Australian Government
Department of Health and Ageing
Therapeutic Goods Administration

Australian Public Assessment Report for Peginterferon alfa-2a/ Ribavirin

Proprietary Product Name: Pegasys RBV/Pegasys/Copegus

Sponsor: Roche Australia Pty Ltd

June 2011

TGA Health Safety Regulation

About the Therapeutic Goods Administration (TGA)

- The TGA is a division of the Australian Government Department of Health and Ageing, and is responsible for regulating medicines and medical devices.
- TGA administers the *Therapeutic Goods Act 1989* (the Act), applying a risk management approach designed to ensure therapeutic goods supplied in Australia meet acceptable standards of quality, safety and efficacy (performance), when necessary.
- The work of the TGA is based on applying scientific and clinical expertise to decision-making, to ensure that the benefits to consumers outweigh any risks associated with the use of medicines and medical devices.
- The TGA relies on the public, healthcare professionals and industry to report problems with medicines or medical devices. TGA investigates reports received by it to determine any necessary regulatory action.
- To report a problem with a medicine or medical device, please see the information on the TGA website.

About AusPARs

- An Australian Public Assessment Record (AusPAR) provides information about the evaluation of a prescription medicine and the considerations that led the TGA to approve or not approve a prescription medicine submission.
- AusPARs are prepared and published by the TGA.
- An AusPAR is prepared for submissions that relate to new chemical entities, generic medicines, major variations, and extensions of indications.
- An AusPAR is a static document, in that it will provide information that relates to a submission at a particular point in time.
- A new AusPAR will be developed to reflect changes to indications and/or major variations to a prescription medicine subject to evaluation by the TGA.

Contents

I. Introduction to Product Submission

Submission Details

Type of Submission	Major Variation
Decision:	Approved
Date of Decision:	13 May 2011
Active ingredient(s):	Peginterferon alfa-2a/ Ribavirin
Product Name(s):	Pegasys RBV/Pegasys/Copegus
Sponsor's Name and Address:	Roche Australia PO Box 255, Dee Why, NSW 2099
Dose form(s):	Solution for Injection/Tablet
Strength(s):	Peginterferon alfa-2a: 135 or 180 µg/0.5mL Ribavirin: 200mg tablets
Container(s):	Prefilled syringes with needles/ Bottle
Pack size(s):	4's (syringes)/ 112's, 140's, 168's (tablets)
Approved Therapeutic use:	*Pegasys RBV:* Pegasys RBV combination therapy is indicated for the treatment of chronic heptitis 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 clinically 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. *Pegasys:* ***Chronic Hepatitis C (CHC)*** The combination of Pegasys and Copegus is indicated for the treatment of chronic heptitis 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. The combination of Pegasys and Copegus is also indicated for the treatment of chronic hepatitis C in patients with clinically stable human immunodeficiency virus (HIV) co-infection who have previously not received interferon therapy. Pegasys monotherapy is indicated for the treatment of chronic hepatitis C in treatment-naïve patients (see Dosage and

	Administration; Chronic Hepatitis C: Treatment-Naive Patients). Patients must be 18 years of age or older and have compensated liver disease. ***Chronic Hepatitis B (CHB)*** Pegasys is indicated for the treatment of chronic hepatitis B in adult patients with evidence of viral replication and liver inflammation and compensated liver disease. *Copegus:* Copegus is indicated in combination with Pegasys (peginterferon alfa-2a) or other interferon alfa agents for the treatment of chronic hepatitis C in previously untreated (treatment- naïve) patients. Copegus in combination with Pegasys is also indicated for the treatment of patients who have failed previous treatment with interferon alfa (pegylated or non-pegylated) alone or in combination therapy with ribavirin. Copegus is also indicated in combination with Pegasys for the treatment of chronic hepatitis C in patients with clinically 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.
Route(s) of administration:	Subcutaneous injection/Oral
Dosage:	See PI.
ARTG Number (s)	91842, 91843/ 91836 and 91837/ 91841

Product Background

Roche Products Pty Ltd has submitted an application to revise the Product Information (PI) document for Pegasys to maintain consistency with the Company Core Data Sheet. Changes are proposed to the following sections of the Product Information:

Indications Inclusion of hepatitis C virus (HCV) patients co-infected with clinically stable human immunodeficiency virus (HIV).

Contraindications Clarification of contraindication of patients with HIV-HCV co-infection with cirrhosis and a Child Pugh score[1] ≥ 6

Precautions Hepatic Impairment: clarity on the use of Child Pugh score

Editorial changes have been made to the *Dosage and Administration* section and throughout the document.

[1] The Child-Pugh score is used to assess the prognosis of chronic liver disease. The score employs five clinical measures of liver disease. Each measure is scored 1-3, with 3 indicating most severe derangement.

Pegasys (peginterferon alfa-2a, PEG-IFN alfa-2a) is a modified interferon alfa formed by the covalent attachment of a branched methoxy polyethylene glycol moiety (PEG) to recombinant interferon alfa-2a.

In treatment of mono-infected HCV patients the combination PEG-IFN alfa-2a and ribavirin has been found to be more effective than PEG-IFN alfa-2a alone, and the ribavirin dose of either 1000 mg or 1200 mg, depending on patient weight, has been found to be more effective in mono-infected patients than the dose of 800 mg.

Because HCV and the HIV share common routes of transmission, co-infection with these two viruses is frequent. Liver disease caused by HCV infection is now a leading cause of morbidity and mortality among HIV-infected patients in the developed world, where opportunistic complications of severe immunodeficiency have declined as a result of the widespread use of antiretroviral therapies. In HIV-HCV co-infected individuals, HIV accelerates the course of HCV associated liver disease progression, particularly in patients who are more severely immune-deficient. As a consequence, HIV-HCV co-infection is associated with increased progression of liver fibrosis and increased rate of liver decompensation, cirrhosis, hepatocellular carcinoma and liver-related mortality. HCV infection in HIV-infected individuals is less responsive to treatment with pegylated interferon plus ribavirin than HCV infection in mono-infected individuals.

