

Data Sheet

Pegasys RBV[®]

Peginterferon alfa-2a (40 kD) solution for injection 135 and 180 mcg in 0.5 mL + ribavirin film-coated tablets 200 mg

Immunostimulating agent/cytokine + direct acting antiviral

Pharmaceutical Form

Pegasys RBV is a combination therapy, containing Pegasys[®] solution for injection and Copegus[®] film-coated tablets.

Pegasys is supplied as a sterile, ready-to-use liquid for subcutaneous injection as prefilled syringes:

- Pegasys 180 mcg prefilled syringe: each single use syringe contains 180 mcg peginterferon alfa-2a in 0.5 mL solution for injection.
- Pegasys 135 mcg prefilled syringe: each single use syringe contains 135 mcg peginterferon alfa-2a in 0.5 mL solution for injection.

A stainless steel needle is also supplied with the syringe to allow for subcutaneous injection.

Copegus is supplied as a 200 mg oval shaped film-coated tablet for oral administration.

Qualitative and Quantitative Composition

Pegasys

Active ingredient

Peginterferon alfa-2a

Excipients

Sodium chloride, benzyl alcohol, sodium acetate, acetic acid, polysorbate 80, water for injections.

Appearance

Clear, colourless light yellow solution practically free of particles supplied in disposable glass syringes.

Copegus

Active Ingredient

Each Copegus film-coated tablet contains 200 mg of ribavirin.

Excipients

Kernel: pregelatinised starch, sodium starch glycolate, microcrystalline cellulose, maize starch, magnesium stearate.

Film-coat: ethyl cellulose, hydroxypropyl methylcellulose, titanium dioxide, talc, iron oxide yellow, iron oxide red, triacetin.

Appearance

Copegus 200 mg tablets are light pink to pink, flat, oval, film-coated tablets with RIB and 200 engraved on one side and ROCHE on the other side.

Clinical Particulars

Therapeutic Indications

Pegasys RBV is indicated for the treatment of chronic hepatitis C (CHC) in:

- non-cirrhotic patients
- cirrhotic patients with compensated liver disease

Dosage and Administration

Before beginning Pegasys RBV combination therapy, standard haematological and biochemical laboratory tests are recommended for all patients (see Warnings and Precautions - Laboratory Tests).

Standard dosage

Chronic hepatitis C: treatment-naïve, prior treatment non-responder and relapser patients

The recommended dosage of Pegasys, in combination with Copegus, is 180 mcg once weekly by subcutaneous administration in the abdomen or thigh.

The duration of Pegasys RBV combination therapy, and the daily dose of Copegus, should be individualised based on the patient's viral genotype (see Table 1). The daily dose of Copegus is to be administered orally in two divided doses (morning and evening) with food.

Table 1 Dosing Recommendations

Genotype	Pegasys dose	Copegus dose	Duration of treatment: naïve patients	Duration of treatment: prior treatment non-responder and relapser patients
Genotype 1, 4*	180 mcg	< 75 kg = 1000 mg 5 tablets (2 morning, 3 evening)	48 weeks	72 weeks
		≥ 75 kg = 1200 mg 6 tablets (3 morning, 3 evening)	48 weeks	72 weeks
Genotype 2, 3	180 mcg	800 mg 4 tablets (2 morning, 2 evening)	24 weeks	48 weeks

* In general, patients infected with genotype 4 are considered hard to treat and limited study data ($n = 49$) are compatible with a posology as for genotype 1.

HIV-HCV Co-infection

The recommended dosage of Pegasys, in combination with 800 mg Copegus, 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.

Predictability of response and non-response in naïve patients

Early virological response by week 12, defined as a 2-log viral load decrease or undetectable levels of HCV RNA has been shown to be predictive for sustained response (see Table 2).

Table 2 Predictive Value of Week 12 Virological Response at the Recommended Dosing Regimen while on Pegasys RBV Combination Therapy

Genotype	Negative			Positive		
	No response by week 12	No sustained response	Predictive Value	Response by week 12	Sustained response	Predictive Value
Genotype 1 ($n = 569$)	102	97	95% (97/102)	467	271	58% (271/467)
Genotype 2 and 3 ($n = 96$)	3	3	100% (3/3)	93	81	87% (81/93)

A similar negative predictive value has been observed in HIV-HCV co-infected patients treated with Pegasys monotherapy or in combination with Copegus (100% or 98%, respectively). Positive predictive values of 45% and 70% were observed for genotype 1 and genotype 2/3 HIV-HCV co-infected patients receiving combination therapy.

Predictability of response and non-response in prior non-responder patients

In non-responder patients treated for 72 weeks, the best on-treatment predictor of response was viral suppression at week 12 (undetectable HCV RNA, defined as HCV RNA < 50 IU/mL). The negative predictive value of viral suppression at week 12 was 96% (324/339) and the positive predictive value was 57% (57/100).

Special dosage instructions

Dose modification

General

When dose modification is required for moderate to severe adverse reactions (clinical and/or laboratory), initial dose reduction of Pegasys to 135 mcg is generally adequate. However, in some cases, dose reduction to 90 mcg or 45 mcg is necessary. Dose increases to or toward the original dose may be considered when the adverse reaction abates (see Warnings and Precautions and Undesirable Effects).

If severe adverse reactions or laboratory abnormalities develop during therapy with Pegasys RBV, modify the dosages of Pegasys and Copegus until the adverse reactions abate. If intolerance persists after Copegus dose adjustment, discontinuation of this medicine may be necessary.

Haematological

Pegasys dose reduction is recommended if the absolute neutrophil count (ANC) is less than $0.75 \times 10^9/L$. For patients with ANC values below $0.5 \times 10^9/L$, treatment should be suspended until ANC values return to more than $1 \times 10^9/L$. Therapy should initially be reinstated at 90 mcg Pegasys and the neutrophil count monitored.

Pegasys dose reduction to 90 mcg is recommended if the platelet count is less than $50 \times 10^9/L$. Cessation of therapy is recommended when platelet count decreases to levels below $25 \times 10^9/L$.

For management of treatment-emergent anaemia, the Copegus dose should be reduced to 600 mg/day (200 mg in the morning and 400 mg in the evening) if either of the following apply:

- A patient without significant cardiovascular disease experiences a fall in haemoglobin to < 100 g/L and ≥ 85 g/L or
- A patient with stable cardiovascular disease experiences a fall in haemoglobin by ≥ 20 g/L during any 4 weeks of treatment.

Copegus should be *discontinued* under the following circumstances:

- If a patient without significant cardiovascular disease experiences a confirmed decrease in haemoglobin to < 85 g/L.
- If a patient with stable cardiovascular disease maintains a haemoglobin value < 120 g/L despite 4 weeks on a reduced dose.

Once the patient's Copegus dose has been withheld due to a laboratory abnormality or clinical manifestation an attempt may be made to restart Copegus at 600 mg daily and further increase the dose to 800 mg daily depending upon the physician's judgment. However, it is not recommended that Copegus be increased to the original dose (1000 mg or 1200 mg).

In case of intolerance to Copegus, Pegasys monotherapy may be continued.

Liver function

Fluctuations in abnormalities of liver function tests are common in patients with CHC. However, as with other alfa 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 135 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 (see Warnings and Precautions).

Special populations

Renal impairment

In patients with end stage renal disease (ESRD), a starting dose of Pegasys 135 mcg once weekly should be used (see Pharmacokinetics in special populations). 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.

Dosage modification for patients undergoing long term haemodialysis

In renally impaired patients undergoing long term haemodialysis, Copegus can be safely administered at a dose of 200 mg daily (see Warnings and Precautions and Pharmacokinetics in special populations).

Hepatic impairment

In patients with compensated cirrhosis (e.g. Child-Pugh A), Pegasys has been shown to be effective and safe. Pegasys has not been studied in patients with decompensated cirrhosis (e.g. Child-Pugh B/C or bleeding oesophageal varices) (see Contraindications).

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

Paediatric use

Safety and effectiveness of Pegasys RBV combination therapy in patients under the age of 18 years have not been evaluated. Pegasys RBV is not recommended for use in children and adolescents under the age of 18.

Pegasys injectable solutions contain 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. Therefore, Pegasys should not be used in neonates or infants (see Contraindications).

Geriatric use

No special Pegasys dosage modification is required for elderly patients based upon pharmacokinetic, pharmacodynamic, tolerability, and safety data from clinical trials.

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.

Contraindications

Pegasys RBV combination therapy is contraindicated:

- in patients with known hypersensitivity to alfa interferons, ribavirin, *E. coli*-derived products, polyethyleneglycol or any component of Pegasys or Copegus
- for use by women who are pregnant, or by men whose female partners are pregnant
- in patients with autoimmune hepatitis
- in patients with decompensated cirrhosis
- for use in neonates and infants up to 3 years of age
- in patients with haemoglobinopathies (e.g. thalassaemia, sickle-cell anaemia)

- in HIV-HCV patients with cirrhosis and a Child-Pugh score ≥ 6 , except if only due to indirect hyperbilirubinemia caused by medicines such as atazanavir and indinavir.

