

Each pre-filled syringe contains 135 or 180 µg of peginterferon alfa-2a, expressed as the amount of interferon alfa-2a, with excipients sodium chloride, benzyl alcohol, sodium acetate, acetic acid, polysorbate 80 and water for injections.

PEGASYS 180 µg/0.5 mL is also available as a pre-filled pen (PEGASYS ProClick).*

COPEGUS

COPEGUS is an oral synthetic nucleoside analogue with anti-viral activity. COPEGUS is a white crystalline powder, freely soluble in water and slightly soluble in ethanol.

COPEGUS is available as light pink, flat, oval shaped film-coated tablet containing 200 mg ribavirin, pregelatinised maize starch, sodium starch glycollate, soluble maize starch, microcrystalline cellulose and magnesium stearate. The light pink film coating contains hydroxypropylcellulose, purified talc, titanium dioxide, iron oxide yellow CI77492, iron oxide red CI77491, ethylcellulose and glycerol triacetate.

PHARMACOLOGY

PHARMACODYNAMICS

PEGASYS

The conjugation of a PEG reagent to interferon alfa-2a forms peginterferon alfa-2a (PEGASYS). 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 peginterferon alfa-2a. Specifically, the size and branching of the 40 kD PEG reagent define the absorption, distribution, and elimination characteristics of peginterferon alfa-2a.

Mechanism of Action

Peginterferon alfa-2a possesses the *in vitro* anti-viral and anti-proliferative 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.

Hepatitis C virus (HCV) RNA levels decline in a biphasic manner in responding patients with hepatitis C who have received peginterferon alfa-2a. The first phase of decline occurs within 24 – 36 h after the first dose of peginterferon alfa-2a and the second phase of decline occurs over the next 4 – 16 weeks in patients who achieve a sustained response. Ribavirin had no significant effect on the initial viral kinetics over the first 4 – 6 weeks in patients treated with peginterferon alfa-2a or interferon alfa in combination with ribavirin.

Peginterferon alfa-2a stimulates the production of effector proteins such as serum neopterin and 2',5'-oligoadenylate synthetase (2',5'-OAS) in a dose-dependent manner. The stimulation of 2',5'-OAS is maximal after single doses of peginterferon alfa-2a 135 to 180 µg and stays maximal throughout the 1 week dosing interval. The magnitude and duration of peginterferon alfa-2a induced 2',5'-oligoadenylate synthetase activity were reduced in subjects older than 62 and in subjects with significant renal impairment (creatinine clearance 20 – 40 mL/min).

COPEGUS

Ribavirin had no significant effect on the initial viral kinetics over the first 4 – 6 weeks in patients treated with the combination of ribavirin and peginterferon alfa-2a or interferon alfa.

Mechanism of Action

Ribavirin has shown *in vitro* activity against some RNA and DNA viruses, as well as, immunomodulation activities. The mechanism by which ribavirin in combination with interferon alfa or peginterferon alfa-2a exerts its effect against HCV is unknown.

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

PHARMACOKINETICS

PEGASYS

The pharmacokinetics of peginterferon alfa-2a were studied in healthy subjects and patients infected with hepatitis C.

Absorption: The absorption of peginterferon alfa-2a 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 µg. Within 24 h, about 80% of the peak serum concentration is reached. The absolute bioavailability of peginterferon alfa-2a is 84% and is similar to that seen with interferon alfa-2a.

Distribution: Peginterferon alfa-2a is found predominately in the bloodstream and extracellular fluid as seen by the volume of distribution at steady-state (V_{ss}) of 6 – 14 L after intravenous (iv) dosing in humans. Based on studies in rats, peginterferon alfa-2a is distributed to the liver, kidney, and bone marrow in addition to being highly concentrated in the blood.

Metabolism: The metabolic profile of peginterferon alfa-2a is not fully characterised.

Elimination: After iv administration, the terminal half-life of peginterferon alfa-2a in healthy subjects is approximately 60 h compared to 3 – 4 h for standard interferon. A mean elimination half-life of 160 h (84 – 353 h) at primary elimination phase was observed in patients after subcutaneous (sc) administration of PEGASYS. The elimination half-life determined after sc administration may not only reflect the elimination phase of the compound, but may also reflect the sustained absorption of peginterferon alfa-2a.

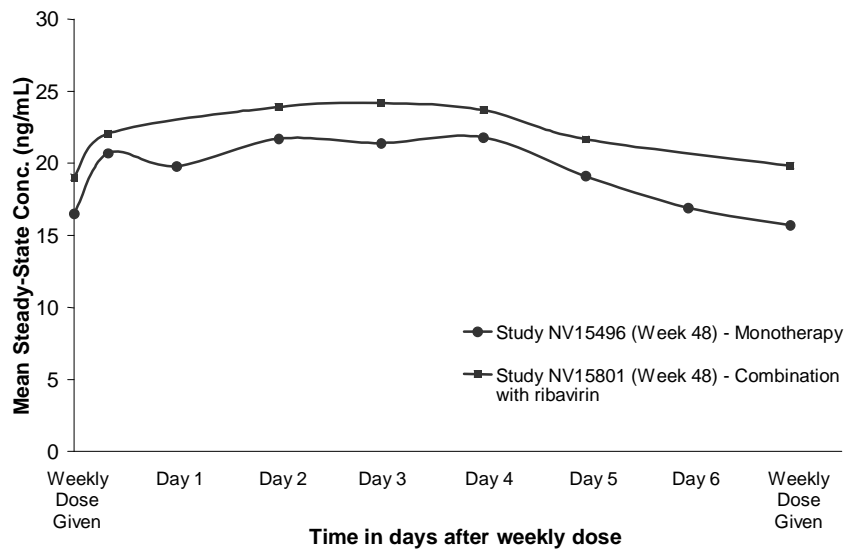
Pharmacokinetic Overview

In patients with CHC, steady-state serum concentrations increase 2- to 3-fold compared with single dose values and reach steady-state within 5 – 8 weeks of once a week 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) (refer to Table 1 and Figure 1).

Table 1. Pharmacokinetic Parameters of PEGASYS After Single and Multiple Doses of 180 µg

Pharmacokinetic Parameter	Healthy Subjects PEGASYS 180 µg (n = 50)	CHC Patients in NV15496 PEGASYS 180 µg (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]
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 CHC Patients Following 180 µg Monotherapy and in Combination with COPEGUS



Pharmacokinetics in Special Populations

Renal Impairment: The apparent clearance of ribavirin is reduced in patients with creatinine clearance ≤50 mL/min, including patients with end stage renal disease on chronic haemodialysis, exhibiting approximately 30% of the value found in patients with normal renal function. Patients not on chronic 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 end stage renal disease on chronic 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 (refer to Dosage and Administration). Plasma ribavirin is removed by haemodialysis with an extraction ratio of approximately 50%.

Gender: The pharmacokinetics of peginterferon alfa-2a were comparable between male and female healthy subjects.

Elderly: The AUC was modestly increased in subjects older than 62 years taking PEGASYS 180 µg, but peak concentrations were similar in those older and younger than 62 years. Based on drug exposure, pharmacodynamic response, and tolerability, a dose modification is not needed in the elderly (refer to *Dosage and Administration*).

Children: The pharmacokinetics of peginterferon alfa-2a has not been established in patients below the age of 18.

Non-cirrhotic and cirrhotic patients: The pharmacokinetics of peginterferon alfa-2a 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.

COPEGUS

Absorption: Ribavirin is absorbed rapidly following oral administration of a single dose (median T_{max} = 1 – 2 h). The mean terminal half-life of ribavirin following single doses of COPEGUS ranged from 140 – 160 h. Ribavirin absorption is extensive with approximately 10% of a radiolabelled 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 the 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.

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

Distribution: 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 concentration 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: a reversible phosphorylation pathway and a degradative pathway involving deribosylation and amide hydrolysis to yield a triazole carboxylic acid metabolite. The triazole carboxylic acid and triazole carboxamide are the principal metabolites. The cytochrome P450 enzyme system is not involved in the metabolism of ribavirin.