Treatments of HIV-HCV co-infected patients with PEG-IFN alfa-2a 180 µg with ribavirin 800 mg was assessed in Study NR15961 (APRICOT) and shown to be more effective than treatment with PEG-IFN alfa-2a and placebo. A summary of this study has been included in the already approved Australian Product Information. The requested change to the indication is based on this previously evaluated study.

For treatment of chronic hepatitis C (CHC) infection in patients co-infected with stable human immunodeficiency virus (HIV), the dosage and administration recommendation of forty-eight weeks treatment with PEG-IFN alfa-2a 180 µg once a week in combination with ribavirin 800 mg once daily is included in the current Australian Product Information and was approved in 2005 by the health authorities in the European Union (EU) and the United States. Approval was based on data from registration Study NR15961 (APRICOT).

Regulatory Status

The status of this submission in various countries and regions around the world is as follows:

Table 1. Regulatory status of Pegasys and Copegus:

Country	Date of submission	Approval
Pegasys		
EU	December 2009	July 2010
USA	December 2009	Not yet approved
Copegus		
EU	December 2010	Not yet approved
USA	December 2009	December 2010

The combination pack, Pegasys RBV is not currently marketed in the EU or the USA.

Product Information

The approved product information (PI) current at the time this AusPAR was prepared can be found as Attachment 1.

II. Quality Findings

No new quality data were submitted with the current Australian submission.

III. Nonclinical Findings

No new nonclinical data were submitted with the current Australian submission.

IV. Clinical Findings

Introduction

Study Protocol No NV18209 was included for clinical evaluation. The study enrolled 415 participants and was a randomized, double blind, multicenter, Phase IV trial comparing the safety and efficacy of Pegasys 180 µg plus Copegus 1000 or 1200 mg to the currently approved combination of Pegasys 180µg plus Copegus 800 mg in interferon-naive patients with chronic hepatitis C genotype 1 virus infection co-infected with the human immunodeficiency virus (HIV-1).

Regulatory Guidance and Advice

The sponsor designed and conducted Study NV18209 to fulfil post approval commitments received from the US and EU health authorities. These commitments were agreed upon at the time of approval for treatment of adults co-infected with HCV and HIV using the combination of PEG-IFN alfa-2a 180 µg plus ribavirin 800 mg. The FDA and EU requests are presented below.

The FDA requested an international, multi-centre, randomized, double-blind trial in genotype 1, CHC patients co-infected with HIV. The study was required to enrol 400 patients, including approximately 100 African American patients and was to evaluate:

- safety and efficacy of peginterferon alfa-2a in combination with higher doses of ribavirin than are currently recommended for these patients
- safety of these regimens in patients of African American descent.

The following requests were made by the EU:

- Provide a feasibility assessment evaluating the possible use of modelling and simulation techniques to extrapolate the expected safety and efficacy of higher ribavirin doses in HCV genotype 1 patients co-infected with HIV.
- Provide safety and tolerability information for the higher ribavirin dose and additional information regarding the impact of the higher ribavirin dose on the efficacy outcome for genotype 1 HCV-HIV co-infected patients.

As a first step in evaluating the proposed dose, a modelling and simulation exercise was conducted. Generalized Additive Models for predicting the sustained virological response and the incidence of anaemia had been developed based on data obtained from Phase III studies in patients with HCV mono-infection. These models were applied to the patient data from NR15961 in order to predict sustained virologic response and the incidence of anaemia in HIV/HCV genotype 1 co-infected patients after a 48 week treatment with a

daily dose of 1000/1200 mg of ribavirin. The results predicted that the response for this subgroup would be 37% and that anaemia would increase from the 14% observed with the 800 mg dose to 23% with the 1000/1200 mg dose. Although the incidence of anaemia was predicted to be higher, it was considered manageable.

Based on the modelled estimate, Study NV18209 was undertaken.

Good Clinical Practice

The conduct of the study was stated to be in full accordance with Good Clinical Practice (GCP). It was noted that there were critical concerns with one of five centres monitored and concerns with the remaining four centres.

Pharmacokinetics

No new data were submitted under this heading.

Drug Interactions

No new data were submitted under this heading.

Pharmacodynamics

No new data were submitted under this heading.

Efficacy

Study Protocol NV18209

Method

The study was Phase IV, international, multicentre with parallel-group design in which double-blinded allocation to ribavirin was centrally randomised 1:2 to Treatment A ribavirin 800 mg or Treatment B ribavirin 1000/1200, and stratified by geographical region, race and diagnosis of cirrhosis.

Primary Efficacy Objective

To evaluate the efficacy of Copegus 1000 or 1200 mg in combination with Pegasys 180 µg compared with the approved dose of Copegus 800 mg in combination with Pegasys 180 µg in patients with HCV genotype 1 infection co-infected with HIV-1, treated for 48 weeks and then followed for 24 weeks.

Primary Safety Objective

To evaluate the safety of treatment with Copegus 1000 or 1200 mg in combination with Pegasys 180 µg in comparison to the approved dose of Copegus 800 mg in combination with Pegasys 180 µg in patients with HCV genotype 1 infection co-infected with HIV-1, treated for 48 weeks and followed for 24 weeks.

Efficacy Endpoints

The primary efficacy end point, Sustained Virological Response, was defined as a last single undetectable HCV RNA determination (< 20 IU/mL) measured at the end of the 24-week follow-up period after the end of treatment, on or after study day 477. Patients without an HCV measurement at the end of the 24-week untreated follow-up period were considered non-responders

Study Treatment

The two groups were each treated with PEG-IFN alfa-2a 180 µg subcutaneously (SC) once a week.

Group A were treated with ribavirin 800 mg daily in divided doses (n = 135).

Group B were treated with ribavirin divided doses of 1000 or 1200 mg, based on patient weight of <75 kg or ≥ 75 kg respectively (n = 275).

Participants were treated for 48 weeks and followed for efficacy and safety for 24 weeks post treatment. Patients could discontinue ribavirin while remaining on PEG-IFN alfa-2a. However, if PEG-IFN alfa-2a was discontinued, the patient had to be discontinued from the study.