Warnings and Precautions

Treatment with Pegasys RBV combination therapy 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 further therapy.

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

Pegasys RBV was associated with decreases in both total white blood cell (WBC) count and ANC, usually starting within the first 2 weeks of treatment (see Undesirable Effects). In clinical studies, progressive decreases after 4 to 8 weeks of treatment were infrequent. Pegasys dose reduction is recommended when ANC decreases to levels below $0.75 \times 10^9/L$ (see Dosage and Administration). For patients with ANC values below $0.5 \times 10^9/L$, treatment should be suspended until ANC values return to more than $1 \times 10^9/L$. In clinical trials with Pegasys RBV, the decrease in ANC was reversible upon dose reduction 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 Undesirable Effects). Pegasys dose reduction is recommended when platelet count decreases to levels below $50 \times 10^9/L$ and cessation of therapy is recommended when platelet count decreases to levels below $25 \times 10^9/L$ (see Dosage and Administration).

Anaemia (haemoglobin ≤ 100 g/L) was observed in 13% of patients in clinical trials treated with Pegasys RBV 1000 mg or 1200 mg for 48 weeks and in 3% with Pegasys RBV 800 mg for 24 weeks (see Undesirable Effects, Laboratory test values – haemoglobin and haematocrit). The maximum drop in haemoglobin occurred within 4 weeks of initiation of Copegus therapy. Full blood counts should be obtained pre-treatment, at weeks 2 and 4 of therapy and periodically thereafter. If there is any deterioration of cardiovascular status, Copegus therapy should be suspended or discontinued (see Dosage and Administration).

It is advised that full blood counts (FBC) be obtained pre-treatment and monitored routinely during therapy. Pegasys RBV should be used with caution in patients with baseline neutrophil counts $< 1.5 \times 10^9/L$, with baseline platelet count $< 90 \times 10^9/L$ or baseline haemoglobin < 120 g/L (see Dosage and Administration). As with other interferons, caution should be exercised when administering Pegasys in combination with other potentially myelosuppressive agents.

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 alfa interferons including Pegasys. Appropriate anti-infective therapy should be started immediately and discontinuation of therapy should be considered.

Autoimmune disorders

Exacerbation of autoimmune disease has been reported in patients receiving alfa interferon therapy; Pegasys RBV should be used with caution in patients with autoimmune disorders.

Use of alfa interferons has been associated with exacerbation or provocation of psoriasis. Pegasys RBV must be used with caution in patients with psoriasis, and in case of appearance or worsening of psoriatic lesions, discontinuation of therapy should be considered.

Endocrine

As with other interferons, Pegasys RBV may cause or aggravate hypothyroidism and hyperthyroidism. Discontinuation of Pegasys RBV should be considered in patients whose thyroid abnormalities cannot be adequately treated. Hyperglycaemia, hypoglycaemia and diabetes mellitus have been observed in patients treated with alfa interferons. Patients with these conditions who cannot be effectively controlled by medication should not begin Pegasys RBV. Patients who develop these conditions during treatment and cannot be controlled with medication should discontinue Pegasys RBV.

Neuropsychiatric

Severe psychiatric adverse reactions may manifest in patients receiving therapy with interferons, including Pegasys RBV. Depression, suicidal ideation, and suicidal attempt may occur in patients with and without previous psychiatric illness. Pegasys RBV should be used with caution in patients who report a history of depression, and physicians should monitor all patients for evidence of depression. Physicians should inform patients of the possible development of depression prior to initiation of Pegasys RBV, and patients should report any sign or symptom of depression immediately. In severe cases therapy should be stopped and psychiatric intervention sought (see Undesirable Effects).

Ophthalmologic

As with other interferons, retinopathy including retinal haemorrhages, cotton wool spots, papilloedema, optic neuropathy, and retinal artery or vein obstruction, which may result in loss of vision, have been reported after treatment with Pegasys. All patients should have a baseline eye examination. Patients with pre-existing ophthalmologic disorders (e.g. diabetic or hypertensive retinopathy) should receive periodic ophthalmologic exams during alfa interferon treatment. Any patient complaining of decreased or loss of vision must have a prompt and complete eye examination. Pegasys RBV should be discontinued in patients who develop new or worsening ophthalmologic disorders.

Hypersensitivity

Serious, acute hypersensitivity reactions (e.g. urticaria, angioedema, bronchoconstriction, anaphylaxis) have been rarely observed during alfa interferon therapy. If such a reaction develops during treatment with Pegasys RBV, discontinue treatment immediately and institute appropriate medical therapy. Transient rashes do not necessitate interruption of treatment.

Pulmonary

As with other alfa interferons, pulmonary symptoms, including dyspnoea, pulmonary infiltrates, pneumonia, and pneumonitis, including fatality, have been reported during therapy with Pegasys RBV. If there is evidence of persistent or unexplained pulmonary infiltrates or pulmonary function impairment, treatment should be discontinued.

Hepatic function

In patients who develop evidence of hepatic decompensation during treatment, Pegasys RBV should be discontinued.

As with other alfa interferons, increases in ALT levels above baseline have been observed in patients treated with Pegasys RBV, including patients with 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).

HIV-HCV Co-infection

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 alfa interferons, including Pegasys. 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 ≥ 7). 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.

Haemolysis and cardiovascular system

If there is any deterioration of haemoglobin blood concentration, Copegus should be suspended or discontinued (see Special dosage instructions).

Although Copegus has no direct cardiovascular effects, anaemia associated with Copegus may result in deterioration of cardiac function, or exacerbation of the symptoms of coronary disease, or both. Thus, patients with a history of significant or unstable cardiac disease in the previous six months should not use Copegus.

Cardiovascular events such as hypertension, supraventricular arrhythmias, congestive heart failure, chest pain and myocardial infarction have been associated with interferon therapies, including Pegasys RBV.

Cardiac status must be assessed before initiation of therapy and monitored clinically during therapy. It is recommended that patients who have pre-existing cardiac abnormalities have an electrocardiogram prior to initiation of therapy, and during the course of treatment. If there is any deterioration of cardiovascular status, Copegus therapy should be stopped and Pegasys therapy should be suspended or discontinued (see Dosage and Administration).

The use of Pegasys RBV in CHC patients who discontinued hepatitis C therapy for haematological adverse events has not been adequately studied. Physicians considering treatment in these patients should carefully weigh the risks versus the benefits of re-treatment.

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 Interactions with other Medicinal Products and other Forms of Interaction).

Renal impairment

Copegus therapy should not be initiated in patients with moderate to severe renal impairment (creatinine clearance ≤ 50 mL/min) who are not undergoing long-term haemodialysis, unless it is considered to be essential. Copegus must be administered with extreme caution. Compared to patients with normal renal function receiving the standard 1000/1200 mg Copegus daily dose, ribavirin

plasma exposures are higher in patients with moderate renal impairment after receiving 600 mg daily of Copegus, and in patients with severe renal impairment receiving as little as 400 mg daily of Copegus.

In patients who develop renal impairment (and not undergoing haemodialysis) during a standard treatment course of Pegasys RBV, Copegus therapy should not be continued.

Copegus therapy may be initiated in patients with end stage renal disease (ESRD) undergoing long term haemodialysis. In these patients, most of whom received haematopoietic growth factors, Copegus can be safely administered at a dose of 200 mg daily. ESRD patients undergoing long term haemodialysis who were administered a 200 mg daily dose exhibited ribavirin plasma exposures that were approximately 20% lower compared to patients with normal renal function receiving the standard 1000/1200 mg Copegus daily dose (see Special Dosage Instructions, Pharmacokinetic Properties).

It is recommended that renal function be evaluated in all patients prior to initiation of Copegus, preferably by estimating the patient's creatinine clearance. Patients on long term haemodialysis receiving Copegus should be carefully monitored.

Organ transplant recipients

The safety and efficacy of Pegasys RBV treatment has not been established in patients with liver and other transplantations. As with other alfa interferons, liver and renal graft rejections have been reported with Pegasys RBV.

Teratogenic risk

Prior to initiation of treatment with Copegus the physician must comprehensively inform the patient of the teratogenic risk of ribavirin, the necessity of effective and continuous contraception, the possibility that contraceptive methods may fail and the possible consequences of pregnancy should it occur during treatment with ribavirin (see Pregnancy).

For women of childbearing potential

Female patients must have a routine pregnancy test performed monthly during treatment and for 6 months thereafter. Female partners of male patients must have a routine pregnancy test performed monthly during treatment and for 6 months thereafter.

Laboratory tests

Before beginning Pegasys RBV, standard haematological and biochemical laboratory tests (full blood count [FBC] and differential, platelet count, electrolytes, serum creatinine, liver function tests, uric acid) are recommended for all patients. After initiation of therapy, haematological tests should be performed at 2 and 4 weeks and biochemical tests should be performed at 4 weeks. Additional laboratory testing should be performed periodically during therapy.