Elimination: Ribavirin and both its triazole carboxamide and triazole carboxylic acid metabolites are excreted renally. Upon multiple dosing, ribavirin accumulates extensively in plasma with a 6-fold ratio of multiple dose to single dose AUC_{12h} . Following oral dosing with 600 mg twice daily, steady-state was reached by approximately 4 weeks, with mean steady-state plasma

concentrations of approximately 2200 ng/mL. Upon discontinuation of dosing the half-life was approximately 300 h, which probably reflects slow elimination from non-plasma compartments.

Effect of Food: The bioavailability of a single oral dose of 600 mg ribavirin 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 are unknown. Ribavirin exposure after multiple dosing when taken with food was comparable in patients receiving PEGASYS and COPEGUS and interferon alfa-2b and COPEGUS. In order to achieve the optimal ribavirin plasma concentrations, it is recommended that COPEGUS is taken with food.

Pharmacokinetics in Special Populations

Renal Impairment: The apparent clearance of ribavirin is reduced in patients with creatinine clearance ≤ 50 mL/min, including patients with end stage renal disease on chronic haemodialysis, exhibiting approximately 30% of the value found in patients with normal renal function. Patients not on chronic 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 end stage renal disease on chronic 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 (refer to Dosage and Administration). Plasma ribavirin is removed by haemodialysis with an extraction ratio of approximately 50%.

Hepatic Impairment: Single dose pharmacokinetics of ribavirin in patients with mild, moderate or severe hepatic impairment are similar to control subjects.

Elderly: 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 a determining factor.

Children: Specific pharmacokinetic studies have not been fully evaluated in patients under the age of 18 years.

Race: Pharmacokinetic properties of multiple dose ribavirin in combination with peginterferon alfa-2a have been studied in HCV infected adult Black, Hispanic and Caucasian patients and no substantial differences were observed between these groups (Study NP17354).

CLINICAL TRIALS

Clinical trials have demonstrated that PEGASYS RBV combination therapy is effective in the treatment of patients with CHC, including cirrhotic patients with compensated liver disease and in patients with HIV-HCV co-infection.

Chronic Hepatitis C: Treatment-Naïve Patients

Patients with Elevated Alanine Transaminase (ALT) Levels

The safety and effectiveness of PEGASYS RBV combination therapy for the treatment of hepatitis C were assessed in two prospective, randomised controlled, multinational clinical trials (NV15942 and NV15801). All patients were adults with compensated CHC, detectable HCV

RNA, persistently elevated ALT levels, a histological diagnosis consistent with CHC, and previously untreated with interferon and/or ribavirin. Approximately 20% of patients in both studies had compensated cirrhosis.

In NV15942, a prospective, randomised controlled, multinational clinical trial, 1284 patients received PEGASYS 180 µg sc once a week and randomised to treatment for either 24 or 48 weeks and a COPEGUS daily dose of 800 mg or 1000/1200 mg (for body weight < 75 kg / ≥ 75 kg). Assignment to the 4 treatment arms was stratified by viral genotype and baseline HCV viral titre.

In NV15801, a prospective, randomised controlled, multinational clinical trial, 1121 patients received either PEGASYS 180 µg sc once a week with placebo, PEGASYS 180 µg sc once a week with COPEGUS 1000 mg (body weight < 75kg) or 1200 mg (body weight ≥ 75kg) daily, or INTRON A® 3 MIU sc three times a week with REBETOL® 1000 mg or 1200 mg daily (REBETRON®) for 48 weeks of therapy followed by 24 weeks of treatment-free follow-up. Ribavirin or placebo treatment assignment was blinded.

Sustained virological response (SVR) was defined as a single undetectable HCV RNA measurement at the end of the treatment-free follow-up period, measured by the qualitative COBAS AMPLICOR HCV test, version 2.0 (lower limit of detection 100 copies/mL equivalent to 50 IU/mL).

Table 2. SVR to Combination Treatment in CHC Patients (Elevated ALT levels)

	NV15942				NV15801		
	24 weeks		48 weeks		48 weeks		
	PEGASYS 180 µg with COPEGUS 800 mg (n = 207)	PEGASYS 180 µg with COPEGUS 1000/1200 mg (n = 280)	PEGASYS 180 µg with COPEGUS 800 mg (n = 361)	PEGASYS 180 µg with COPEGUS 1000/1200 mg (n = 436)	PEGASYS 180 µg (n = 224)	PEGASYS 180 µg with COPEGUS 1000/1200 mg (n = 453)	INTRON A 3 MIU with REBETOL 1000/1200 mg (n = 444)
						[A≥80%]	<i>p</i> -values*
All Genotypes	55% (114/207)	64% (179/280)	52% (187/361)	63% (275/436)	29% (66/224)	56% (255/453)	45% (200/444)
						[75%]	<i>p</i> = 0.001
Genotype 1	29% (29/101)	42% (49/118)	41% (102/250)	52% (142/271)	21% (30/145)	46% (138/298)	36% (104/285)
						[67%]	<i>p</i> = 0.016
Genotype non-1†	80% (85/106)	80% (130/162)	77% (85/111)	81% (133/165)	45% (31/69)	76% (106/140)	61% (89/145)
						[88%]	<i>p</i> = 0.008

† majority genotype 2-3

* *p*-value assessed by Cochran-Mantel-Haenszel test stratified by country and HCV genotype

In NV15942 the SVR for patients infected with genotype 1 was significantly higher after 48 weeks of treatment than after 24 weeks (*p* = 0.001) and with the higher dose of COPEGUS (*p* = 0.005). For patients infected with genotype 2 and 3 there was no statistically significant difference between 48 and 24 weeks of treatment and between the low and high dose of COPEGUS (refer to Table 2). For genotype 4 patients (*n* = 36), the SVR was highest in patients treated for 48 weeks with COPEGUS 1000/1200 mg (*n* = 9/11, 82%). The SVR in cirrhotic patients followed the same pattern as that of the overall population.

In NV15801, the SVR rate was 43% in cirrhotic patients treated with PEGASYS RBV combination therapy compared to 33% in the INTRON A in combination with REBETOL treatment group. 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, compared to 72% and 76% in the PEGASYS alone and interferon alfa-2b and ribavirin groups, respectively. Histological response was defined as ≥ 2 point decrease in total Knodell HAI score at end of follow-up as compared to pre-treatment. Paired biopsies were obtained in 17% of patients.

Patients with Normal ALT Levels

The safety and effectiveness of PEGASYS RBV for the treatment of hepatitis C were assessed in a phase III, prospective, randomised, open-label, multinational clinical trial (NR16071). All patients were non-cirrhotic adults with compensated CHC, detectable HCV RNA, persistently normal ALT levels, defined as serum ALT levels equal to or below the upper limit of normal, documented on at least 3 occasions, a minimum of 4 weeks apart. The patient population across the 3 study groups was 60% female, 85% Caucasian with a median age of 43 years. Median pre-treatment HCV RNA titres were 520 – 600 IU/mL and approximately 26% had no evidence of fibrotic liver disease.

In NR16071, 514 patients were randomised to receive PEGASYS 180 μ g sc once a week with COPEGUS 800 mg daily for either 24 weeks followed by a 48 week treatment-free period; 48 weeks followed by a 24 week treatment-free period; or no treatment for 72 weeks. The SVR rates reported in the treatment arms of this study were similar to the corresponding treatment arms from study NV15942. No patients in the control arm achieved a SVR.

Patients infected with HCV genotype 1 had statistically significantly higher SVR rates when treated for 48 weeks (40%) than when treated for 24 weeks (13%) [odds ratio = 4.47, 95% CI (2.47, 8.08), $p < 0.001$]. In patients infected with genotype non-1, SVR was not statistically different between patients treated for 48 weeks (75%) than when treated for 24 weeks (65%) [odds ratio = 1.69, 95% CI (0.79, 3.61), $p = 0.177$]. Of note, SVR was similar in patients with HCV genotype 2 or 3 infection whether these patients were treated for 48 weeks (78%) or 24 weeks (72%) [odds ratio = 1.40, 95% CI (0.59, 3.30), $p = 0.452$] (refer to Table 3).