Systemic antiviral treatments with established or perceived activity against HCV, antineoplastic and immunomodulatory treatments (including steroids at supra-physiological doses and radiation) were not allowed during the study. Other drugs were excluded due to the potential for overlapping toxicities. The total daily dose of paracetamol was not to exceed 4 grams per day. Use of zidovudine was strongly discouraged as the combination has been associated with greater frequency of reports of severe neutropenia and severe anaemia.

In case of intolerance to study medication, dose adjustments and supportive therapy (such as erythropoietin for anaemia, granulocyte colony stimulating factor for neutropenia) were allowed. The use of growth factors to facilitate entry into the study was prohibited.

Blinding of Treatment

The protocol specified dose reduction of ribavirin in certain circumstances. Consideration was given to maintenance of blinding when dose reduction was required.

Compliance with Treatment

Compliance with treatment was documented in a patient held drug diary. Each PEG-IFN alfa-2a injection was recorded and initialled by the person administering the injection. For ribavirin, each missed or reduced dose was recorded and initialled. Patients were required to return used and unused study medication bottles.

Study Population

The study enrolled 415 males and females ≥ 18 years of age, with HCV genotype 1 infection and stable HIV-1 disease and with CD4+ cell count[2] ≥ 100/µL Participants were to have chronic liver disease consistent with chronic hepatitis C infection on a biopsy obtained within the previous 18 months as judged by a central pathologist. The study included up to 20% of patients with cirrhosis or incomplete cirrhosis.

The Child-Pugh total score at screening was to equal 5 for a patient with cirrhosis or bridging fibrosis/transition to cirrhosis for consideration and enrolment into the study. The only exception, and in keeping with protocol amendment approved after the commencement of the study, was an elevation in Child-Pugh total score of ≥ 6, secondary to total bilirubin due to concomitant medication (such as atazanavir and indinavir) or a clinical condition (such as Gilbert's syndrome). An elevation in Child Pugh total score of ≥ 6, secondary to low albumin, INR[3], ascites or hepatic encephalopathy was not acceptable.

[2] A measure of the number of "helper" T cells that carry the CD4 glycoprotein on their cell surface and that help B cells produce certain antibodies. The human immunodeficiency virus (HIV) binds to CD4 and kills T cells bearing this glycoprotein. Thus, the CD4 cell count is an indicator of the progress of an HIV infection and helps measure the effectiveness of anti-HIV drugs. CD4 T cells mainly produce interleukin 2, an autocrine and paracrine T cell growth factor; preactivated or memory CD4 T cells secrete a much larger array of lymphokines on restimulation

[3] International normalized ratio, a system established by the World Health Organization (WHO) and the International Committee on Thrombosis and Hemostasis for reporting the results of blood coagulation (clotting) tests.

Statistical methods

Primary Analysis Population: All Patients Treated included all patients randomized who received at least one dose of either study drug.

Primary Efficacy Objective Analysis: The Mantel-Haenszel estimate of the common odds ratio, adjusted by geographic region, cirrhotic status and non-Hispanic African-American race, with associated two-sided 95% confidence interval.

Sample sizes of 133 and 267 patients for Copegus 800 mg daily and Copegus 1000 or 1200 mg daily, respectively, provide the following probabilities of detecting the specified differences in sustained virological response (SVR)with 0.05 level two-sided chi-square test of significance: (Table 2 below)

Table 2. Probability of detecting differences

Copegus 800 mg SVR	Copegus 1000 or 1200 mg SVR	Probability
0.30	0.40	0.49
0.30	0.45	0.83

Analytic Methods

Analyses of HCV RNA

The detection and quantification of HCV RNA titers was conducted and all samples were analysed, in accordance with manufacturer instructions.

HCV Genotyping
Serum samples were collected at screening to determine HCV genotype.

Histological Evaluation of Pre-treatment Liver Biopsies
Histological evaluations were performed on pre-treatment and any optional post-treatment liver biopsies by a central pathologist and the results transmitted to the clinical database. Biopsies were evaluated in terms of the degree of periportal or periseptal interface hepatitis (piecemeal necrosis); confluent necrosis; focal lytic necrosis, apoptosis, and focal inflammation; portal inflammation; fat content; and fibrosis according to the Ishak-modified histological activity index (HAI) scoring system, which was provided in the protocol.

Protocol Amendments

The protocol was amended twice, both occurring after study commencement in June 2006. Arguably the most significant of the protocol revisions (dated April 30 2007) was an amended Child-Pugh Score screening criterion (score of < 6) and required additional visits for the subpopulation of cirrhotic patients with Child-Pugh score ≥ 6 who continued participation in the study. This was done in consultation with the FDA.

Results

Disposition of Patients

Of the 630 patients screened, a total of 415 patients were randomized to the two treatment arms: 138 in the PEG-IFN alfa-2a 180 µg + RBV 800 mg (RBV 800) group and 277 in the PEG-IFN alfa-2a 180 µg + RBV 1000/1200 group (RBV 1000/1200).

The proportions of patients who completed 12 and 24 weeks of treatment were similar between the two treatment groups. However by 48 weeks, the percentage of patients completing 48 weeks of treatment was lower in the RBV 800 group (43%) than in the RBV

1000/1200 group (48%) primarily due to patients prematurely discontinuing for insufficient therapeutic response and for adverse events (AEs). The percentage of patients who completed the follow-up visit was similar in the two treatment groups but lower than the 48 weeks of treatment (Table 3). An overview of the analysis populations is included in Table 4.

Premature Withdrawal from Treatment with PEG-IFN alfa 2a

The proportion of patients who were prematurely withdrawn from PEG-IFN alfa-2a treatment for either safety or non-safety reasons was 57% of the RBV 800 group and 52% of the RBV 1000/1200 group. Safety-related reasons for premature withdrawal from PEG-IFN alfa-2a were comparable in both treatment groups.

The proportion of reported premature withdrawals for non-safety-related reasons was 45% of the RBV 800 group and 40% of the RBV 1000/1200 group. The most frequent non-safety reason for premature withdrawals was insufficient therapeutic response with similar percentages in both treatment groups.