Acceptable baseline values that may be considered as a guideline prior to initiation of Pegasys RBV are:

- haemoglobin ≥ 120 g/L (females); ≥ 130 g/L (males)
- platelet count $\geq 90 \times 10^9/L$
- absolute neutrophil count (ANC) $\geq 1.5 \times 10^9/L$
- TSH and T₄ within normal limits or adequately controlled thyroid function

- HIV-HCV co-infection: CD4+ \geq 200/mcL or CD4+ \geq 100/mcL to $<$ 200/mcL and HIV-RNA $<$ 5000 copies/mL using Amplicor HIV-1 Monitor Test, v 1.5

Interactions with other Medicinal Products and other Forms of Interaction

No pharmacokinetic interactions between peginterferon alfa-2a and ribavirin have been observed in ongoing clinical trials in which Pegasys is used in combination with Copegus.

Treatment with Pegasys 180 mcg once weekly for 4 weeks had no effect on the pharmacokinetics profiles of tolbutamide (CYP 2C9), mephenytoin (CYP 2C19), debrisoquine (CYP 2D6), and dapsone (CYP 3A4) in healthy male subjects. Peginterferon alfa-2a is a modest inhibitor of cytochrome P450 1A2, as a 25% increase in theophylline's AUC was observed in the same study. Comparable effects on theophylline's pharmacokinetics have been seen after treatment with standard alfa interferons. Alfa interferons have been shown to affect the oxidative metabolism of some medicines 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 RBV concomitantly.

In a pharmacokinetic study of 24 HCV patients concomitantly receiving methadone maintenance therapy (median dose 95 mg; range 30 mg – 150 mg), treatment with Pegasys 180 mcg subcutaneously once weekly for 4 weeks was associated with mean methadone levels that were 10% – 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.

Ribavirin concentrations are similar when given as monotherapy or in combination with peginterferon alfa-2a or interferon alfa-2b.

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

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.

Antacid

The bioavailability of ribavirin 600 mg was decreased by co-administration with an antacid containing magnesium, aluminium and methicone; AUC_{0-∞} 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.

Nucleoside analogues

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 Copegus with either zidovudine or stavudine might lead to increased HIV plasma viraemia. Therefore, it is recommended that plasma HIV RNA levels be closely monitored in patients treated with Copegus concurrently with either of these two agents. If HIV RNA levels increase, the use of Copegus concomitantly with reverse transcriptase inhibitors must be reviewed.

No evidence of medicine interaction was observed in 47 HIV-HCV co-infected patients who completed a 12 week pharmacokinetic sub-study to examine the effect of ribavirin on the intracellular phosphorylation of some nucleoside reverse transcriptase inhibitors (NRTI's; lamivudine, zidovudine or stavudine). Plasma exposure of ribavirin did not appear to be affected by concomitant administration of NRTI's.

Didanosine (ddl)

Ribavirin potentiated the antiretroviral effect of didanosine (ddl) *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 ddl might increase the risk of adverse reactions related to ddl (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 ddl in patients with HIV disease did not result in further reductions in viraemia or an increase in adverse reactions. Plasma pharmacokinetics of ddl were not significantly affected by concomitant ribavirin in this study, although intracellular ddATP was not measured.

Co-administration of Copegus and didanosine is not recommended. Exposure to didanosine or its active metabolite (dideoxyadenosine 5'-triphosphate) is increased when didanosine is co-administered with ribivirin. Reports of fatal hepatic failure, as well as peripheral neuropathy, pancreatitis, and symptomatic hyperlactataemia/lactic acidosis have been reported with use of ribivirin.

Telbivudine

A non-Roche clinical trial investigating the combination of telbivudine 600 mg daily, with pegylated interferon alfa-2a, 180 mcg once weekly by subcutaneous administration, indicates that the combination is associated with an increased risk for developing peripheral neuropathy. The mechanism behind these events is not known. Such an increased risk can not be excluded for other interferons (pegylated or standard). Moreover, the benefit of the combination of telbivudine with interferon alfa (pegylated or standard) is not currently established.

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 haematologic monitoring be done during concomitant azathioprine use to identify signs of myelotoxicity, at which time treatment with these medicines should be stopped (see Warnings and Precautions; Laboratory tests)

Use in Special Populations

Use in Pregnancy – Category X

Pegasys RBV must not be used by women who are pregnant or by men whose female partners are pregnant.

Evaluation of experimental animal studies showed reproductive toxicity for Copegus. 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 foetuses and offspring was reduced.

Extreme care must be taken to avoid pregnancy in female patients. Pegasys RBV must not be initiated until a report of a negative pregnancy test has been obtained immediately prior to initiation of therapy.

Any birth control method can fail. Therefore, it is critically important that women of childbearing potential and their partners must use 2 forms of effective contraception simultaneously, during treatment and for 6 months after treatment has been concluded; routine monthly pregnancy tests must be performed during this time. If pregnancy does occur during treatment or within 6 months from stopping treatment the patient must be advised of the significant teratogenic risk of ribavirin to the foetus.

Pegasys has not been studied for its effect on fertility. As with other alfa interferons, prolongation of the menstrual cycle accompanied by both a decrease and a delay in the peak of 17β -oestradiol and progesterone levels have been observed following administration of peginterferon alfa-2a to female monkeys. A return to normal menstrual rhythm followed discontinuation of treatment.

Pegasys 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 25×10^6 IU/kg/day.

Pegasys 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. However, as with other alfa interferons, women of childbearing potential receiving Pegasys therapy should be advised to use effective contraception during therapy.

Nursing mothers

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

Male patients and their female partners

Extreme care must be taken to avoid pregnancy in partners of male patients taking Copegus. Ribavirin accumulates intracellularly and is cleared from the body very slowly. In animal studies, ribavirin produced changes in sperm at doses below the clinical dose. It is unknown whether the ribavirin that is contained in sperm will exert its known teratogenic effects upon fertilisation of the ova. Therefore, men must be instructed to use a condom to minimise delivery of ribavirin to their partners. Male patients and their female partners of childbearing age must be counselled to use 2 forms of effective contraception during treatment with Copegus and for 6 months after treatment has been concluded. Women must have a negative pregnancy test before therapy is started.

Effects on Ability to Drive and Use Machines

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

Undesirable Effects

The adverse reactions observed with other alfa interferons, alone or in combination with ribavirin, may be expected with Pegasys or Pegasys RBV, respectively.

Experience from clinical trials

The frequency and severity of the most commonly reported adverse reactions are similar in patients treated with Pegasys or Pegasys RBV and alfa interferon or alfa interferon with ribavirin, respectively.

The most frequently reported adverse reactions with Pegasys and Pegasys RBV were mostly mild to moderate in severity and were manageable without the need for modification of dosage or discontinuation of therapy.

Chronic Hepatitis C

Treatment naïve patients

In clinical trials, the incidence of withdrawal from treatment for all naïve patients due to adverse events and laboratory abnormalities was 9% for Pegasys monotherapy and 13% for Pegasys RBV 1000/1200 mg given for 48 weeks. Respectively, only 1% or 3% of patients required discontinuation of either Pegasys or Pegasys RBV for laboratory abnormalities. The withdrawal rates for patients with cirrhosis were similar to those of the overall population. In comparison to 48 weeks of treatment with Pegasys RBV 1000/1200 mg, reducing treatment exposure to 24 weeks and daily dose of ribavirin to 800 mg resulted in a reduction in serious adverse events (11% vs. 3%), premature withdrawals for safety reasons (13% vs. 5%) and the need for ribavirin dose modification (39% vs. 19%).

Prior treatment non-responder patients

In study MV17150 the frequency of withdrawal from Pegasys treatment was 12% and Copegus treatment was 13% due to adverse events or laboratory abnormalities, for patients in the 72 week arms. In comparison, in 48-week treatment arms, 6% withdrew from Pegasys and 7% withdrew from Copegus treatment. Similarly for patients with cirrhosis, withdrawal rates from Pegasys plus Copegus combination treatment were higher in the 72-week treatment arms, (13% and 15%) compared with the 48-week arms (6% and 6%). Patients who withdrew from previous therapy due to haematological toxicity were excluded from enrolling in this trial.

In the HALT C study, patients with advanced fibrosis or cirrhosis (Ishak score of 3 – 6) were enrolled with baseline platelet counts as low as 50 000/mm³ and treated for 48 weeks. Due to a high prevalence of the advanced cirrhosis/fibrosis state and the low baseline platelet counts among patients in this study, the frequency of haematologic lab abnormalities in the first 20 weeks of the trial were as follows: haemoglobin < 10 g/dL, 26.3%; ANC < 750/mm³, 30%; and platelets < 50 000/mm³, 13% (see Warnings and Precautions).