Table 3. SVR to Combination Treatment in CHC Patients (Normal ALT Levels)

	PEGASYS 180 μg with COPEGUS 800 mg 24 weeks (n = 212)	PEGASYS 180 μg with COPEGUS 800 mg 48 weeks (n = 210) p-values*	Untreated Control 48 weeks (n = 69) p-values**
All Genotypes SVR (week 72)	30% (63/212)	52% (109/210) $p \leq 0.001$	0% $p \leq 0.001$
Genotype 1 SVR (week 72)	13% (19/144)	40% (57/141) $p \leq 0.001$	0% $p \leq 0.001$
Genotype 2, 3 SVR (week 72)	72% (42/58)	78% (46/59) $p = 0.452$	0%
Genotype non-1† SVR (week 72)	65% (44/68)	75% (52/69) $p = 0.177$	0% $p \leq 0.001$

† majority genotype 2-3

* *p*-value assessed by Cochran-Mantel-Haenszel test stratified by country and HCV genotype, for 24 versus 48 weeks of treatment

** *p*-value assessed by Cochran-Mantel-Haenszel test stratified by country and HCV genotype, for 48 weeks of treatment versus untreated

A further analysis was conducted for HCV genotype 1 patients with normal ALT activity to predict the SVR that may have been achieved when treated with a higher dose of COPEGUS. According to the predictive model, this group of patients has the potential to achieve a higher SVR when treated for 48 weeks with PEGASYS 180 µg sc once a week and COPEGUS 1000/1200 mg daily than when treated with COPEGUS 800 mg daily for 48 weeks. Based on this analysis, it is recommended that HCV genotype 1 patients with normal ALT receive COPEGUS 1000/1200 mg.

Predictability of Response in Treatment-Naïve Patients

In combination trials, an early virological response was defined as undetectable levels of HCV RNA or a 99% reduction (2 log drop) in viral titre from baseline by week 12 of therapy. Of patients experiencing an early virological response, 66% went on to achieve a SVR. In monotherapy trials, 98% of total patients treated with PEGASYS 180 µg once a week and who achieved a SVR had an early virological response by week 12. In HIV-HCV co-infected patients treated with PEGASYS RBV and who achieved a SVR, 98% achieved an early virological response.

In NV15801 trial, patients who had an early virological response by week 12 and adhered to at least 80% ($A \geq 80\%$) of the planned PEGASYS RBV combination treatment achieved a higher SVR regardless of genotype.

Chronic Hepatitis C: Prior Treatment Non-responder Patients

Study MV17150

In this open label, randomised, Phase III study, a total of 950 patients, who were previous non-responders to peginterferon alfa-2b in combination with ribavirin therapy (at least 12 weeks prior treatment), were randomised to 4 different treatments: PEGASYS 360 µg once a week for 12 weeks, followed by 180 µg once a week for a further 60 weeks; PEGASYS 360 µg once a week for 12 weeks, followed by 180 µg once a week for a further 36 weeks; PEGASYS 180 µg once a week for 72 weeks; or PEGASYS 180 µg once a week for 48 weeks. All patients received COPEGUS (1000 or 1200 mg daily) 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 4. 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 5.

Table 4. EOT Virological Response and SVR in Previous Peginterferon alfa-2b/Ribavirin Non-responders

Study MV17150				
	A	B	C	D
	PEGASYS 360 µg 12 wk then 180 µg 60 wk COPEGUS 1000/1200 mg 72 wk (n = 317)	PEGASYS 360 µg 12 wk then 180 µg 36 wk COPEGUS 1000/1200 mg 48 wk (n = 156)	PEGASYS 180 µg 72 wk COPEGUS 1000/1200 mg 72 wk (n = 156)	PEGASYS 180 µg 48 wk COPEGUS 1000/1200 mg 48 wk (n = 313)
EOR	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; and a *p*-value of 0.0036

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

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

EOT = end of treatment; SVR = sustained virological response; wk = weeks

Table 5. SVR in Previous Peginterferon alfa-2b/Ribavirin Non-responders: Pooled Treatment Comparisons

Study MV17150 (pooled groups)				
	72 wk Groups	48 wk Groups	360 µg Groups	180 µg Groups
	(360 µg 12 wk then 180 µg 60 wk + 180 µg 72 wk) (n = 473)	(360 µg 12 wk then 180 µg 36 wk + 180 µg 48 wk) (n = 469)	(360 µg 12 wk then 180 µg 60 wk + 360 µg 12 wk then 180 µg 36 wk) (n = 473)	(180 µg 72 wk + 180 µg 48 wk) (n = 469)
SVR	16%*	8%*	13%	10%

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

SVR = sustained virological response; wk = weeks

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 6.

Table 6. SVR Rates After Treatment with PEGASYS RBV Combination Therapy in Non-responders to Previous Treatment with Peginterferon alfa-2b/Ribavirin

	Peginterferon alfa-2b/ribavirin Non-responders re-treated for 48 weeks	Peginterferon alfa-2b/ribavirin Non-responders re-treated for 72 weeks
	% SVR (responders/total)	% SVR (responders/total)
Overall SVR	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; SVR = sustained virological response

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 µg once a week and COPEGUS 1000/1200 mg daily. Patients who achieved undetectable levels of HCV RNA after 20 weeks of treatment remained on PEGASYS RBV combination therapy 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 subpopulation 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 (refer to Table 7). There was no difference in disease progression/cirrhosis with or without treatment (33% versus 34%).

Table 7. SVR Rates by Treatment Duration and Non-responder Population

	HALT-C Study				Study MV17150
Treatment Duration	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)

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).

Chronic Hepatitis C: Prior Treatment Relapser Patients

In an open-label study (Study WV16143) conducted in patients who relapsed after 24 weeks of treatment with peginterferon alfa and ribavirin, a total of 64 patients (45 patients with genotype 1, 14 with genotype 2/3 and 5 with other genotypes) were re-treated with 48 weeks of PEGASYS 180 µg once a week and weight-based COPEGUS daily. SVR was achieved in 51% of patients infected with genotype 1 and 64% of patients with genotype 2 or 3.

HIV-HCV Co-infection

In NR15961, 860 patients with CHC co-infected with human immunodeficiency virus (HIV-HCV) were randomised to a partially-blinded, controlled clinical trial. All patients were adults with compensated liver disease, detectable HCV, elevated ALT, serologically and histologically proven CHC, serological evidence of HIV-1 infection, CD4 cell count > 100 cells/µL and stable HIV-1 disease with or without anti-retroviral therapy. Patients received either PEGASYS 180 µg sc once a week with placebo, PEGASYS 180 µg sc once a week with COPEGUS 800 mg daily or ROFERON-A 3 MIU three times a week with COPEGUS 800 mg daily for 48 weeks of therapy followed by 24 weeks of treatment-free follow-up. The SVRs for the 3 treatment groups are summarised for all patients and by genotype in Table 8.

Table 8. SVR in HIV-HCV Co-infected Patients (Study NR15961)

	PEGASYS 180 µg with placebo 48 weeks	PEGASYS 180 µg with COPEGUS 800 mg 48 weeks	ROFERON-A 3 MIU with COPEGUS 800 mg 48 weeks
All Genotypes	20% (58/286)*	40% (116/289)*	12% (33/285)*
Genotype 1	14% (24/175)	29% (51/176)	7% (12/171)
Genotype non-1†	36% (32/90)	62% (59/95)	20% (18/89)

† majority genotype 2 and 3

* PEGASYS 180 µg with COPEGUS 800 mg vs. ROFERON-A 3 MIU with COPEGUS 800 mg: Odds Ratio (95% CI) = 5.40 (3.42 to 8.54), *p*-value (stratified Cochran-Mantel-Haenszel test) ≤ 0.0001; PEGASYS 180 µg with COPEGUS 800 mg vs. PEGASYS 180 µg: Odds Ratio (95% CI) = 2.89 (1.93 to 4.32), *p*-value (stratified Cochran-Mantel-Haenszel test) ≤ 0.0001

Patients treated with PEGASYS RBV achieved higher SVR irrespective of HCV genotype or baseline viral titre than patients treated with conventional ROFERON-A with COPEGUS or with PEGASYS alone.