Premature Withdrawal from Treatment with Ribavirin
The proportion of patients who were prematurely withdrawn from ribavirin treatment for either safety or non-safety reasons and did not complete the 48 weeks of treatment was 58% of the RBV 800 group (58%) and 53% of the RBV 1000/1200 group. Safety-related reasons for premature withdrawal from RBV treatment were comparable in both treatment groups. The proportion of withdrawals for non-safety-related reasons was 45% of the RBV 800 group and 41% of the RBV 1000/1200 group.

Table 3. Disposition of Patients (All Patients Randomized)

Patient Disposition	PEG-IFN alfa-2a 180 ug + Ribavirin 800 mg		PEG-IFN alfa-2a 180 ug + Ribavirin 1000 or 1200 mg	
Patients randomized	138	100%	277	100%
Patients who received study drug	135	98%	275	99%
Patients who completed 12 weeks of treatment	120	89%	243	88%
Patients who completed 24 weeks of treatment	93	69%	196	71%
Patients who completed 48 weeks of treatment	58	43%	131	48%
Patients who completed 24 weeks of follow-up	55	41%	119	43%

NOTE: Patients who withdrew from treatment whose last HCV RNA measurement was undetectable were encouraged to return for their end-of-follow-up assessments at week 72. (For all other patients prematurely withdrawn, follow-up to week 72 was optional.) Thus the number of patients who completed follow-up may be higher than the number of patients who completed 24 or 48 weeks of treatment.

Table 4. Overview of Analysis Populations

	PEG-IFN alfa-2a 180 ug + Ribavirin 800 mg	PEG-IFN alfa-2a 180 ug + Ribavirin 1000 or 1200 mg
No. of Patients Randomized	138	277
No. Included in All Patients Randomized	138	277
No. Excluded from All Patients Randomized	-	-
No. Included in All Patients Treated	135	275
No. Excluded from All Patients Treated	3	2
NO INTAKE OF STUDY MEDICATION	3	2
No. Included in Per Protocol	120	241
No. Excluded from Per Protocol	18	36
LESS THAN 12 INJECTIONS OF PEGASYS AND TOTAL NUMBER OF DAYS ON COPEGUS THERAPY LESS THAN 84 DAYS	14	32
NO POST BASELINE HCV RNA ASSESSMENT	2	8
NO INTAKE OF STUDY MEDICATION	3	2
BASELINE HCV RNA TITER <=600 IU/ML	-	2
NO EVIDENCE OF HCV GENOTYPE 1 OR WITH MIXED GENOTYPE	-	1
PREVIOUS TREATMENT WITH IFN, PEGYLATED INTERFERON, LEVOVIRIN, VIRAMIDINE, INVESTIGATIONAL PROTEASE OR POLYMERASE INHIBITOR OR RIBAVIRIN	1	-
No. Included in Safety Population	135	274
No. Excluded from Safety Population	3	3
NO INTAKE OF STUDY MEDICATION	3	2
NO POST BASELINE SAFETY INFORMATION	-	1

Protocol Violations

Twelve percent of patients in both treatment groups had a protocol deviation, none of which resulted in the exclusion of the patient from the primary analysis population. The most common protocol deviation in both treatment groups was from the study entry criterion: absolute neutrophil count less than the protocol specified number. This protocol deviation was stated not to have any clinical impact.

Demographic Characteristics

The majority of patients were male (80%) and the median age was 46.0 years. The majority of patients were Caucasians; 64% of both groups. Approximately 25% of patients in both groups were Hispanic. In all parameters summarised in 5 below, the two groups appeared comparable.

Table 5. Summary of Demographic Characteristics (All Patients Treated)

	PEG-IFN alfa-2a 180 ug + Ribavirin 800 mg (N=135)	PEG-IFN alfa-2a 180 ug + Ribavirin 1000 or 1200 mg (N=275)
Sex		
n	135	275
MALE	106 79%	224 81%
FEMALE	29 21%	51 19%
Race		
n	135	275
CAUCASIAN	86 64%	176 64%
BLACK	46 34%	92 33%
AFRICAN AMERICAN	40 30%	79 29%
NON-AFRICAN AMERICAN	6 4%	13 5%
ASIAN	1 <1%	1 <1%
AMERICAN INDIAN OR ALASKA NATIVE	0 0%	4 1%
OTHER	2 1%	2 <1%
Ethnicity		
n	135	275
HISPANIC (LATINO)	33 24%	76 28%
NON-HISPANIC (NON-LATINO)	102 76%	199 72%
Race and Ethnicity		
n	135	275
NON-HISPANIC AFRICAN AMERICAN	40 30%	77 28%
OTHER	95 70%	198 72%
Age in years		
n	135	275
Mean	45.2	45.5
Std Dev	8.39	8.16
Std Error Mean	0.72	0.49
Median	46.0	46.0
Min - Max	19 - 66	20 - 67
Age in Subgroups		
<65 years	134 99%	273 99%
>=65 years	1 <1%	2 <1%
Weight in kg		
n	135	275
Mean	77.19	77.99
Std Dev	14.112	17.524
Std Error Mean	1.215	1.057
Median	76.90	77.00
Min - Max	41 - 118	45 - 167
Height in cm		
n	134	274
Mean	173.2	172.9
Std Dev	8.81	9.11
Std Error Mean	0.76	0.55
Median	173.0	173.0
Min - Max	147 - 195	149 - 198

	PEG-IFN alfa-2a 180 ug + Ribavirin 800 mg (N=135)	PEG-IFN alfa-2a 180 ug + Ribavirin 1000 or 1200 mg (N=275)
Body Surface Area in sqm		
n	134	274
Mean	1.910	1.907
Std Dev	0.1921	0.2182
Std Error Mean	0.0166	0.0132
Median	1.915	1.900
Min - Max	1.36 - 2.43	1.42 - 2.93
Body Mass Index in kg/sqm		
n	134	274
Mean	25.786	25.897
Std Dev	3.9559	4.7378
Std Error Mean	0.3417	0.2862
Median	25.554	25.059
Min - Max	17.30 - 40.29	17.11 - 49.95

n represents number of patients contributing to summary statistics.