HIV-HCV Co-infection

In study NR15961, 180 mcg Pegasys with or without 800 mg ribavirin in HIV-HCV co-infected patients, the clinical adverse events reported on Pegasys monotherapy or Pegasys RBV were similar to those observed in HCV mono-infected patients. Limited safety data ($n = 51$) is available in co-infected

patients with CD4+ cell counts < 200/mcL. In study NR15961, the incidence of withdrawal from treatment for clinical adverse events, laboratory abnormalities or AIDS-defining events was 16% for Pegasys monotherapy, and 15% for Pegasys RBV 800 mg, given for 48 weeks. Respectively, 4% or 3% of patients required discontinuation of Pegasys or Pegasys RBV, due to blood and lymphatic system disorder adverse events. In combination therapy, Pegasys dose modification occurred in 39%, and ribavirin dose modification occurred in 37%, of the co-infected patients. Serious adverse events were reported in 21% and 17% of those receiving Pegasys monotherapy or Pegasys RBV, respectively.

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.

Study NV18209 compared 48 weeks of treatment with either Pegasys 180 mcg plus ribavirin 1000 or 1200 mg or Pegasys 180 mcg plus ribavirin 800 mg in interferon-naïve patients with HIV-HCV co-infected patients (HCV genotype 1 virus). 275 patients received the ribavirin 1000/1200 mg regime and 135 patients received the 800 mg regime. 80% of patients were male, median age 46 years, 64% Caucasian and 30% non-Hispanic African Americans. Over half of the patients in both treatment groups prematurely withdrew from either treatment and from either treatment group for safety (12 – 13%) or non-safety reasons (40 – 45%). The primary non-safety reason for premature withdrawal was insufficient therapeutic response (25 – 26%). The incidence of withdrawal for safety reasons was 12% (abnormal laboratory tests 4%, adverse events 8 – 9%). The incidence of adverse reactions of $\geq 10\%$ of patients in study NV18209 were similar to those within Table 3 for HIV-HCV co-infected patients, with no increased frequency for Pegasys plus ribavirin 1000/1200 mg compared with Pegasys plus ribavirin 800 mg except for anaemia (see Laboratory Test Values).

Table 3 shows those adverse reactions occurring in $\geq 10\%$ of patients who have received Pegasys, Pegasys RBV or interferon alfa-2b plus ribavirin in different indications.

Table 3 Adverse Reactions (≥ 10% Incidence in Any Treatment Group)

Body System	HCV (treatment naïve)				HIV-HCV (treatment naïve)	HCV (prior treatment non-responder)
	Pegasys 180 mcg 48 wk (NV15801 + monotherapy program) <i>n</i> = 827 %	Pegasys 180 mcg + 800 mg ribavirin 24 wk (NV15942) <i>n</i> = 207 %	Pegasys 180 mcg + 1000 mg or 1200 mg ribavirin 48 wk (NV15801 + NV15942) <i>n</i> = 887 %	IFN alfa-2b + 1000 mg or 1200 mg ribavirin 48 wk (NV15801) <i>n</i> = 443 %	Pegasys 180 mcg + 800 mg ribavirin 48 wk (NV15961) <i>n</i> = 288 %	Pegasys 180 mcg + 1000 mg or 1200 mg ribavirin 72 wk (MV17150) <i>n</i> = 156 %
Metabolism and nutrition disorders						
Anorexia	16	20	27	26	23	15
Weight decrease	5	2	7	10	16	9
Psychiatric disorders						
Insomnia	20	30	32	37	19	29
Depression	18	17	21	28	22	16
Irritability	17	28	24	27	15	17
Concentration impairment	9	8	10	13	2	5
Anxiety	6	8	8	12	8	6
Nervous system disorders						
Headache	52	48	47	49	35	32
Dizziness (excluding vertigo)	15	13	15	14	7	10
Respiratory, thoracic and mediastinal disorders						
Dyspnoea	5	11	13	14	7	11
Cough	4	8	13	7	3	17
Gastrointestinal disorders						
Nausea	24	29	28	28	24	24
Diarrhoea	16	15	14	10	16	13
Abdominal pain	15	9	10	9	7	9
Skin and subcutaneous tissue disorders						
Alopecia	23	25	24	33	10	18
Pruritus	13	25	21	18	5	22
Dermatitis	9	15	16	13	1	1
Dry Skin	5	13	12	13	4	17
Musculoskeletal, connective tissue and bone disorders						
Myalgia	37	42	38	49	32	22
Arthralgia	26	20	22	23	16	15
General disorders and administration site conditions						
Fatigue	49	45	49	53	40	36
Pyrexia	35	37	39	54	41	20
Rigors	30	30	25	34	16	12
Injection site reaction	22	28	21	16	10	12
Pain	11	9	10	9	6	6
Asthenia	7	18	15	16	26	30

Undesirable effects reported in $\geq 1\%$ but $< 10\%$ on Pegasys RBV combination or Pegasys monotherapy were:

Infections and infestations: herpes simplex, URI infection, bronchitis, oral candidiasis

Blood and the lymphatic system disorders: lymphadenopathy, anaemia, thrombocytopenia

Endocrine disorders: hypothyroidism, hyperthyroidism

Neuropsychiatric: memory impairment, taste disturbance, paraesthesia, hypoaesthesia, tremor, weakness, emotional disorders, mood alteration, nervousness, aggression, libido decreased, migraine, somnolence, hyperaesthesia, nightmares, syncope, anxiety

Eye disorders: vision blurred, xerophthalmia, eye inflammation, eye pain

Ear and labyrinth disorders: vertigo, earache

Cardiac disorders: palpitations, oedema peripheral, tachycardia

Vascular disorders: flushing

Respiratory, thoracic and mediastinal disorders: sore throat, rhinitis, nasopharyngitis, sinus congestion, dyspnoea exertional, epistaxis

Gastrointestinal disorders: vomiting, dyspepsia, flatulence, dry mouth, mouth ulceration, gingival bleeding, stomatitis, dysphagia, glossitis

Skin and subcutaneous tissue disorders: skin disorder, rash, eczema, psoriasis, urticaria, photosensitivity reaction, sweating increased, night sweats

Musculoskeletal, connective tissue and bone disorders: bone pain, back pain, neck pain, muscle cramps, muscle weakness, musculoskeletal pain, arthritis

Reproductive system and breast disorders: impotence

General disorders and administration site conditions: influenza-like illness, malaise, lethargy, hot flushes, chest pain, thirst

Other adverse reactions reported in $\geq 1\%$ to $\leq 2\%$ of HIV-HCV patients receiving Pegasys RBV included: hyperlactacidaemia/lactic acidosis, influenza, pneumonia, affect lability, apathy, tinnitus, pharyngolaryngeal pain, cheilitis, acquired lipodystrophy and chromaturia.

As with other alfa interferon therapies, uncommon to rare cases of the following serious adverse events have been reported in patients receiving Pegasys RBV or Pegasys monotherapy during clinical trials: lower respiratory tract infection, skin infection, otitis externa, endocarditis, suicide, substance overdose, hepatic dysfunction, fatty liver, cholangitis, malignant hepatic neoplasm, peptic ulcer, gastrointestinal bleeding, pancreatitis, arrhythmia, atrial fibrillation, pericarditis, autoimmune phenomena (e.g. ITP, thyroiditis, psoriasis, rheumatoid arthritis, SLE), myositis, peripheral neuropathy, sarcoidosis, interstitial pneumonitis with fatal outcome, pulmonary embolism, corneal ulcer, coma and cerebral haemorrhage, TTP, psychotic disorder and hallucination.

Laboratory test values

In clinical trials of Copegus in combination with Pegasys or interferon alfa-2a, the majority of cases of abnormal laboratory values were managed with dose modifications (see Special dosage instructions).

Haematology

As with other interferons, treatment with either Pegasys or Pegasys RBV was associated with decreases in haematological values, which generally improved with dosage modification and returned to pre-treatment levels within 4 to 8 weeks upon cessation of therapy (see Warnings and Precautions and Dosage and Administration; Special dosage instructions). Although haematological toxicities of neutropenia, thrombocytopenia and anaemia 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.

Haemoglobin and haematocrit

Haemolysis is the defining toxicity of ribavirin therapy. A decrease in haemoglobin levels to < 100 g/L was observed in up to 15% of patients treated for 48 weeks with Copegus 1000/1200 mg in combination with Pegasys and up to 19% of patients in combination with interferon alfa-2a. When Copegus 800 mg was combined with Pegasys for 24 weeks, 3% of patients had a decrease in haemoglobin levels to < 100 g/L. It is not expected that patients will need to discontinue therapy because of decrease in haemoglobin levels alone. In most cases the decrease in haemoglobin occurred early in the treatment period and stabilised concurrently with a compensatory increase in reticulocytes.