A subsequent study (NV18209) in patients co-infected with HCV genotype 1 and HIV compared PEGASYS 180 µg/week and either COPEGUS 800 mg or 1000 mg (<75 kg)/1200 mg (≥75 kg) daily for 48 weeks. The results are reported in Table 9 and showed that the study was not powered for efficacy considerations.

Table 9. SVR in HIV-HCV Co-infected Patients (Study NV18209)

	PEGASYS 180 µg with COPEGUS 800 mg 48 weeks (n = 138)	PEGASYS 180 µg with COPEGUS 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 COPEGUS groups were consistent with the known safety profile of PEGASYS plus COPEGUS combination treatment and not indicative of any relevant differences, with the exception of a slight increase in anaemia in the high dose COPEGUS arm.

INDICATIONS

PEGASYS RBV combination therapy is indicated for the treatment of chronic hepatitis C in patients who have received no prior interferon therapy (treatment-naïve patients) and patients who have failed previous treatment with interferon alfa (pegylated or non-pegylated) alone or in combination therapy with ribavirin.

PEGASYS RBV combination therapy is also indicated for the treatment of chronic hepatitis C in patients with stable human immunodeficiency virus (HIV) who have previously not received interferon therapy.

Patients must be 18 years of age or older and have compensated liver disease.

CONTRAINDICATIONS

Use in Pregnancy: Category X

COPEGUS must not be used in pregnant women or by men whose female partners are pregnant or are not using adequate contraception.

Extreme care must be taken to avoid pregnancy in female patients.

Women of childbearing potential should not be given COPEGUS until pregnancy is excluded. It is strongly recommended that a pregnancy test be performed immediately prior to the initiation of COPEGUS therapy. Women and their male partners should be counselled to each use an effective form of contraception during COPEGUS therapy and for 6 months following treatment.

If pregnancy does occur during treatment or within 6 months after stopping treatment the patient must be advised of the significant teratogenic risk of COPEGUS to the foetus.

PEGASYS RBV is also contraindicated in:

- patients with a known hypersensitivity to alfa interferons, to *E.coli*-derived products, to polyethylene glycol, to ribavirin, or to any component of the injection or tablet
- patients with autoimmune hepatitis
- patients with decompensated cirrhosis
- patients with HIV-HCV co-infection with cirrhosis and a Child Pugh score ≥ 6 , except if only due to indirect hyperbilirubinemia caused by medicines such as atazanavir and indinavir
- patients with a history of severe pre-existing cardiac disease, including unstable or uncontrolled cardiac disease in the previous 6 months (refer to *Precautions*)
- patients with haemoglobinopathies (e.g. thalassaemia, sickle-cell anaemia)
- women who are breast-feeding
- neonates and infants up to the age of 3 years, because of the excipient benzyl alcohol.

PRECAUTIONS

General

PEGASYS RBV combination therapy should be administered under guidance of a qualified physician and may lead to moderate to severe adverse experiences requiring dose reduction, temporary dose cessation or discontinuation of therapy (refer to *Dosage and Administration*).

Based on clinical trials, the use of COPEGUS monotherapy is not effective in the treatment of CHC, and therefore COPEGUS tablets should not be used alone.

The use of PEGASYS RBV combination therapy in chronic hepatitis C 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.

Neuropsychiatric

Severe psychiatric adverse reactions may manifest in patients receiving therapy with interferons, including PEGASYS RBV. Depression, suicidal ideation, suicide, relapse of drug dependence and drug overdose may occur in patients with or 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 combination therapy and patients should report any sign or symptom of depression immediately. In severe cases therapy should be stopped and psychiatric intervention sought.

Hepatic Impairment

Patients who develop evidence of hepatic decompensation during treatment should discontinue PEGASYS RBV.

HCV: As with other alfa interferons, increases in ALT levels above baseline have been observed in patients treated with PEGASYS RBV combination therapy, 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 (refer to *Dosage and Administration*).

HIV-HCV: HIV-HCV co-infected patients with advanced cirrhosis receiving concomitant highly active anti-retroviral therapies (HAART) may be at an increased risk of hepatic decompensation and possibly death when treated with ribavirin in combination with alfa interferons, including PEGASYS. In study NR15961, among 123 HIV-HCV cirrhotic patients receiving HAART, 14 (11%) of these patients across all treatment arms developed hepatic decompensation resulting in 6 (5%) deaths. Of the 14 patients, 13 were on NRTIs at the onset of hepatic decompensation.

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). Treatment with PEGASYS should be discontinued immediately in patients with hepatic decompensation. Baseline variables in co-infected cirrhotic patients that may be associated with hepatic decompensation include increased serum bilirubin, decreased haemoglobin, decreased platelet count, increased alkaline phosphatase, and treatment with didanosine.

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.

Endocrine

As with other interferons, PEGASYS RBV may cause or aggravate hypothyroidism and hyperthyroidism. Discontinuation 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 combination therapy. Patients who develop these conditions during treatment and cannot be controlled with medication should discontinue PEGASYS RBV combination therapy.

Autoimmune

Exacerbation of autoimmune disease has been reported in patients receiving alfa interferon therapy. PEGASYS RBV combination therapy 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 combination therapy 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.

Hypersensitivity

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

Cardiovascular

As cardiac disease may be worsened by ribavirin-induced anaemia, HCV patients with a history of significant or unstable cardiac disease in the previous 6 months should not use COPEGUS (ribavirin). Cardiovascular events such as hypertension, supraventricular arrhythmias, congestive heart failure, chest pain and myocardial infarction have been associated with interferon therapy, including PEGASYS RBV. Because cardiac disease may be worsened by ribavirin-induced anaemia, PEGASYS RBV should be administered with caution to patients with pre-existing significant or unstable disease. Patients should be assessed before initiation of therapy and should be appropriately monitored during therapy. If there is any deterioration of cardiovascular status, COPEGUS therapy should be suspended or discontinued (refer to *Dosage and Administration*). It is recommended that patients who have pre-existing cardiac abnormalities have an electrocardiogram prior to and during the course of treatment. If there is any deterioration of cardiovascular status, therapy should be suspended or discontinued.

Bone Marrow Suppression

It is advised that complete blood counts be obtained pre-treatment and monitored routinely during therapy. PEGASYS RBV combination therapy should be used with caution in patients with baseline neutrophil counts < 1500 cells/mm³, with baseline platelet count $< 90,000$ cells/mm³ or haemoglobin decrease < 120 g/L (refer to *Dosage and Administration, Dose Modification*). As with other interferons, caution should be exercised when administering PEGASYS RBV combination therapy with other potentially myelosuppressive agents.

Pancytopenia (marked decreases in RBCs, neutrophils and platelets) and bone marrow suppression have been reported in the literature to occur within 3 – 7 weeks after the concomitant administration of COPEGUS and azathioprine. This myelotoxicity was reversible within 4 – 6 weeks upon withdrawal of HCV antiviral therapy and concomitant azathioprine and did not recur upon reintroduction of either treatment alone (refer to *Interactions with Other Medicines*).

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 RBV. All patients should have a baseline eye examination. Patients with pre-existing ophthalmological disorders (e.g. diabetic or hypertension retinopathy) should receive periodic eye examinations during alfa interferon therapy. Any patient complaining of decreased or loss of vision must have a prompt and complete eye examination. PEGASYS RBV treatment should be discontinued in patients who develop new or worsening ophthalmologic disorders.

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 and severe infections (bacterial, viral, fungal) have been reported during treatment with alfa interferons including PEGASYS RBV combination therapy. Appropriate anti-infective therapy should be started immediately and discontinuation of therapy should be considered.

Organ Transplant Recipients

The safety and efficacy of PEGASYS RBV treatment have 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.