Baseline Disease Characteristics

The baseline serum alanine aminotransferase (ALT), diagnosis of cirrhosis and mode of HCV infection were comparable among patients from the two treatment groups. Almost 80% of patients in each group had HCV genotype 1a and approximately 20% had HCV genotype 1b.

Baseline median HCV RNA titre was higher in the RBV 1000/1200 group than in the RBV 800 group: 4320 x 10^3 IU/mL versus 3465 x 10^3 IU/mL respectively.

Fifty-five percent of both groups were in the intravenous drug use group with nearly 25% reporting homosexual contact as the secondary HIV risk. The mean time since HIV diagnosis was similar: 12.5 and 11.5 years for the RBV 800 group and RBV 1000/1200 group, respectively. More patients were diagnosed with AIDS in the RBV 800 group (55%) than in the RBV 1000/1200 group (46%). The mean number of years since acquired immune deficiency syndrome (AIDS) diagnosis was approximately 8.25 in both groups. The percentage of patients with a history of AIDS-defining events was the same in both treatment groups

The majority of patients (93% and 92%) received antiretroviral therapy (ART) prior to the study. Approximately 88% of patients in both treatment groups were receiving ART at baseline with similar use between groups. During the study, 91% of both groups received ART and the use was well balanced. The use of zidovudine, which was discouraged in the study, fell from ~ 20% at baseline to ~ 16% during the progress of the study.

The majority of patients took concomitant medication both at baseline and during the conduct of the study. Non-ART medications were taken at baseline by ≥ 10% of patients in both groups included vitamins and minerals, selective serotonin re-uptake inhibitors, antidepressants, non-steroidal anti-inflammatories, benzodiazepines, opioid analgesics, analgesics and antihistamines. The most frequently used class of concomitant medications were analgesics, non-steroidal anti-inflammatory agents, vitamins and minerals, and selective serotonin re-uptake inhibitors.

Efficacy Results

There was no statistical difference detected in SVR: 19% in the RBV 800 group versus 22% in the RBV 1000/1200 group. The odds ratio was 1.15 (95% CI: 0.68, 1.93)

Clinical evaluator comment

Although one of the co-primary objectives related to efficacy, the study design was not conducive to determining a significant difference in efficacy of the two treatment regimens; power and sample size calculations were not done based on the expected difference in results and the study had only 49% power to detect a true difference of 10%. In addition, less than one half of patients remained at the end of the study, one quarter of both groups prematurely discontinued the study because of insufficient therapeutic response, between 8% and 13% of patients failed to return and 4% to 5% refused treatment. On the basis of these considerations, the main utility of the study to the evaluator would appear be to assess safety.

For the two treatment regimens the reported efficacy was not significantly different. The proportions with sustained virological response in this study were less than that reported in Study NR15961 and less than anticipated using the modelling and simulation exercise using the Generalized Additive Models applied to the patient data from NR15961. The sponsor speculated that this may have been due to enrolment of patients with known characteristics associated with poorer prognosis: enrolment only of patients infected with HCV genotype 1 and inclusion of a substantial minority of non-Hispanic African American patients who were also generally heavier, older, had higher baseline HCV RNA titres and were more often diagnosed with AIDS than the all treated patient population.

Safety

Introduction

All patients were to be assessed for safety at all study visits during treatment and follow-up. Patients who prematurely discontinued the study and who had evidence of a virological response were expected to return for their regular scheduled visits at Weeks

48 and 72. Female patients of reproductive age were to continue pregnancy testing at four week intervals for a total of six months after stopping study medications. Safety data was reviewed by an independent safety review board.

In reviewing safety the evaluator was mindful that the submitted study assessed safety of combined treatment of chronic hepatitis C and HIV-1 infection and while pegylated interferon alfa has an established adverse event profile, it would not be entirely possible to attribute adverse events reported in the study, to use of one medication alone. [4]

Patient exposure

Duration of treatment and cumulative dose of study drugs is summarised in Table 6 below.

Table 6. Duration of treatment and cumulative dose of study drugs (Safety Population)

	PEG-IFN alfa-2a 180 ug + Ribavirin 800 mg (N=135)	PEG-IFN alfa-2a 180 ug + Ribavirin 1000 or 1200 mg (N=274)
Duration of Treatment (weeks)		
1 - 4	135 100%	274 100%
5 - 8	128 95%	258 94%
9 - 12	122 90%	249 91%
13 - 16	117 87%	239 87%
17 - 20	104 77%	221 81%
21 - 24	97 72%	206 75%
25 - 28	88 65%	192 70%
29 - 32	79 59%	170 62%
33 - 36	70 52%	156 57%
37 - 40	65 48%	146 53%
41 - 44	64 47%	139 51%
45 - 48	60 44%	134 49%
Cumulative PEG-IFN alfa-2a (ug) Dose		
N	135	274
Mean	5710	5984
Std Dev	2821	2799
Std Error Mean	243	169
Median	6435	7020
Min - Max	180 - 8820	180 - 8820
Cumulative Ribavirin (mg) Dose		
N	135	274
Mean	173990	252842
Std Dev	87361	125228
Std Error Mean	7519	7565
Median	179000	272200
Min - Max	4800 - 270800	1000 - 438000

NOTE: Patients who had treatment interrupted and then resumed treatment are included as having received treatment for the full period of time.

Adverse Events

Most patients in both treatment groups reported at least one adverse event (AE), regardless of relationship (96% to 98%). In the RBV 800 group and the RBV 1000/1200 group, 27% and 21% of patients, respectively, experienced severe adverse events; 16% and 17%, respectively reported serious adverse events (SAEs), with 2% and 1%, respectively, considered life-threatening by intensity (Table 7).

The frequency of SAEs and related SAEs were similar in both treatment groups. The percentage of patients who required dose modification of the PEG-IFN alfa-2a dose due to AEs or laboratory AEs was similar in both treatment groups. However, a greater

[4] In some cases the clinical evaluator was not sure if the data in the tables in the Safety section referred to the Safety population or not as the title at times indicated that patients that completed the 48 weeks of treatment were included in the analysis rather than those who received one dose of study medication.

percentage of patients in the RBV 1000/1200 group required dose modification of their ribavirin dose compared to the RBV 800 group (27% versus 21%, respectively). A similar percentage of patients in the two treatment groups withdrew from the study due to safety issues (Table 7).

