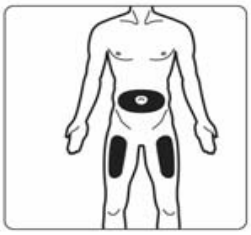
1. Visually check the autoinjector
Take the autoinjector out of the refrigerator. Visually examine the autoinjector, as well as the medicine through the viewing window. Do not shake. Do not remove the blue cap. If there is foam on the medicine, put the autoinjector back in the refrigerator and use at a later time.

Dispose of the autoinjector and use another if:
- the medicine is cloudy.
- the medicine contains particles.
- the medicine is any colour besides colourless to light yellow.
- any part of the autoinjector appears to be damaged.
- the expiration date has passed. You will find the expiration date on the box as well as on the label of the autoinjector itself.
- Contact your health care provider or pharmacist if the medicine in the autoinjector is cloudy or contains particles.

Keep the blue protective cap on the autoinjector until Step 4.

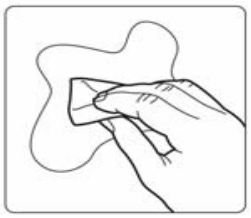
2. Allow the autoinjector to adjust to room temperature
Allow the refrigerated autoinjector to adjust to room temperature for about 20 minutes to warm up. Do not warm up autoinjector in any other way.

3. Choose and prepare an injection site
- Pick a place on your stomach or thigh (black areas in the picture). Avoid the 2 inch area around your belly-button (navel) and your waistline. You should use a different place each time you give yourself an injection. To minimize discomfort from injections, you may want to gently tap the area where you plan to give yourself an



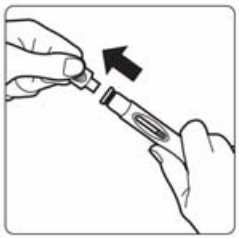
injection.

- Clean the injection site using an alcohol swab. Let the skin dry for 10 seconds. Be sure not to touch the cleaned area prior to injection.



4. Remove blue cap

- Hold the autoinjector firmly with one hand and pull off the protective blue cap with the other hand.



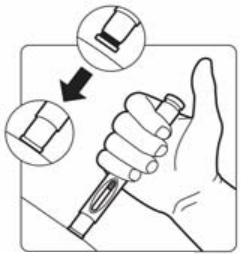
NOTE: The cap contains a loose-fitting metal tube. Once the cap is removed, the autoinjector should be used immediately to avoid contamination. If it is not used within 5 minutes, the autoinjector should be disposed and a new autoinjector should be used. **Never re-attach the protective blue cap after removal.**

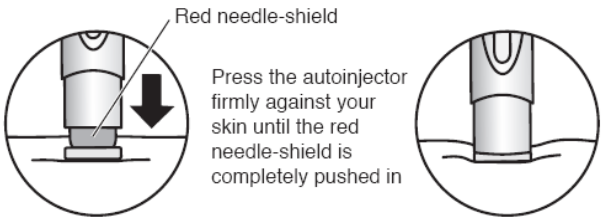
5. Place the autoinjector on the injection site

- Hold the autoinjector comfortably in your hand. Pinch and hold a fold of skin at the injection site with your free hand, such that the needle-shield can rest on the skin-fold firmly and safely.
- Place autoinjector straight up and down at a right angle (90°) on the injection site.

NOTE: Do not press the blue activation button yet.

- Press the autoinjector firmly against the skin until the red needle-shield is completely pushed in.
  - *The autoinjector is now unlocked and ready for injection.*

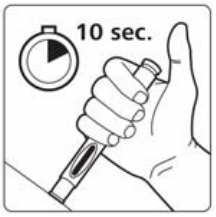




6. Give Injection

- While holding autoinjector firmly in place, press the blue activation button with your thumb and **immediately release the blue button. Make sure to take your thumb off the blue activation button and do not press it again.**
  - *You should hear a "click" sound, telling you that the injection has started.*
  - *The red indicator will move down in the viewing window during the injection.*

- Keep the autoinjector pressed firmly on the skin for **10 seconds** for injection to complete.
  - *You might hear a second click as the blue activation button pops back up.*
  - *The viewing window will now be completely red, confirming that the full dose has been delivered.*



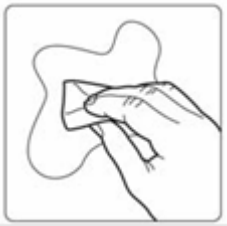
- Lift the autoinjector straight up (90° angle).
  - *The red needle-shield will automatically move out and lock to prevent needlestick injuries.*

CAUTION: If the viewing window is not completely filled by the red indicator:

- the needle-shield may not have locked.
  - Do not touch the tip of the autoinjector, since needlestick injuries may occur.
- you may not have received an entire dose.
  - Do not try to use the autoinjector again.
  - Do not repeat the injection with another autoinjector.
  - **Call your healthcare provider for instructions.**

7. After the injection

- Throw away used autoinjector and cap in a puncture-resistant disposable container immediately after use. Recapping is not required.
- Wipe the injection site with an alcohol swab.
- Wash your hands with soap and water.



- Throw away full containers according to directions provided by your healthcare provider.

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Hoffmann-La Roche Limited
Mississauga, Ontario L5N 5M8

REPORTING SUSPECTED SIDE EFFECTS

You can report any suspected adverse reactions associated with the use of health products to the Canada Vigilance Program by one of the following 3 ways:

- **Report online at www.healthcanada.gc.ca/medeffect**
- **Call toll-free at 1-866-234-2345**
- **Complete a Canada Vigilance Reporting Form and:**
  - **Fax toll-free to 1-866-678-6789, or**
  - **Mail to: Canada Vigilance Program**
    Health Canada
    Postal Locator 0701E
    Ottawa, Ontario
    K1A 0K9

Postage paid labels, Canada Vigilance Reporting Form and the adverse reaction reporting guidelines are available on the MedEffect™ Canada Web site at www.healthcanada.gc.ca/medeffect.

NOTE: Should you require information related to the management of side effects, contact your health professional. The Canada Vigilance Program does not provide medical advice.

MORE INFORMATION

This brochure does not contain all known information about PEGASYS RBV. If you have any further questions or concerns about your treatment with PEGASYS RBV, please contact your doctor or pharmacist.

This document plus the full product monograph, prepared for health professionals can be found at:
www.rochecanada.com

This leaflet was prepared by Hoffmann-La Roche Limited

Last revised:

*Injection needle manufactured by Terumo Europe N. V., Interleuvenlaan 40 Leuven, ZZ, Belgium 3001

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