Effects on Laboratory Tests

Before beginning PEGASYS RBV combination therapy, standard haematological and biochemical laboratory tests are recommended for all patients. Pregnancy screening and monthly pregnancy test monitoring while receiving PEGASYS RBV combination therapy should be done for all women of childbearing potential. After initiation of therapy, haematological tests should be performed at week 2 and 4 and biochemical tests should be performed at week 4. Additional testing should be performed periodically during therapy. HIV-HCV co-infected patients treated with PEGASYS RBV have increased frequency of haematological adverse events and should be monitored carefully.

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

- haemoglobin \geq 120 g/L (females); 130 g/L (males)
- platelet count \geq 90 000 cells/mm³
- absolute neutrophil count (ANC) \geq 1500 cells/mm³
- thyroid stimulating hormone (TSH) and T₄ within normal limits or adequately controlled thyroid function
- HIV-HCV co-infection: CD₄₊ \geq 200/ μ L or CD₄₊ \geq 100/ μ L to $<$ 200/ μ L and HIV-1 RNA $<$ 5000 copies/mL using Amplicor HIV-1 Monitor test, version 1.5.

PEGASYS RBV combination therapy was associated with decreases in both total white blood cell (WBC) count and absolute neutrophil count (ANC), usually starting within the first 2 weeks of treatment (refer to *Adverse Effects*). In clinical trials, progressive decreases after 4 – 8 weeks were infrequent. Dose reduction is recommended when ANC decreases to levels below 750 cells/mm³ (refer to *Dosage and Administration*). For patients with ANC values below 500 cells/mm³ treatment should be suspended until ANC values return to more than 1000 cells/mm³. In clinical trials with PEGASYS RBV combination therapy, the decrease in ANC was reversible upon dose reduction or cessation of therapy. While fever may be associated with flu-like syndrome reported commonly during interferon therapy, other causes of persistent fever must be ruled out, particularly in patients with neutropenia.

PEGASYS RBV combination therapy was associated with decreases in platelet count, which returned to pre-treatment (baseline) levels during the post-treatment observation period (refer to *Adverse Effects*). Dose reduction is recommended when platelet count decreases to levels below 50,000 cells/mm³, and cessation of therapy is recommended when platelet count decreases to levels below 25,000 cells/mm³ (refer to *Dosage and Administration*).

Anaemia (haemoglobin \leq 100 g/L) was observed in 13% and 3% of patients in clinical trials treated with PEGASYS RBV combination therapy for 48 weeks and 24 weeks, respectively (refer

to *Adverse Effects: Laboratory Test Values*). The risk of developing anaemia is higher in the female population. The maximum drop in haemoglobin occurred within 4 weeks of initiation of COPEGUS therapy. Complete blood counts should be obtained pre-treatment, at week 2 and week 4 of therapy and periodically thereafter. If there is any deterioration of cardiovascular status, ribavirin therapy should be suspended or discontinued (refer to *Dosage and Administration*).

The occurrence of thyroid function abnormalities or the worsening of pre-existing thyroid disorders has been reported with the use of alfa interferons, including PEGASYS RBV combination therapy. Discontinuation of therapy should be considered in patients whose thyroid abnormalities cannot be adequately treated.

Renal Impairment

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 (refer to *Dosage and Administration*).

COPEGUS therapy should not be initiated in patients with moderate to severe renal impairment (creatinine clearance ≤ 50 mL/min) who are not receiving chronic haemodialysis, unless it is considered to be essential. If serum creatinine rises to > 20 mg/L, COPEGUS discontinuation or dose modification must be considered. COPEGUS must be administered with extreme caution.

Patients with moderate or severe renal impairment (creatinine clearance ≤ 50 mL/min) not receiving chronic haemodialysis did not tolerate 600 mg and 400 mg daily doses of COPEGUS, respectively. Compared to patients with normal renal function (creatinine clearance > 80 mL/min) 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. Caution should be exercised in prescribing PEGASYS to patients with severe renal impairment.

In patients who develop renal impairment (and are not receiving haemodialysis) during a standard treatment course of COPEGUS in combination with PEGASYS, COPEGUS therapy should not be continued.

For patients with end stage renal disease receiving chronic haemodialysis, COPEGUS therapy may be initiated at a dose of 200 mg daily. In a study in which patients with end stage renal disease on chronic haemodialysis were administered a 200 mg daily dose, patients exhibited ribavirin plasma exposures that were approximately 20% lower than those of patients with normal renal function receiving the standard 1000/1200 mg COPEGUS daily dose.

It is recommended that the renal function be evaluated in all patients prior to initiation of COPEGUS preferably by estimating the creatinine clearance. Patients on chronic haemodialysis receiving COPEGUS should be carefully monitored (refer to *Dosage and Administration*).

Paediatric Use

Safety and effectiveness have not been established in patients below the age of 18. Therefore, PEGASYS RBV is not recommended for use in children under 18 years of age.

PEGASYS injectable solutions contain benzyl alcohol and should not be used in neonates and infants up to the age of 3 years. 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 reactions may occur in neonates or infants is not known (refer to *Contraindications*).

Use in the Elderly

No dosage modification is required for elderly patients based upon pharmacokinetic, pharmacodynamic, tolerability, and safety data from clinical trials (refer to *Pharmacokinetics*). However, as in younger patients, renal function must be determined prior to administration of COPEGUS.

Carcinogenesis and Mutagenesis

PEGASYS

PEGASYS has not been tested for its carcinogenic potential. 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.

COPEGUS

In a short term carcinogenicity study in p53(+/-) knockout mice, ribavirin at up to 100 mg/kg/day PO for 26 weeks (0.7x the clinical exposure, based on AUC) did not increase tumour incidences. In a lifetime study in Wistar rats at doses of up to 60 mg/kg bw/day ribavirin was not carcinogenic. The systemic exposure achieved in this study was 0.3 times that in humans receiving a therapeutic dose. The low animal/human exposure ratios limit the capability of the study to predict the carcinogenic risk of ribavirin to humans. Ribavirin produced positive findings in several genotoxicity assays (see below). Potential carcinogenicity cannot be ruled out.

Ribavirin was positive *in vitro* in Balb/3T3 cell transformation assay and the mouse lymphoma (L5178Y) assay and *in vivo* in mouse micronucleus assays. It was negative in a range of other assays for gene mutations (*Salmonella typhimurium*, host-mediated assay) and chromosomal damage (dominant lethal assays).

Effects on Fertility

PEGASYS

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 delay in the peak of 17 β -estradiol 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. Peginterferon alfa-2a has not been studied for its effect on male fertility.

COPEGUS

Ribavirin at oral doses up to 100 mg/kg/day did not affect fertility in male rats mated with untreated female rats, but it slightly reduced sperm counts at 100 mg/kg/day (0.4x the clinical exposure, based on AUC), and reduced spermatid counts, lowered epididymal weights and induced testicular tubular atrophy at 160 mg/kg/day PO (approximately 0.9x the clinical exposure). In mice, ribavirin induced sperm abnormalities (morphology and counts) in mice at 15 mg/kg/day PO (approximately 0.1x the clinical exposure). Upon cessation of treatment, the testicular effects were reversible within 1 – 2 spermatogenesis cycles i.e. approximately 1.5 – 3 months. No testicular toxicity was observed in dogs at up to 20 mg/kg/day for 6 months or in monkeys following 4 weeks of dosing at up to 100 mg/kg/day (similar to the clinical exposure).

Extreme care must be taken to avoid pregnancy in partners of male patients taking ribavirin or female patients of child-bearing potential. Ribavirin accumulates intracellularly and is cleared from the body very slowly. It is unknown whether the ribavirin in sperm will exert its known

teratogenic effects upon fertilisation of the ova (refer to *Use in Pregnancy*). Women of childbearing potential and their male partners (male or female as patient) must be counselled to use effective contraception during therapy and for 6 months after therapy.