Table 7. Overview of adverse events during Treatment and 24 Weeks Post-treatment (Safety Population)

	PEG-IFN alfa-2a 180 µg + RBV 800 mg N = 135 (%)	PEG-IFN alfa-2a 180 µg + RBV 1000/1200 mg N = 274 (%)
No. of Pts with Any AE	132 (98%)	264 (96%)
Severe AEs	36 (27%)	57 (21%)
Life-threatening AEs	3 (2%)	4 (1%)
Related AEs[a]	129 (96%)	258 (94%)
AIDS-defining events	0	4 (1%)
SAEs	21 (16%)	46 (17%)
Related SAEs[a]	11 (8%)	16 (6%)
Deaths		
During treatment	0	1
During follow-up	0	1
Premature withdrawals for AEs, laboratory AEs, or AIDS-defining events		
PEG-IFN alfa-2a	16 (12%)	33 (12%)
RBV	17 (13%)	34 (12%)
Dose modification for AEs and laboratory AEs[b]		
PEG-IFN alfa-2a	30 (22%)	54 (20%)
RBV	28 (21%)	75 (27%)

[a]Events judged by the investigator to be remotely, possibly, or probably related to treatment.
[b]Patients who had a dose withheld or reduced for an administrative reason are not included in this table. Patients who had treatment permanently discontinued but who did not have the dose of study drug modified before discontinuation of treatment are also not included in this table.

The most frequently observed types of disorders in both study groups were: general disorders and administration site conditions, gastrointestinal disorders, psychiatric disorders, nervous system disorders, infections and infestations, blood and lymphatic system disorders and musculoskeletal and connective tissue disorders (Table 8).

The AEs occurring in ≥ 5% of patients in any of the two treatment groups were those known to be associated with interferon therapy. Among the most common were flu-like symptoms such as fatigue, pyrexia, chills, headache, myalgia, arthralgia, nausea, vomiting, diarrhoea and asthenia. Psychiatric disorders such as insomnia, depression, and anxiety, as well as irritability, were also frequently reported AEs. The incidence of these interferon-associated AEs was similar in the two treatment groups. Neutropenia was reported in a similar percentage in both treatment groups (24% in the RBV 800 group and 23% in the RBV 1000/1200 group). However, clinically significant anaemia was reported in proportionately fewer patients in the RBV 800 group compared with the RBV 1000/1200 group (24% versus 32%, respectively).

AEs associated with HIV disease or ART, such as peripheral neuropathy, oral candidiasis, and acquired lipodystrophy, occurred with similar frequency in the two treatment groups.

Most patients in both treatment groups experienced AEs that were assessed as remotely, possibly, or probably related to treatment by the investigator (96% to 94%) and the majority of AEs reported in the both study groups were reported to be either mild or moderate in intensity. Some 27% and 21% of patients in the RBV 800 mg and RBV 1000/1200 groups, respectively, experienced severe AEs.

Table 8. Summary of Most Frequent AEs (at Least 5% of Patients) Grouped by Body System during Treatment and 24 Weeks Post-treatment (Safety Population)

Body System/ Adverse Event	PEG-IFN alfa-2a 180 ug + Ribavirin 800 mg N = 135 No. (%)	PEG-IFN alfa-2a 180 ug + Ribavirin 1000 or 1200 mg N = 274 No. (%)
ALL BODY SYSTEMS		
Total Pts with at Least one AE	132 (98)	264 (96)
Total Number of AEs	1166	2387
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS		
Total Pts With at Least one AE	105 (78)	211 (77)
FATIGUE	64 (47)	129 (47)
PYREXIA	36 (27)	63 (23)
CHILLS	26 (19)	44 (16)
IRRITABILITY	20 (15)	32 (12)
PAIN	14 (10)	32 (12)
ASTHENIA	14 (10)	29 (11)
MALAISE	8 (6)	18 (7)
GASTROINTESTINAL DISORDERS		
Total Pts With at Least one AE	79 (59)	166 (61)
NAUSEA	35 (26)	69 (25)
DIARRHOEA	31 (23)	60 (22)
VOMITING	20 (15)	25 (9)
ABDOMINAL PAIN	8 (6)	13 (5)
DYSPEPSIA	4 (3)	17 (6)
CONSTIPATION	7 (5)	10 (4)
PSYCHIATRIC DISORDERS		
Total Pts With at Least one AE	65 (48)	149 (54)
INSOMNIA	35 (26)	78 (28)
DEPRESSION	30 (22)	68 (25)
ANXIETY	16 (12)	26 (9)
NERVOUS SYSTEM DISORDERS		
Total Pts With at Least one AE	70 (52)	139 (51)
HEADACHE	48 (36)	93 (34)
DIZZINESS	17 (13)	30 (11)
INFECTIONS AND INFESTATIONS		
Total Pts With at Least one AE	52 (39)	139 (51)
UPPER RESPIRATORY TRACT INFECTION	8 (6)	27 (10)
URINARY TRACT INFECTION	5 (4)	16 (6)
BRONCHITIS	9 (7)	10 (4)
BLOOD AND LYMPHATIC SYSTEM DISORDERS		
Total Pts With at Least one AE	58 (43)	127 (46)
ANAEMIA	33 (24)	89 (32)
NEUTROPENIA	32 (24)	62 (23)
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS		
Total Pts With at Least one AE	70 (52)	113 (41)
MYALGIA	39 (29)	53 (19)
ARTHRALGIA	23 (17)	38 (14)
BACK PAIN	16 (12)	19 (7)
MUSCLE SPASMS	8 (6)	9 (3)

Table 8 continued.