Although treatment with Pegasys monotherapy was associated with small gradual decreases in haemoglobin and haematocrit, less than 1% of all patients, including those with cirrhosis, required dose modification for anaemia. Approximately 10% of patients on 48 weeks Pegasys RBV 1000/1200 mg required dose modification for anaemia. Anaemia (haemoglobin < 100 g/L) was reported in 7%, 14% and 28% of HIV-HCV co-infected patients treated with Pegasys monotherapy or Pegasys RBV 800 mg and 1000/1200 mg respectively in studies NR15961 and NV18209.

In study NV18209, patients with anaemia were clinically managed with the use of growth factors and transfusions 26% and 37% of patients in the Pegasys plus Copegus 800 mg group and in the Pegasys plus Copegus 1000/1200 mg groups respectively, and with dose modification of either treatment in 13% and 21% of patients, respectively.

White blood cells

Pegasys treatment was associated with decreases in values for both total WBC count and ANC. Approximately 4% of patients on Pegasys and 5% on Pegasys RBV had transient decreases in ANC to levels below $0.5 \times 10^9/L$ at some time during therapy. In HIV-HCV co-infected patients, 13% and 11% of those receiving Pegasys monotherapy and Pegasys RBV, respectively, had decreases in ANC levels below $0.5 \times 10^9/L$.

Platelet count

Pegasys treatment was associated with decreases in values for platelet counts. In clinical trials, approximately 5% of patients had decreases in platelet counts to levels below $50 \times 10^9/L$, mostly in patients with cirrhosis and who entered the study with baseline platelet counts as low as $75 \times 10^9/L$. In HIV-HCV patients, 10% and 8% of those receiving Pegasys monotherapy and Pegasys RBV, respectively, had decreases in platelets below $50 \times 10^9/L$.

Thyroid function

Pegasys treatment was associated with clinically significant abnormalities in thyroid laboratory values requiring clinical intervention (see Warnings and Precautions). The frequencies observed with Pegasys were similar to those observed with other interferons.

Triglycerides

Triglyceride levels are found to be elevated in patients receiving alfa interferon therapy, including Pegasys.

Anti-interferon antibodies

Three percent of patients (25/835) receiving Pegasys or Pegasys RBV developed low-titre neutralising anti-interferon antibodies. The clinical and pathological significance of the appearance of serum neutralising antibodies is unknown. No apparent correlation of antibody development to clinical response or adverse events was observed.

Post marketing

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

Dehydration has been reported rarely with Pegasys RBV.

Rarely, alfa interferon including Pegasys RBV may be associated with pancytopenia, and very rarely aplastic anaemia has been reported.

As with other alfa interferons, serous retinal detachment has been reported with Pegasys RBV.

As with other alfa interferons, liver and renal graft rejections have been reported with Pegasys, alone or in combination with Copegus.

Overdose

Overdoses with Pegasys involving at least two injections on consecutive days (instead of weekly interval) up to daily injections for one week (i.e. 1260 mcg/week) have been reported. None of these patients experienced unusual, serious or treatment-limiting events. Weekly doses of up to 540 and 630 mcg have been administered in renal cell carcinoma and chronic myelogenous leukaemia clinical trials, respectively. Dose-limiting toxicities were fatigue, elevated liver enzymes, neutropenia and thrombocytopenia consistent with interferon therapy.

No cases of overdose of Copegus have been reported in clinical trials. Hypocalcaemia and hypomagnesaemia have been observed in persons administered dosages greater than four times the maximal recommended dosages. In many of these cases ribavirin was administered intravenously. Ribavirin is not effectively removed by haemodialysis.

Pharmacological Properties and Effects

Efficacy/Clinical Studies

Clinical studies have demonstrated that Pegasys or Pegasys RBV is effective in the treatment of patients with CHC, including cirrhotic patients with compensated liver disease as well as, in patients with HIV-HCV co-infection.

Confirmatory clinical trials

Chronic hepatitis C: naïve patients

All clinical trials recruited interferon-naïve patients with CHC confirmed by detectable levels of serum HCV RNA, elevated levels of ALT and a liver biopsy consistent with chronic hepatitis. Study NV15495 specifically recruited patients with a histological diagnosis of cirrhosis (about 80%) or transition to cirrhosis (about 20%).

For treatment regimens, duration of therapy and study outcome see Tables 4 and 5. Virological response was defined as undetectable HCV RNA as measured by the COBAS AMPLICOR™ HCV Test, version 2.0 (limit of detection 100 copies/mL equivalent to 50 IU/mL) and sustained response as one negative sample approximately 6 months after end of therapy.

Table 4 Virological Response in CHC

	Pegasys Monotherapy				Pegasys RBV		
	Non-cirrhotic and cirrhotic		Cirrhotic		Non-cirrhotic and cirrhotic		
	Study NV15496 + NV15497 + NV15801		Study NV15495		Study NV15942	Study NV15801	
	Pegasys 180 mcg (n = 701) 48 weeks	Interferon alfa-2a 6 MIU/3 MIU & 3 MIU (n = 478) 48 weeks	Pegasys 180 mcg (n = 87) 48 weeks	Interferon alfa-2a 3 MIU (n = 88) 48 weeks	Pegasys 180 mcg & Copegus 1000/1200 mg (n = 436) 48 weeks	Pegasys 180 mcg & Copegus 1000/1200 mg (n = 453) 48 weeks	Interferon alfa-2b 3 MIU & Copegus 1000/1200 mg (n = 444) 48 weeks
Response at end of treatment	55 - 69%	22 - 28%	44%	14%	68%	69%	52%
Overall sustained response	28 - 39%	11 - 19%	30%*	8%*	63%	54%**	45%**

* 95% CI for difference: 11% to 33%, p -value (stratified Cochran-Mantel-Haenszel test) = 0.001

** 95% CI for difference: 3% to 16% p -value (stratified Cochran-Mantel-Haenszel test) = 0.003

The virological responses of patients treated with Pegasys RBV based on genotype and viral load are summarised in Table 5. The results of study NV15942 provide the rationale for recommending treatment regimen based on genotype (see Table 1).

The difference between treatment regimens was in general not influenced by viral load or presence/absence of cirrhosis; therefore treatment recommendations for genotype 1, 2 or 3 are independent of these baseline characteristics.

Table 5 SVR based on Genotype and Viral Load after Pegasys RBV

	Study NV15942				Study NV15801	
	Pegasys 180 mcg & Copegus 800 mg 24 weeks	Pegasys 180 mcg & Copegus 1000/1200 mg 24 weeks	Pegasys 180 mcg & Copegus 800 mg 48 weeks	Pegasys 180 mcg & Copegus 1000/1200 mg 48 weeks	Pegasys 180 mcg & Copegus 1000/1200 mg 48 weeks	Interferon alfa-2b & 3 MIU & Copegus 1000/1200 mg 48 weeks
Genotype 1	29% (29/101)	42% (49/118)*	41% (102/250)*	52% (142/271)*	45% (134/298)	36% (103/285)
Low viral load	41% (21/51)	52% (37/71)	55% (33/60)	65% (55/85)	53% (61/115)	44% (41/94)
High viral load	16% (8/50)	26% (12/47)	36% (69/190)	47% (87/186)	40% (73/182)	33% (62/189)
Genotype 2/3	84% (81/96)	81% (117/144)	79% (78/99)	80% (123/153)	71% (100/140)	61% (88/145)
Low viral load	85% (29/34)	83% (39/47)	88% (29/33)	77% (37/48)	76% (28/37)	65% (34/52)
High viral load	84% (52/62)	80% (78/97)	74% (49/66)	82% (86/105)	70% (72/103)	58% (54/93)
Genotype 4	(0/5)	(8/12)	(5/8)	(9/11)	(10/13)	(5/11)

* Pegasys 180 mcg Copegus 1000/1200 mg, 48 w vs. Pegasys 180 mcg Copegus 800 mg, 48 w: Odds Ratio (95% CI) = 1.52 (1.07 to 2.17); *p*-value (stratified Cochran-Mantel-Haenszel test) = 0.020

* Pegasys 180 mcg Copegus 1000/1200 mg, 48 w vs. Pegasys 180 mcg Copegus 1000/1200 mg, 24 w: Odds Ratio (95% CI) = 2.12 (1.30 to 3.46); *p*-value (stratified Cochran-Mantel-Haenszel test) = 0.002.

Superior efficacy of Pegasys compared to interferon alfa-2a was demonstrated also in terms of histological response, including patients with cirrhosis, as well as, in HIV-HCV co-infected patients.

Chronic hepatitis C: prior treatment non-responder patients

Study MV17150

In study MV17150, patients who were previous non-responders to peginterferon alfa-2b plus ribavirin therapy were randomised to four different treatments: Pegasys 360 mcg/week for 12 weeks, followed by 180 mcg/week for a further 60 weeks; Pegasys 360 mcg/week for 12 weeks, followed by 180 mcg/week for a further 36 weeks; Pegasys 180 mcg/week for 72 weeks; or Pegasys 180 mcg/week for 48 weeks. All patients received Copegus (1000 or 1200 mg/day) in combination with Pegasys. The end-of-treatment (EOT) virological response and SVR following the 24-week treatment-free period comparing duration of therapy or Pegasys induction dosing are summarised in Table 6. The SVRs following the 24 week treatment-free period from a pooled analysis comparing duration of therapy or Pegasys induction dosing are summarised in Table 7.