Use in Pregnancy: Category X

PEGASYS RBV combination therapy should not be used in pregnant women or by men whose female partners are pregnant. PEGASYS RBV combination therapy should be used with caution in fertile women and men. Fertile women and partners of fertile women should not receive PEGASYS RBV combination therapy unless the patient and his/her partner are using effective contraception. Based on the multiple dose half-life of ribavirin of 12 days, effective contraception must be used for 6 months post-treatment (i.e. 15 half-lives of clearance for COPEGUS) (refer to *Contraindications*).

PEGASYS

Safe use in human pregnancy has not been established. Therefore, PEGASYS should be used during pregnancy only if the potential benefit justifies the potential risk to the foetus.

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.

Abortion was observed in all dose groups (1, 5 and 25 million IU/kg/day). No teratogenic effects were seen in delivered offspring. However, as with other alfa interferons, women of childbearing potential receiving PEGASYS therapy should be advised to use effective contraception during therapy.

COPEGUS

Ribavirin should not under any circumstances be administered during pregnancy (refer to *Contraindications*).

Ribavirin has demonstrated significant teratogenic and/or embryocidal potential in all animal species in which adequate studies have been conducted. In rats and rabbits, a gavage dose of 1 mg/kg/day, and in hamsters a dose of 2.5 mg/kg/day, administered during the period of organogenesis, was associated with embryotoxic or teratogenic effects. Malformations of the skull, palate, eye, jaws, limbs, skeleton, and gastrointestinal tract were noted. No teratogenic effects were observed in the rat or rabbit at 0.3 mg/kg/day (approximately 0.003 times the maximum recommended clinical dose, based on body surface area adjusted for a 60 kg adult).

Use in Lactation

It is not known whether peginterferon alfa-2a, its metabolites or ribavirin are excreted in human milk. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from PEGASYS or COPEGUS, a decision should be made either to discontinue nursing or PEGASYS RBV combination therapy, taking into account the importance of the therapy to the mother.

Effects on Ability to Drive and Operate Machinery

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

Interactions with other Medicines

No pharmacokinetic interactions between PEGASYS and COPEGUS have been observed during clinical trials.

Any potential for interactions may persist for up to 2 months after cessation of COPEGUS therapy due to the long half-life.

PEGASYS

Treatment with PEGASYS once a week 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. PEGASYS 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 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 RBV therapy concomitantly.

Chinese medicine:

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

Methadone:

In a pharmacokinetic study of 24 HCV patients concomitantly receiving methadone maintenance therapy (median dose 95 mg; range 30 mg to 150 mg), treatment with PEGASYS 180 µg sc once a week 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.

Telbivudine:

A clinical trial investigating the combination of telbivudine 600 mg daily, with PEGASYS 180 µg sc once a week, 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 cannot 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.

COPEGUS

Interaction studies have been conducted with COPEGUS in combination with interferon alfa or PEGASYS and antacids. COPEGUS concentrations are similar when given concomitantly with interferon alfa or PEGASYS. COPEGUS concentrations are similar when given as monotherapy or in combination with interferon alfa-2b.

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. There is no evidence from toxicity studies that ribavirin induces liver enzymes, therefore there is minimal potential for P450 enzyme based interactions.

Antacids:

The bioavailability of ribavirin 600 mg was decreased by co-administration with an antacid containing magnesium, aluminium and methicone, AUC_{0-12h} decreased by 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.

Azathioprine:

COPEGUS has an inhibitory effect on inosine monophosphate dehydrogenase and may therefore 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.

Pancytopenia (marked decreases in RBCs, neutrophils and platelets) and bone marrow suppression have been reported in the literature to occur within 3 – 7 weeks after the concomitant administration of COPEGUS and azathioprine. This myelotoxicity was reversible within 4 – 6 weeks upon withdrawal of HCV antiviral therapy and concomitant azathioprine and did not recur upon reintroduction of either treatment alone (refer to *Bone Marrow Suppression*).

In individual cases where the benefit of administering COPEGUS 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.

Nucleoside analogues:

In study NR15961, cases of hepatic decompensation (some fatal) were observed among HIV-HCV co-infected cirrhotic patients receiving HAART (refer to *Precautions: Hepatic Function*).

In vitro studies have shown Ribavirin can 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 drug 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 (lamivudine, zidovudine, or stavudine). Plasma exposure of ribavirin did not appear to be affected by concomitant administration of NRTIs.

Didanosine: 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 COPEGUS. Reports of fatal hepatic failure, as well as peripheral neuropathy, pancreatitis and symptomatic hyperlactataemia/lactic acidosis have been reported in clinical trials. This potential interaction may also apply to other purine analogues and the co-administration of ribavirin with these agents is not recommended.

Zidovudine: In study NR 15961, patients who were administered zidovudine in combination with PEGASYS RBV developed severe neutropenia (ANC < 500) and severe anaemia (haemoglobin < 80 g/L) more frequently than similar patients not receiving zidovudine (neutropaenia 15% vs. 9%) (anaemia 5% vs. 1%).

ADVERSE EFFECTS

Experience from Clinical Trials

The frequency and severity of the most commonly reported adverse reactions with PEGASYS RBV are similar to those seen in patients treated with other alfa interferons and ribavirin.

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.

Chronic Hepatitis C

Treatment-naïve patients

Patients with elevated ALT levels: In clinical trials, the incidence of withdrawal from treatment for all patients due to adverse reactions and laboratory abnormalities was 9% for PEGASYS monotherapy and 13% for PEGASYS RBV combination therapy with COPEGUS 1000/1200 mg given for 48 weeks. Only 3% of patients on PEGASYS RBV combination therapy required discontinuation due to 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 combination therapy with COPEGUS 1000/1200 mg, reducing treatment exposure to 24 weeks and daily dose of COPEGUS 800 mg resulted in a reduction in the serious adverse reactions (11% vs. 3%), premature withdrawals for safety reasons (13% vs. 5%) and the need for COPEGUS dose modification (39% vs. 19%).

Patients with normal ALT levels: The safety profile of PEGASYS RBV in HCV patients with normal ALT was consistent with that previously observed in HCV patients with elevated ALT. Similarly, 24 week treatment was better tolerated than 48 weeks (refer to Table 10).

Table 10. Adverse Reactions Occurring in $\geq 10\%$ of Hepatitis C patients with Normal ALT Levels

	PEGASYS 180 μg with COPEGUS 800 mg 24 weeks (n = 212) %	PEGASYS 180 μg with COPEGUS 800 mg 48 weeks (n = 210) %	Untreated Control 48 weeks (n = 69) %
General disorders and administration site conditions			
Fatigue	51	51	17
Pyrexia	30	43	3
Rigors	24	25	1
Asthenia	22	23	10
Injection site reaction	16	16	-
Decreased appetite	8	16	1
Back pain	9	10	9
Psychiatric disorders			
Insomnia	35	36	7
Depression	26	27	6
Irritability	27	26	1
Anxiety	10	8	3
Musculoskeletal and connective tissue disorders			
Myalgia	38	44	7
Arthralgia	32	30	4
Nervous system disorders			
Headache	44	56	7
Dizziness	89	17	1
Skin and subcutaneous tissue disorders			
Alopecia	20	28	-
Pruritus	16	20	1
Rash	14	16	-
Dermatitis	-	-	-
Dry skin	11	9	-
Gastrointestinal disorders			
Nausea	32	40	1
Diarrhoea	19	26	4
Vomiting	12	13	3
Upper abdominal pain	9	12	7
Dyspepsia	9	10	-
Respiratory, thoracic and mediastinal disorders			
Cough	14	19	1
Dyspnoea	14	15	-
Pharyngitis	9	10	4
Metabolism and nutrition disorders			
Anorexia	16	13	1

Prior treatment non-responder patients

In study MV17150, which included 72 and 48 weeks treatment of prior pegylated interferon alfa-2b/ribavirin non-responder patients (refer to *Clinical Trials*), the frequency of withdrawal due to adverse events or laboratory abnormalities from PEGASYS treatment was 12% and COPEGUS treatment was 13%. In comparison, in the 48 week treatment arms, 6% withdrew from PEGASYS and 7% withdrew from COPEGUS treatment. Similarly for patients with cirrhosis, withdrawal rates from PEGASYS and COPEGUS 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 (refer to *Clinical Trials*). 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 < 100 g/L, 26.3%; absolute neutrophil count (ANC) < 750/mm³, 30%; and platelet < 50 000/mm³, 13% (refer to *Precautions: Effects on Laboratory Tests*).