SKIN AND SUBCUTANEOUS TISSUE DISORDERS		
Total Pts With at Least one AE	50 (37)	118 (43)
RASH	12 (9)	26 (9)
ALOPECIA	9 (7)	19 (7)
DRY SKIN	9 (7)	17 (6)
PRURITUS	5 (4)	21 (8)
NIGHT SWEATS	7 (5)	10 (4)
HYPERHIDROSIS	7 (5)	8 (3)
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS		
Total Pts With at Least one AE	39 (29)	92 (34)
COUGH	10 (7)	25 (9)
DYSPNOEA	10 (7)	25 (9)
EPISTAXIS	3 (2)	14 (5)
METABOLISM AND NUTRITION DISORDERS		
Total Pts With at Least one AE	39 (29)	85 (31)
DECREASED APPETITE	34 (25)	61 (22)
INVESTIGATIONS		
Total Pts With at Least one AE	26 (19)	57 (21)
WEIGHT DECREASED	21 (16)	50 (18)

Investigator text for Adverse Events encoded using MedDRA version 11.1.
Percentages are based on N.
Multiple occurrences of the same adverse event in one individual counted only once.

The overall reporting frequency of depression occurring during treatment and the 24 weeks of follow-up was 22% for the RBV 800 group and 27% for the RBV 1000/1200 group (Table 9). Severe depression was reported in five patients in the RBV 800 group and three patients in the RBV 1000/1200 group and serious depression was reported in < 1% of patients in both groups. In patients who became depressed, between 17% and 20% in the two treatment groups received anti-depressant therapy and the majority of reported events of depression were assessed by the investigator as remotely, possibly, or probably related to study drug (87% and 93%, respectively). Three patients, all in the RBV 1000/1200 mg treatment group had their dose of study drug modified or discontinued due to depression. The incidence of premature withdrawal from treatment due to depression was 3% and 1%.

Table 9. Incidence and Severity of Depression during Treatment and 24 Weeks Post-treatment (Safety Population)

	PEG-IFN alfa-2a 180 ug + Ribavirin 800 mg (N=135)		PEG-IFN alfa-2a 180 ug + Ribavirin 1000 or 1200 mg (N=274)	
No. of pts with depression(a)	30	22%	73	27%
Severe depression	5	4%	3	1%
Life-threatening depression	0	0%	0	0%
Serious depression	1	<1%	2	<1%
Treatment for depression	23	17%	54	20%
Dose modified for depression	0	0%	3	1%
Suicidal ideation	1	<1%	1	<1%
Suicide attempt	1	<1%	0	0%
Suicide	0	0%	1	<1%
Premature withdrawals for depression-related events(b)	4	3%	3	1%

(a)Depression includes the following terms: BIPOLAR DISORDER; CRYING; DEPRESSED MOOD; DEPRESSION; DISSOCIATION; MAJOR DEPRESSION.
(b)Withdrawals for any of the depression-related events (ie, depression and/or suicidal ideation, suicide attempt, or suicide).

Deaths

Two patients died during treatment or follow-up, both in the 1000/1200 mg RBV group. The causes of the deaths were lung adenocarinoma and completed suicide, both of which were considered by the investigator to be unrelated to the study treatment.

Serious adverse events

The percentages of patients experiencing SAEs were 16% and 17% in RBV 800 mg and the RBV 1000/1200 groups, respectively. Serious adverse events considered by the investigator to be at least remotely related to treatment were reported in 8%, and 6% of patients in the RBV 800 and RBV 1000/1200 groups respectively.

The most common serious adverse events were reported in the system organ classes (SOCs): Infections and infestations (7% and 5%), Blood and lymphatic system disorders (4% and 4%), and Gastrointestinal disorders (2% and 2%). Other than anaemia, all individual SAEs were reported at < 1% in either treatment group.

Serious blood and lymphatic system disorders occurred in 4% of patients in both treatment groups. Serious anaemia was reported in five patients (4%) in the RBV 800 group and in eight patients (3%) in the RBV 1000/1200 group. Serious haemolytic anaemia was reported by two patients from the RBV 1000/1200 group. Serious thrombocytopenia occurred in two patients, one in each of the two treatment groups and one patient experienced serious autoimmune thrombocytopenia (RBV 1000/1200 group). One patient in the RBV 800 group developed pancytopenia. There were no reports of serious neutropenia.

Serious infections were reported by 9 (7%) patients in the RBV 800 group and 15 (5%) patients in the RBV 1000/1200 group. A variety of different types of serious infections were observed and the majority of these were confirmed or presumed to be bacterial in nature. There were no fungal infections and no opportunistic infections reported. The presence of infectious organisms was confirmed by a positive culture in 13 patients with bacterial infection. One patient was confirmed to have a viral infection (Influenza B virus).

The most common serious infection was pneumonia which was reported in two patients from the RBV 800 group and two patients from the RBV 1000/1200 group. The next most frequent serious infection was bronchitis which occurred in one patient in the RBV 800 group and two patients in the RBV 1000/1200 group. Only one of the 27 reported serious infections were considered to be at least remotely related to treatment.

Serious anaemic events were observed in 4% in the RBV 800 group and 3% in the RBV 1000/1200 group. Two patients in each group reported serious haemolytic anaemia, both in the RBV 1000/1200 group.

All but one of the serious anaemia events were assessed as at least remotely related to study drug treatment. The event of worsening anaemia in one patient treated with RBV 1000/1200 mg was assessed as unrelated to study drug and resolved without sequelae but the patient withdrew from the study.

Six patients withdrew from the study due to serious anaemic events including one patient in the RBV 800 group and five in the RBV 1000/1200 group. Four of the patients were also treated with zidovudine including one patient in the RBV 800 group and three in the RBV 1000/1200 group.

The total number of patients with at least one treatment was similar between groups however the percent treated with haematopoietic stimulants was less in the RBV 800 mg group than in the RBV 1000/1200 group; 22% versus 31%, respectively.

The percentage of patients who received transfusions during treatment and follow-up was similar in both treatment groups: 6% in the RBV 800 mg treatment group and 7% in the RBV 1000/1200 mg treatment group.