Table 6 EOT Virological Response and SVR in Previous Peginterferon alfa-2b/Ribavirin Non-responders

Study MV17150				
	Induction dosing 72 week treatment	Induction dosing 48 week treatment	Standard dosing 72 week treatment	Standard dosing 48 week treatment
	Pegasys 360 mcg 12 weeks then 180 mcg 60 weeks + Copegus 1000/1200 mg	Pegasys 360 mcg 12 weeks then 180 mcg 36 weeks + Copegus 1000/1200 mg	Pegasys 180 mcg 72 weeks + Copegus 1000/1200 mg	Pegasys 180 mcg 48 weeks + Copegus 1000/1200 mg
	<i>n</i> = 317	<i>n</i> = 156	<i>n</i> = 156	<i>n</i> = 313
EOT	31%	33%	31%	28%
SVR	16% ^{#*}	7% [§]	14%	9%

[#] A vs. B: 95% confidence interval of 1.36 to 5.67; odds ratio 2.77; *p*-value 0.0036

[§] B vs. C: 95% confidence interval of 0.23 to 1.03; odds ratio 0.49; *p*-value 0.0494

*A vs. D: 95% confidence interval of 1.21 to 3.31; odds ratio 2.0; *p*-value 0.0060

Table 7 SVR in Previous Peginterferon alfa-2b/Ribavirin Non-responders: Pooled Treatment Comparisons

Study MV17150 (pooled groups)				
	72 week Groups	48 week Groups	360 mcg Groups	180 mcg Groups
	360 mcg 12 weeks then 180 mcg 60 weeks & 180 mcg 72 weeks	360 mcg 12 weeks then 180 mcg 36 weeks & 180 mcg 48 weeks	360 mcg 12 weeks then 180 mcg 60 weeks & 360 mcg 12 weeks then 180 mcg 36 weeks	180 mcg 72 weeks & 180 mcg 48 weeks
	<i>n</i> = 473	<i>n</i> = 469	<i>n</i> = 473	<i>n</i> = 469
SVR	16%*	8%*	13%	10%

* 95% confidence interval of 1.40 to 3.52; odds ratio 2.22; *p*-value 0.00061

The SVR rate after 72 weeks treatment was superior to that after 48 weeks. Differences in SVR, based on treatment duration and demographics found in study MV17150, are displayed in Table 8.

Table 8 SVR Rates after Treatment with Pegasys RBV in Non-responders to Previous Treatment with Peginterferon alfa-2b/Ribavirin

	Peginterferon alfa-2b/ribavirin Non-responders re-treated for 48 weeks % SVR (responders/total)	Peginterferon alfa-2b/ribavirin Non-responders re-treated for 72 weeks % SVR (responders/total)
Overall SVR for prior non-responder patients	8% (38/469)	16% (74/473)
Genotype 1/4	7% (33/450)	15% (68/457)
Genotype 2/3	25% (4/16)	33% (5/15)
Genotype		
1	7% (31/426)	14% (60/430)
2	0% (0/4)	33% (1/3)
3	33% (4/12)	33% (4/12)
4	8% (2/24)	30% (8/27)
Baseline Viral Load		
HVL (> 800 000 IU/mL)	7% (25/363)	12% (46/372)
LVL (≤ 800 000 IU/mL)	13% (11/84)	31% (27/86)

HVL = high viral load; LVL = low viral load

HALT-C Study

In the HALT-C study, patients with CHC and advanced fibrosis or cirrhosis who had not responded to previous treatment with interferon alfa or peginterferon alfa monotherapy or combination ribavirin therapy were treated with Pegasys 180 mcg/week and Copegus 1000/1200 mg/day. Patients who achieved undetectable levels of HCV RNA after 20 weeks of treatment remained on Pegasys RBV for a total of 48 weeks and were then followed for 24 weeks after the EOT. The SVR rates varied depending upon the previous treatment regimen. Treatment outcome was poorest among patients who were non-responders to peginterferon in combination with ribavirin, identifying the most difficult to treat sub-population of non-responder patients. The SVR in this treatment arm of the HALT-C study was comparable with the rate observed in the 48 week treatment arms of study MV17150. Despite higher SVR rates in non-responders to interferon or peginterferon monotherapy, efficacy in these less difficult to treat non-responders remains substantially lower than what is achievable in treatment-naïve patients (see Table 9).

Table 9 SVR Rates by Treatment Duration and Non-responder Population

Treatment Duration	HALT-C Study				Study MV17150
	Interferon % SVR (responders/total)	Peginterferon % SVR (responders/total)	Interferon + Ribavirin % SVR (responders/total)	Peginterferon + Ribavirin % SVR (responders/total)	Peginterferon + Ribavirin % SVR (responders/total)
48 weeks	27% (70/255)	34% (13/38)	13% (90/692)	11% (7/61)	8% (38/469)
72 weeks	-	-	-	-	16% (74/473)

Chronic Hepatitis C: Prior Treatment Relapser Patients

In a study in predominantly genotype 1 CHC patients who had relapsed after 48 weeks of combination treatment with peginterferon alfa-2 plus ribavirin, patients were treated for 72 weeks with the combination of either Pegasys 180 mcg/week plus weight-based Copegus daily, or consensus interferon ((9 mcg)) daily plus weight-based Copegus daily. The SVR was 42% for patients treated with Pegasys/Copegus combination therapy for 72 weeks.

In an open-label study in genotype 2 and 3 CHC patients who relapsed after treatment for 24 weeks with Pegasys RBV, patients were treated with Pegasys 180 mcg/week and Copegus 1000 or 1200 mg (by weight) daily combination therapy for 48 weeks and then followed treatment-free for 24 weeks. The SVR rate was 64%.

HIV-HCV co-infection

In study NR15961, 860 HIV-HCV co-infected patients were randomised and treated with Pegasys 180 mcg/week and placebo, Pegasys 180 mcg/week and ribavirin 800 mg/day 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 summarised for all patients and by genotype in Table 10.

Table 10 SVR in HIV-HCV Co-infected Patients (Study NR15961)

	Pegasys 180 mcg + Placebo 48 weeks	Pegasys 180 mcg + Ribavirin 800 mg 48 weeks	Interferon alfa-2a 3 MIU + Ribavirin 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 180 mcg ribavirin 800 mg vs. Interferon alfa-2a 3 MIU ribavirin 800 mg: 95% CI for difference: 22% to 35%, *p*-value (stratified Cochran-Mantel-Haenszel test) = < 0.0001

* Pegasys 180 mcg ribavirin 800 mg vs. Pegasys 180 mcg: 95% CI for difference: 13% to 27%, *p*-value (stratified Cochran-Mantel-Haenszel test) = < 0.0001

A subsequent study (NV18209) in patients co-infected with HCV genotype 1 and HIV compared Pegasys 180 mcg/week and either ribavirin 800 mg or 1000 mg (<75 kg)/1200 mg (≥75 kg) daily for

48 weeks. The results are reported in Table 11 and showed that the study was not powered for efficacy considerations.

Table 11 SVR in HIV-HCV Co-infected Patients (Study NV18209)

	Pegasys 180 mcg + Ribavirin 800 mg 48 weeks (n = 138)	Pegasys 180 mcg + Ribavirin 1000/1200 mg 48 weeks (n = 277)
Completed	55/138 (40 %)	119/277 (43 %)
% SVR (responders/total)	19 % (26/138)	22 % (60/277)

Odds Ratio (95% CI) = 1.17 (0.69 – 1.98), p-value = 0.56

The safety profiles in both ribavirin groups were consistent with the known safety profile of Pegasys plus ribavirin combination treatment and not indicative of any relevant differences, with the exception of a slight increase in anaemia in the high dose ribavirin arm.

Pegasys

Pharmacodynamic properties

The conjugation of PEG reagent (bis-monomethoxypolyethylene glycol) to interferon alfa-2a forms a pegylated interferon alfa-2a. 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*. The structure of the PEG moiety directly affects the clinical pharmacology of Pegasys. Specifically, the size and branching of the 40 kD PEG moiety define the absorption, distribution and elimination characteristics of Pegasys.

Mechanism of action

Pegasys 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.

HCV RNA levels decline in a biphasic manner in responding patients with hepatitis C who have received Pegasys. The first phase of decline occurs within 24 – 36 hours after the first dose of Pegasys and the second phase of decline occurs over the next 4 – 16 weeks in patients who achieve a sustained response. Pegasys 180 mcg/week enhances the virion clearance and improves the virological end of treatment responses compared to treatment with standard alfa interferons.