HIV-HCV co-infection

In study NR15961, 180 µg PEGASYS with and without 800 mg COPEGUS in HIV-HCV co-infected patients, adverse reactions reported with PEGASYS RBV combination therapy were similar to that observed in HCV infected patients. The incidence of withdrawal from treatment due to adverse reactions, laboratory abnormalities or AIDS-defining events was 15% for PEGASYS RBV given for 48 weeks. Three percent of patients required discontinuation of PEGASYS RBV due to blood and lymphatic system disorder adverse events. Serious adverse reactions were reported in 17% of patients receiving 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 viraemia during therapy or follow-up.

Study NV18209 compared 48 weeks of treatment with either PEGASYS 180 µg plus COPEGUS 1000 or 1200 mg or PEGASYS 180 µg plus COPEGUS 800 mg in interferon-naïve patients with HIV-HCV co-infected patients (HCV genotype 1 virus). 275 patients received the COPEGUS 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 ≥ 10% of patients in study NV18209 were similar to those within Table 11 for HIV-HCV co-infected patients, with no increased frequency for PEGASYS plus COPEGUS 1000/1200 mg compared with PEGASYS plus COPEGUS 800 mg except for anaemia (refer to *Laboratory Test Values*).

Table 11 shows those adverse reactions occurring in ≥ 10% of HCV patients, HIV-HCV co-infected patients and HCV patients who did not respond to previous peginterferon alfa-2b treatment receiving PEGASYS RBV.

Table 11. Adverse Reactions Occurring in $\geq 10\%$ of Patients in Hepatitis C Clinical Trials

	HCV			HIV-HCV	HCV Peginterferon alfa-2b Non-responders
	PEGASYS 180 μg with COPEGUS 800 mg 24 weeks (n = 207) %	PEGASYS 180 μg with COPEGUS 1000 or 1200 mg 48 weeks (n = 887) %	Interferon alfa-2b with ribavirin 1000 or 1200 mg 48 weeks (n = 443) %	PEGASYS 180 μg with COPEGUS 800 mg 48 weeks (n = 288) %	PEGASYS 180 μg with COPEGUS 1000 or 1200 mg 72 weeks (n = 156) %
General disorders and administration site conditions					
Fatigue	45	49	53	40	36
Rigors*	30	25	34	16	12
Pyrexia*	37	39	54	41	20
Injection Site Reaction	28	21	16	10	12
Pain	9	10	9	6	6
Asthenia	18	15	16	26	30
Psychiatric disorders					
Depression*	17	21	28	22	16
Irritability	28	24	27	15	17
Anxiety	8	8	12	8	6
Musculoskeletal and connective tissue disorders					
Myalgia	42	38	49	32	22
Arthralgia	20	22	23	16	15
Nervous system disorders					
Headache	48	47	49	35	32
Insomnia	30	32	37	19	29
Dizziness	13	15	14	7	10
Concentration Impairment	8	10	13	2	5
Skin and subcutaneous tissue disorders					
Alopecia*	25	24	33	10	18
Pruritus	25	21	18	5	22
Dermatitis	15	16	13	1	1
Dry Skin	13	12	13	4	17
Gastrointestinal disorders					
Nausea	29	28	28	24	24
Diarrhoea	15	14	10	16	13
Abdominal pain	9	10	9	7	9
Respiratory, thoracic and mediastinal disorders					
Dyspnoea	11	13	14	7	11
Cough	8	13	7	3	17
Metabolism and nutrition disorders					
Anorexia	20	27	26	23	15
Weight Decrease	2	7	10	16	9

* In HCV clinical trials, statistically significant difference between PEGASYS RBV and Interferon alfa-2b/ribavirin treatments

Commonly reported adverse reactions (1 - 10%) in patients treated with PEGASYS RBV combination therapy were:

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

Infections and infestations: herpes simplex, upper respiratory tract infection, bronchitis, oral candidiasis

Ear and labyrinth disorders: vertigo, earache

Vascular disorders: flushing

Blood and lymphatic system disorders: lymphadenopathy, anaemia, thrombocytopenia

Cardiac disorders: palpitations, oedema peripheral, tachycardia

Gastrointestinal disorders: vomiting, dyspepsia, gingival bleeding, mouth ulceration, flatulence, gastritis, dry mouth, gingivitis, cheilitis, constipation, stomatitis, dysphagia, glossitis

Endocrine disorders: hypothyroidism, hyperthyroidism

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

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

Respiratory, thoracic and mediastinal disorders: exertional dyspnoea, sore throat, nasopharyngitis, sinus congestion, rhinitis, pulmonary congestion, chest tightness, upper respiratory tract infection, epistaxis, pneumonia

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

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

Other adverse reactions reported in 1 – 2% of HIV-HCV patients receiving PEGASYS RBV combination therapy included hyperlactacidaemia/lactic acidosis, influenza, pneumonia, affect lability, apathy, tinnitus, pharyngolaryngeal pain, cheilitis, acquired lipodystrophy and chromaturia.

As with other interferons, uncommon to rare cases of the following serious adverse reactions have been reported in patients receiving PEGASYS RBV combination therapy during clinical trials:

General disorders and administration site conditions: substance overdose

Cardiac disorders: arrhythmia, endocarditis, cerebral haemorrhage, atrial fibrillation, pericarditis

Gastrointestinal disorders: peptic ulcer, gastrointestinal bleeding, reversible pancreatic reaction (i.e. amylase/lipase increase with or without abdominal pain)

Hepatobiliary disorders: hepatic dysfunction, fatty liver, cholangitis, malignant hepatic neoplasm, pancreatitis

Metabolism and nutrition disorders: autoimmune phenomena [e.g. immune thrombocytopenic purpura (ITP), thyroiditis, psoriasis, rheumatoid arthritis, systemic lupus erythematosus (SLE)]

Musculoskeletal and connective tissue disorders: myositis

Neuropsychiatric: peripheral neuropathy, coma, depression, suicide, psychotic disorder, hallucinations

Respiratory, thoracic and mediastinal disorders: interstitial pneumonitis with fatal outcome, pulmonary embolism, lower respiratory tract infection, sarcoidosis

Eye disorders: corneal ulcer

Ear and labyrinth disorders: otitis externa

Skin and subcutaneous tissue disorders: skin infection, thrombotic thrombocytopenic purpura (TTP)

Post-Marketing Experience

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.

Dehydration has been reported rarely with PEGASYS RBV.

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

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

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

Laboratory Test Values

Haematology: As with other interferons, treatment with PEGASYS RBV combination therapy was associated with decreases in haematological values, which generally improved with dosage modification and returned to pre-treatment levels within 4 – 8 weeks upon cessation of therapy (refer to *Precautions: Effects on Laboratory Tests* and *Dosage and Administration*). Although neutropenia, thrombocytopenia and anaemia occurred more frequently in HIV-HCV patients, the majority could be managed by dose modification, the use of growth factors and, infrequently, required premature discontinuation of treatment.

Haemoglobin and Haematocrit: Haemoglobin decreased among patients on PEGASYS RBV combination therapy began at week 1, with stabilisation by week 4. On average, the maximal decrease in haemoglobin was 30 g/L. Haemoglobin decreases in individual patients may be greater. Haemoglobin values returned to pre-treatment levels within 4 – 8 weeks of cessation of COPEGUS therapy in most patients (refer to *Precautions* and *Dosage and Administration*). Anaemia (haemoglobin < 100 g/L) was reported in 14% and 28% of HIV-HCV co-infected patients treated with PEGASYS RBV in studies NR15961 and NV18209, respectively.