Pegasys stimulates the production of effector proteins such as serum neopterin and 2',5'-oligoadenylate synthetase in a dose-dependent manner. The stimulation of 2',5'-oligoadenylate synthetase is maximal after single doses of 135 – 180 mcg of Pegasys and stays maximal throughout the one-week dosing interval. The magnitude and duration of 2',5'-oligoadenylate synthetase activity induced by Pegasys were reduced in subjects older than 62 years and in subjects with significant renal impairment (creatinine clearances of 20 – 40 mL/min). The clinical relevance of these findings with pharmacodynamic markers of Pegasys is not known.

Pharmacokinetic properties

The pharmacokinetics of Pegasys were studied in healthy volunteers and hepatitis C virus-infected patients (see Table 12).

Absorption

The absorption of Pegasys is sustained with peak serum concentrations reached 72 – 96 h after dosing. Serum concentrations are measurable within 3 – 6 h of a single, subcutaneous injection of Pegasys 180 mcg. Within 24 h, about 80% of the peak serum concentration is reached. The absolute bioavailability of Pegasys is 84% and is similar to that seen with interferon alfa-2a.

Distribution

Pegasys is found predominately in the bloodstream and extracellular fluid as seen by the volume of distribution at steady-state (V_{ss}) of 6 to 14 L after intravenous dosing in humans. Based on studies in rats, the medicine is distributed to the liver, kidney, and bone marrow as well as being highly concentrated in the blood.

Metabolism

Metabolism is the main clearance mechanism for Pegasys. The metabolic profile of Pegasys is not fully characterised. In humans the systemic clearance of Pegasys is about 100 mL/h, which is 100-fold lower than that of the native interferon alfa-2a. Studies in rats indicate the metabolic products of Pegasys are excreted in the urine and to a lesser degree in the bile. The kidneys eliminate less than 10% of a dose as the intact peginterferon alfa-2a. While the PEG moiety remains attached to the interferon alfa-2a, both the PEG and the interferon alfa-2a are metabolised.

Elimination

After intravenous administration, the terminal half-life of Pegasys in healthy subjects is approximately 60 h compared with values of 3 – 4 h for standard interferon. The terminal half-life after subcutaneous administration in patients is longer with a mean value of 160 h (84 – 353 h).

The terminal half-life determined after subcutaneous administration may not only reflect the elimination phase of the compound, but may also reflect the sustained absorption of Pegasys.

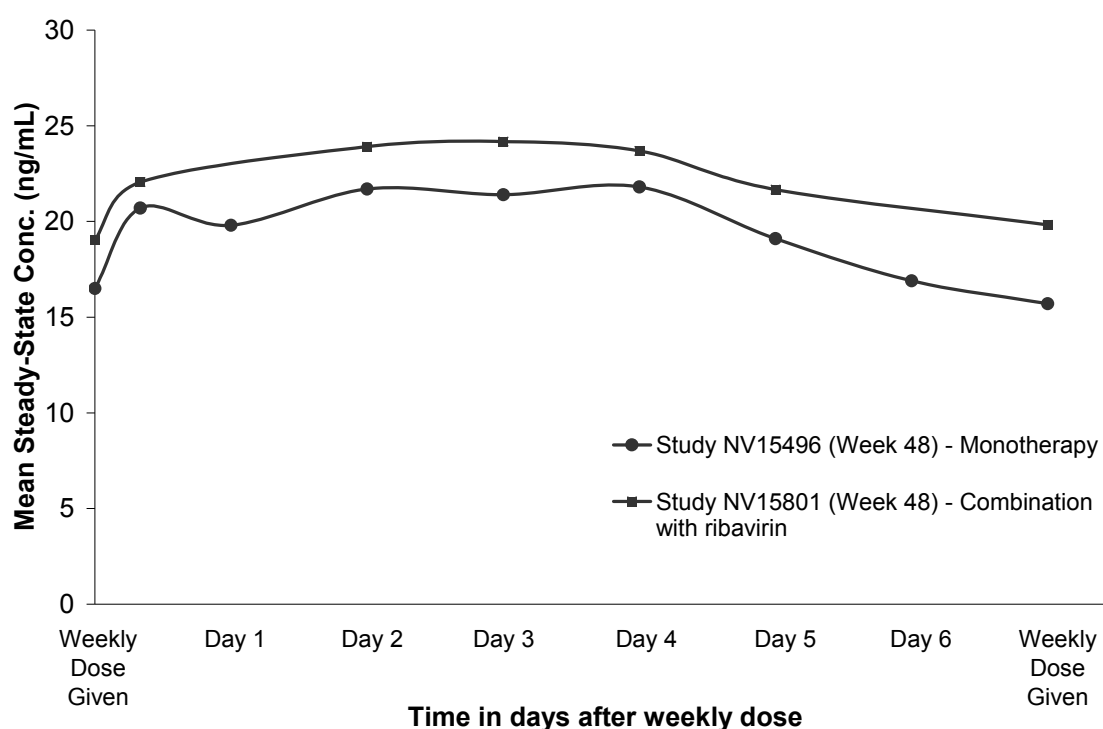
Dose-proportional increases in AUC and C_{max} are seen in healthy subjects and patients with CHC after once weekly dosing of Pegasys. The pharmacokinetic parameters of Pegasys are given in Table 12 for healthy subjects receiving a single subcutaneous injection of 180 mcg of Pegasys and for patients with CHC receiving 48 weeks of 180 mcg of Pegasys once weekly.

Table 12 Pharmacokinetic Parameters of Pegasys after Single and Multiple Dose of 180 mcg

Pegasys pharmacokinetic parameter	Healthy Subjects 180 mcg sc (n = 50)	CHC Patients in NV15496 180 mcg sc Treatment (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 _{1-168 h} (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]

In patients with CHC, steady state serum concentrations increase 2- to 3-fold compared with single-dose values and reach steady state 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 – 2.0. Peginterferon alfa-2a serum concentrations are sustained throughout 1 full week (168 h) (see Figure 1).

Figure 1 Mean Steady-State PEG-IFN alfa-2a concentrations in patients with CHC following 180 mcg Pegasys monotherapy (NV15496) and in combination with Copegus (NV15801)



Pharmacokinetics in special populations

Patients with renal impairment

No significant relationship between Pegasys pharmacokinetics and creatinine clearance was seen in 23 subjects with normal renal function to significant renal impairment (20 to > 100 mL/min creatinine clearance). In patients with end stage renal disease undergoing haemodialysis, there is a 25% – 45% reduction in the clearance, and doses of 135 mcg result in similar exposure as 180 mcg doses in patients with normal renal function. 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 Dosage and Administration).

Gender

The pharmacokinetics of Pegasys were comparable between male and female healthy subjects.

Elderly

The AUC was modestly increased in subjects older than 62 years, but peak concentrations were similar in those older and younger than 62 years. Based on exposure, pharmacodynamic response, and tolerability, a lower starting dose of Pegasys is not needed in the geriatric patient (see Dosage and Administration).

Non-cirrhotic and cirrhotic patients

The pharmacokinetics of Pegasys were similar between healthy subjects and patients with hepatitis C. Comparable exposure and pharmacokinetic profiles were seen in patients with cirrhosis with compensated liver disease and patients without cirrhosis.

Site of administration

Subcutaneous administration of Pegasys should be limited to the abdomen and thigh. Exposure to Pegasys was decreased in studies following administration of Pegasys in the arm compared to administration in the abdomen and thigh.

Preclinical safety

The preclinical toxicity studies conducted with Pegasys were limited due to species specificity of interferons. Acute and chronic toxicity studies have been carried out in cynomolgus monkeys, and the findings observed in peginterferon alfa-2a dosed animals were similar in nature to those produced by interferon alfa-2a.

Pegasys plus ribavirin

When used in combination with ribavirin, Pegasys did not cause any effects in monkeys not previously seen with either active substance alone. The major treatment-related change was reversible mild to moderate anaemia, the severity of which was greater than that produced by either active substance alone.

Carcinogenesis

Pegasys has not been tested for its carcinogenic potential.

Mutagenesis

Pegasys 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

Reproductive toxicity studies have not been performed with Pegasys. As with other alfa interferons, prolongation of the menstrual cycle was observed following administration of peginterferon alfa-2a to female monkeys.

Teratogenicity

Treatment with interferon alfa-2a resulted in a statistically significant increase in abortifacient activity in rhesus monkeys. Although no teratogenic effects were seen in the offspring delivered at term, adverse effects in humans cannot be excluded.

Copegus

Pharmacodynamic properties

Mechanism of action

Ribavirin is a synthetic nucleoside analogue that shows *in vitro* activity against some RNA and DNA viruses. The mechanism by which ribavirin in combination with alfa interferon or peginterferon alfa-2a exerts its effects against HCV is unknown.

Oral formulations of ribavirin monotherapy have been investigated as therapy for CHC in several clinical trials. Results of these investigations showed that ribavirin monotherapy had no effect on eliminating hepatitis virus (HCV RNA) or improving hepatic histology after 6 – 12 months of therapy and 6 months of follow-up.

Pharmacokinetic properties

Absorption

Ribavirin is absorbed rapidly following oral administration of a single dose of Copegus (median T_{max} = 1 – 2 h). The mean terminal phase half-life of ribavirin following single doses of Copegus range from 140 – 160 h. Ribavirin data from the literature demonstrates absorption is extensive with approximately 10% of a radiolabeled dose excreted in the faeces. However, absolute bioavailability is approximately 45 – 65%, which appears to be due to first pass metabolism. There is a linear relationship between dose and AUC_{0-t} following single doses of 200 – 1200 mg ribavirin. Mean apparent oral clearance of ribavirin following single 600 mg doses of Copegus ranges from 22 – 29 L/h. Volume of distribution is approximately 4500 L following administration of Copegus. Ribavirin does not bind to plasma proteins.

Food effect

The bioavailability of a single oral 600 mg dose Copegus was increased by co-administration of a high fat meal. The ribavirin exposure parameters of $AUC_{(0-192h)}$ and C_{max} increased by 42% and 66%, respectively, when Copegus was taken with a high fat breakfast compared to being taken in the fasted state. The clinical relevance of results from this single dose study is unknown. Ribavirin exposure after multiple dosing when taken with food was comparable in patients receiving peginterferon alfa-2a and Copegus and interferon alfa-2b and ribavirin. In order to achieve optimal ribavirin plasma concentrations, it is recommended to take ribavirin with food.

Distribution

Ribavirin has been shown to produce high inter- and intra-subject pharmacokinetic variability following a single oral dose of Copegus (intra-subject variability of $\geq 25\%$ for both AUC and C_{max}), which may be due to extensive first pass metabolism and transfer within and beyond the blood compartment.

Ribavirin transport in non-plasma compartments has been most extensively studied in red cells, and has been identified to be primarily via an e_s -type equilibrative nucleoside transporter. This type of transporter is present on virtually all cell types and may account for the high volume of distribution of ribavirin. The ratio of whole blood:plasma ribavirin concentrations is approximately 60:1; the excess of ribavirin in whole blood exists as ribavirin nucleotides sequestered in erythrocytes.

Metabolism

Ribavirin has two pathways of metabolism: 1) a reversible phosphorylation pathway, 2) a degradative pathway involving deribosylation and amide hydrolysis to yield a triazole carboxylic acid metabolite. Ribavirin and both its triazole carboxamide and triazole carboxylic acid metabolites are excreted renally.

Upon multiple dosing, ribavirin accumulates extensively in plasma with a six-fold ratio of multiple-dose to single-dose AUC_{12hr} based on literature data. Following oral dosing with 600 mg bd, steady-state was reached by approximately 4 weeks, with mean steady state plasma concentrations of approximately 2200 ng/mL.

Elimination

Upon discontinuation of dosing the half-life was approximately 300 h, which probably reflects slow elimination from non-plasma compartments.

Pharmacokinetics in special populations

Patients with renal impairment

The pharmacokinetics of ribavirin are altered in patients with renal dysfunction due to a 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.

Patients with moderate or severe renal impairment (creatinine clearance ≤ 50 mL/min) not undergoing long-term haemodialysis did not tolerate 600 mg and 400 mg daily doses of Copegus, respectively and exhibited higher ribavirin plasma exposures compared to patients with normal renal function (creatinine clearance > 80 mL/min) receiving the standard dose of Copegus (see Special Dosage Instructions and Pharmacokinetic Properties).

In a study of patients with ESRD undergoing long term haemodialysis, most of whom received haematopoietic growth factors, Copegus was safely administered at a dose of 200 mg daily. In this study, ESRD patients undergoing long term haemodialysis who were administered a 200 mg daily dose exhibited ribavirin plasma exposures that were approximately 20% lower compared to patients with normal renal function receiving the standard 1000/1200 mg Copegus daily dose. (see Special Dosage Instructions).

The apparent clearance of ribavirin is reduced in patients with creatinine clearance ≤ 50 mL/min, including patients with ESRD on long term haemodialysis, exhibiting approximately 30% of the value found in patients with normal renal function. Patients not undergoing long term haemodialysis with moderate or severe renal impairment (creatinine clearance ≤ 50 mL/min) did not tolerate daily doses of 600 mg and 400 mg of Copegus, respectively. Despite reduced Copegus dosing in these patients, ribavirin plasma exposure (AUC) was found to be higher compared to patients with normal renal function (creatinine clearance > 80 mL/min) receiving the standard Copegus dose. Patients with ESRD undergoing long term haemodialysis tolerated 200 mg daily doses of Copegus and exhibited mean ribavirin exposure (AUC) approximately 80% of the value found in patients with normal renal

function (see Special Dosage Instructions). Plasma ribavirin is removed by haemodialysis with an extraction ratio of approximately 50%.

Patients with hepatic dysfunction

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

Elderly patients (≥ 65 years of age)

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

Patients under the age of 18 years

Specific pharmacokinetic studies have not been fully evaluated in patients under the age of 18 years. Copegus in combination with Pegasys is indicated for the treatment of CHC only in patients 18 years of age or older.

Race

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

Preclinical safety

Carcinogenicity

In a p53 (+/-) mouse carcinogenicity study and a rat 2-year carcinogenicity study at doses up to the maximum tolerated doses of 100 mg/kg/day and 60 mg/kg/day, respectively, ribavirin was not oncogenic. 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.

Impairment of fertility

In repeat dose studies in mice to investigate ribavirin-induced testicular and sperm effects, abnormalities in sperm occurred at doses in animals well below therapeutic doses. Upon cessation of treatment, essentially total recovery from ribavirin-induced testicular toxicity occurred within one or two spermatogenic cycles.

Other

Erythrocytes are a primary target of toxicity for ribavirin in animal studies. Anaemia occurs shortly after initiation of dosing, but is rapidly reversible upon cessation of treatment.

Genotoxicity studies have demonstrated that ribavirin does exert some genotoxic activity. Ribavirin was active in an *in vitro* Transformation Assay. Genotoxic activity was observed *in vivo* mouse micronucleus assay. A dominant lethal assay in rats was negative, indicating that if mutations occurred in rats they were not transmitted through male gametes. The potential of carcinogenic risk to humans cannot be excluded.

Administration of ribavirin and peginterferon alfa-2a in combination did not produce any unexpected toxicity in monkeys. The major treatment-related change was reversible mild to moderate anaemia, the severity of which was greater than that produced by either active substance alone.

Pharmaceutical Particulars

Incompatibility

It is inappropriate to mix Pegasys with other products.

Storage

These medicines should not be used after the expiry date shown on the pack.

Store the Pegasys RBV combination pack in the refrigerator at 2 – 8 °C. Do not freeze or shake.

Store Pegasys in the refrigerator at 2 – 8 °C. Do not freeze or shake. Store in the original package to protect from light.

Copegus film-coated tablets do not need to be kept at 2 – 8 °C. Once the Pegasys RBV combination therapy pack has been started, the Copegus film-coated tablet pack may be removed and stored separately below 30 °C.

Special Instructions for Use, Handling and Disposal

Parenteral products such as Pegasys should be inspected visually for particulate matter and discolouration before administration, whenever solution and container permit.

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 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 and needles should be supplied to the patients.

The release of medicines into the environment should be minimised. Medicines should not be disposed of via wastewater and disposal through household waste should be avoided. Unused or expired medicines should be returned to a pharmacy for disposal.

Copegus tablets should not be broken or crushed. Since ribavirin is considered a potential teratogen, caution should be observed in handling broken tablets.

Packs

Pegasys RBV Combination Therapy 4 x 135 mcg PFS/112 tablets

Each pack contains:

- 1 x Pegasys 135 mcg prefilled syringe 4's
- 1 x Copegus 200 mg film-coated tablets 112's

Pegasys RBV Combination Therapy 4 x 180mcg PFS/112 tablets

Each pack contains:

- 1 x Pegasys 180 mcg prefilled syringe 4's
- 1 x Copegus 200 mg film-coated tablets 112's

Pegasys RBV Combination Therapy 4 x 135mcg PFS/168 tablets

Each pack contains:

- 1 x Pegasys 135 mcg prefilled syringe 4's
- 1 x Copegus 200 mg film-coated tablets 168's

Pegasys RBV Combination Therapy 4 x 180mcg PFS/168 tablets

Each pack contains:

- 1 x Pegasys 180 mcg prefilled syringe 4's
- 1 x Copegus 200 mg film-coated tablets 168's

Medicine Classification

Prescription Medicine

Name and Address

Roche Products (New Zealand) Limited
PO Box 12492 Penrose
Auckland 1642
NEW ZEALAND

Telephone: (09) 635 1500
Fax: (09) 635 1522
Toll Free: 0800 656 464

Date of Preparation

19 May 2011