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 RBV combination therapy was associated with decreases in values for both total WBC count and ANC. Approximately 4% of patients had transient decreases in ANC to levels below 500 cells/mm³ at some time during therapy. In HIV-HCV co-infected patients, 11% of those receiving PEGASYS RBV had decreases in ANC levels below 500 cells/mm³.

Platelet Count: PEGASYS RBV 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 50 000 cells/mm³ mostly in patients with cirrhosis and who entered the trial with baseline platelet counts as low as 75 000 cells/mm³. In HIV-HCV co-infected patients, 8% of patients receiving PEGASYS RBV had decreases in platelets below 50 000 cells/mm³.

Thyroid Function: PEGASYS RBV combination therapy was associated with clinically significant abnormalities in thyroid laboratory values requiring clinical intervention (refer to *Precautions: Effects on Laboratory Tests*). The frequencies observed with PEGASYS RBV were similar to those observed with other interferons.

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

Anti-interferon Antibodies: Two percent of patients receiving PEGASYS RBV combination therapy 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 reactions was observed.

DOSAGE AND ADMINISTRATION

Before beginning PEGASYS RBV combination therapy, standard haematological and biochemical laboratory tests are recommended for all patients (refer to *Precautions: Effects on Laboratory Tests*).

Chronic Hepatitis C: Treatment-Naïve Patients

The recommended dose for PEGASYS RBV combination therapy is PEGASYS 180 µg once a week by subcutaneous administration in the abdomen or thigh. The dose of COPEGUS is dependent on the patient's body weight (refer to Table 12). The recommended duration of PEGASYS RBV combination therapy should be individualised based on the patient's viral genotype. COPEGUS should be administered in divided doses (morning and evening) with food.

Table 12. Dosing Recommendation for Chronic Hepatitis C Patients

Genotype†	PEGASYS dose	COPEGUS dose	Number of COPEGUS 200 mg tablets to be taken		Duration
Genotype 1, 4	180 µg	< 75 kg = 1000 mg	2 morning	3 evening	48 weeks
		≥ 75 kg = 1200 mg	3 morning	3 evening	48 weeks
Genotype 2, 3	180 µg	800 mg	2 morning	2 evening	24 weeks

† Data on genotypes 5 and 6 are too few to make definitive dosing recommendations

Consideration should be given to discontinuing therapy after 12 weeks of treatment if the patient has failed to demonstrate an early virological response (refer to *Clinical Trials*).

Chronic Hepatitis C: Prior Treatment Non-responder and Relapser Patients

The recommended dosage of PEGASYS RBV combination therapy is PEGASYS 180 µg once a week by subcutaneous administration in the abdomen or thigh. For patients < 75 kg and ≥ 75 kg, 1000 mg and 1200 mg of COPEGUS respectively, should be administered daily. COPEGUS should be administered in divided doses (morning and evening) with food.

The recommended duration of therapy is up to 72 weeks in genotype 1 or 4 patients and 48 weeks in genotype 2 or 3 patients.

HIV-HCV Co-infection

The recommended dose of PEGASYS RBV combination therapy is PEGASYS 180 µg once a week by subcutaneous administration in the abdomen or thigh and COPEGUS 800 mg daily. The recommended duration of therapy is 48 weeks. Efficacy of a treatment period shorter than 48 weeks has not been studied in HCV genotype 2 and 3 infected patients co-infected with HIV.

Dose Modification

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

Haematological

Table 13. PEGASYS Haematological Dose Modification Guidelines

Laboratory Values	Reduce PEGASYS dose if:	Discontinue PEGASYS if:
Absolute Neutrophil Count (ANC)	< 750 cells/mm ³ , reduce dose to 135 µg	< 500 cells/mm ³ , treatment should be suspended until ANC values return to more than 1000 cells/mm ³ Initially reinstitute at 90 µg and monitor ANC
Platelet Count	< 50 000 cells/mm ³ , reduce to 90 µg	< 25 000 cells/mm ³

Table 14. COPEGUS Haematological Dosage Modification Guidelines

Laboratory Values	Reduce COPEGUS dose to 600 mg per day* if:	Discontinue COPEGUS if:
Haemoglobin: patients with no cardiac disease	< 100 g/L	< 85 g/L
Haemoglobin: patients with history of stable cardiac disease	≥ 20 g/L decrease in haemoglobin during any 4 week period during treatment	< 120 g/L despite 4 weeks on a reduced dose

* 1 morning and 2 evening

If the laboratory 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

original dosing is not recommended. In cases of intolerance to COPEGUS, PEGASYS monotherapy may be continued.

Special Populations

Renal Impairment

In patients with end stage renal disease (creatinine clearance 20 – 40 mL/min), a starting dose of PEGASYS 135 µg once a week should be used. The pharmacokinetics of COPEGUS are altered in patients with renal impairment due to reductions of apparent clearance in these patients (refer to *Pharmacokinetics*). 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 creatinine clearance < 50 mL/min must not be treated with COPEGUS (refer to *Precautions*). If serum creatinine rises to > 20 mg/L, COPEGUS combination therapy must be discontinued.

In renally impaired patients receiving chronic haemodialysis, COPEGUS may be administered at a dose of 200 mg daily (refer to *Pharmacology: Pharmacokinetics in Special Populations and Precautions: Renal Impairment*).

Hepatic Impairment

In patients with compensated cirrhosis, PEGASYS has been shown to be effective and safe. PEGASYS has not been studied in patients with decompensated cirrhosis (refer to *Contraindications*). No pharmacokinetic interaction appears between COPEGUS and hepatic function. Therefore, no dose adjustment of COPEGUS is required in patients with hepatic impairment.

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 15. Modified Assessment

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

* Grading according to Trey, Burns and Saunders (1966)

Children

Safety and effectiveness have not been established in patients below the age of 18. In addition, PEGASYS injectable solutions contain benzyl alcohol, therefore, PEGASYS should not be used in neonates or infants up to the age of 3 years (refer to *Contraindications*).

Elderly

No dosage modification is required for elderly patients based upon pharmacokinetic, pharmacodynamic, tolerability and safety data from clinical trials. However, as in younger patients, renal function must be determined prior to administration of COPEGUS.

OVERDOSAGE

Overdoses with PEGASYS involving at least 2 injections on consecutive days (instead of weekly intervals) up to daily injections for one week (i.e. 1260 µg/week) have been reported. None of these patients experienced unusual, serious or treatment-limiting events. Weekly doses of up to 540 and 630 µg 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.

Treatment of overdose should consist of general supportive measures.

Contact the Poisons Information Centre for advice on management of overdose.

PRESENTATION AND STORAGE CONDITIONS

PEGASYS RBV is a combination pack containing PEGASYS (peginterferon alfa-2a) injection solution and COPEGUS (ribavirin) tablets.

PEGASYS RBV is available in the following combination packs:

- PEGASYS 180 µg pre-filled syringe x 4 + COPEGUS 112, 140 or 168 tablets
- PEGASYS 135 µg pre-filled syringe x 4 + COPEGUS 168 tablets
- PEGASYS ProClick 180 µg pre-filled pen x 4 + COPEGUS 112, 140 or 168 tablets*

PEGASYS is for single use in one patient only. Discard any residue.

PEGASYS RBV combination packs are to be refrigerated at 2 to 8°C. Do not freeze or shake. Protect from light.

After dispensing, COPEGUS tablets may be removed from the PEGASYS RBV combination pack and stored at below 30°C.

Parenteral drug products should be inspected visually for particulate matter and discoloration before administration, whenever solution and container permit.

* Presentations not currently distributed in Australia.

Disposal of Medicines



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 medicine should be returned to a pharmacy for disposal.

NAME AND ADDRESS OF THE SPONSOR

Roche Products Pty Limited
ABN 70 000 132 865
4–10 Inman Road
Dee Why NSW 2099
AUSTRALIA

Customer enquiries: 1800 233 950

POISON SCHEDULE OF THE MEDICINE

Prescription Only Medicine – S4

Date of first inclusion in the Australian Register of Therapeutic Goods (ARTG): 28 May 2003

Date of most recent amendment: 3 November 2011