A total of five serious cardiovascular events were reported during treatment and the 24 weeks of follow-up, two in the RBV 800 group and three in the RBV 1000/1200 group. All events were considered unrelated to study drug. However, two events were associated with a haemoglobin concentration below 10 g/dL, suggesting the possibility that drug-induced anaemia could have been a precipitating factor in these patients. In both treatment groups, there was only one serious cardiovascular event, pericarditis, which lead to modification or discontinuation of study drug dose.

Withdrawal for adverse events

PEG-IFN alfa-2a: The same percentages of patients in the two treatment groups were prematurely withdrawn from PEG-IFN alfa-2a treatment for AEs, laboratory AEs, or AIDS-defining events (12%). Blood and lymphatic system disorders, most frequently anaemia, were the most common reason for premature treatment withdrawal and accounted for the premature withdrawal of 4% of patients in each of the two treatment groups.

Ribavirin: The percentage of patients who were prematurely withdrawn from RBV treatment for AEs, laboratory AEs, or AIDS-defining events was 13% in the RBV 800 group and 12% in the RBV 1000/1200 group. As with the premature withdrawal of PEG-IFN treatment, blood and lymphatic system disorders, in particular anaemia, were the most common reason for premature treatment withdrawal and accounted for the premature withdrawal of 4% of patients in each of the two treatment groups.

Dose modification for adverse events

Dose modifications were defined as one or more doses of study drugs that were temporarily or permanently reduced or withheld for safety reasons. Patients who had treatment prematurely discontinued for safety reasons but did not have the dose of study drug modified before discontinuation are not included as having a dose modification of study drugs.

It should be noted that laboratory AEs were collected on the adverse event page of the eCRF and appear in the AE tables in this report, only if they were serious, led to premature discontinuation of study drug, or required treatment with medication or modification of ongoing concomitant medication.

PEG-IFN alfa-2a: A comparable percentage of patients in the RBV 800 and the RBV 1000/1200 group (22% and 20%, respectively) had their PEG-IFN alfa-2a dose modified for AEs or laboratory AEs.

Laboratory variables

Changes from baseline

In the two treatment groups, mean and median white blood cell, lymphocyte, and neutrophil counts decreased during treatment as did mean and median platelet counts and haemoglobin concentrations. At the end of treatment, these results returned to, or close to baseline levels, for platelets and lymphocytes.

The most common marked haematological laboratory abnormalities included low haematocrit, haemoglobin, low white blood cell counts, and low platelets. The proportion of patients with markedly low haematocrit (24% versus 35%) and haemoglobin (32% versus 45%) was higher in the treatment group with a higher dose of RBV. However, the same percentage of patients with markedly low white blood cell counts occurred in both

treatment groups (79%) and the proportion of patients with markedly low platelets (35% versus 28%) was higher in the RBV 800 group.

For both treatment groups, mean and median values of most clinical chemistry parameters did not change, or only changed slightly, remaining within normal ranges during treatment. Exceptions were ALT and aspartate aminotransferase (AST) activity and triglyceride concentrations. In both treatment groups, mean and median ALT and AST concentrations were elevated at baseline, decreased to normal during treatment and were within the normal range or slightly above by the end of treatment and follow-up. In both treatment groups, mean fasting triglyceride concentrations were mildly elevated at baseline, increased during treatment, and remained slightly above the normal range at the end of treatment and follow-up. However, median fasting triglyceride levels in the two treatment groups were within normal range at baseline, increased during treatment, and were within the normal range by the end of treatment follow-up.

The most common marked biochemical laboratory abnormalities included high serum ALT, serum AST activity, indirect bilirubin, total bilirubin count, low phosphate, and calcium but these abnormalities were similar in the two treatment groups.

Laboratory abnormalities associated with study treatment

Neutropenia

The median neutrophil counts decreased rapidly from baseline during the first four weeks of study treatment; to between 1.27 x 10^9 cells/L (RBV 800 group) and 1.52 x 10^9 cells/L (RBV 1000/1200 group). The decrease was similar in both treatment groups. Following the initial decrease, neutrophil counts stabilized for the remainder of the respective treatment periods and remained at approximately 1.48 x 10^9 cells/L to 1.57 x 10^9 cells/L, respectively. Median neutrophil counts increased rapidly after the end of the scheduled treatment and had returned to levels close to their baseline values by Week 52 in both groups (2.10 x 10^9 cells/L in the RBV 800 group and 2.24 x 10^9 cells/L in the RBV 1000/1200 group). At Week 72, median neutrophil counts in both treatment groups were slightly above baseline.

Between 89% to 93% of the two treatment groups had baseline neutrophil counts > 1.5 x 10^9 cells/L. Baseline neutrophil counts in most of the remaining patients were between 1 and 1.5 x 10^9 cells/L (Grade 1[5]). Two patients in the RBV 800 group and one patient in the RBV 1000/1200 group had a baseline neutrophil count that was at least 0.75 x 10^9 cells/L and less than 1.0 x 10^9 cells/L (Grade 2). The percentage of patients who experienced a three-grade decrease from baseline in neutrophil counts during the study was between 20% and 23%. Fourteen percent of patients in the RBV 800 group and 7% of patients in the RBV 1000/1200 group experienced a four-grade shift from a normal baseline in neutrophil count. Similar percentages of patients in both groups had no change in their neutrophil count grade during the study.

The percentage of patients whose lowest neutrophil count was < 0.75 x 10^9 cells/L at some time during treatment or follow-up was 39% in the RBV 800 group and 31% in the RBV 1000/1200 group. The percentage of patients with a lowest neutrophil count of < 0.5 x 10^9 cells/L during treatment or follow-up was 18% and 9% in the RBV 800 group and the RBV 1000/1200 group, respectively.

An overview of neutropenia occurring during the study is provided in Table 10. Overall, the two groups were similar in percentages of patients with incidences of AEs, SAEs, dose modifications of either PEG-IFN alfa-2 or RBV, premature withdrawal of either PEG-IFN alfa-2 or RBV leading to withdrawal from treatment and use of growth factors for

[5] AIDS Clinical Trials Group (ACTG) grading

neutropenia. Patients with neutropenia were clinically managed by temporary or permanent reduction of their PEG-IFN alfa-2a dose and/or the use colony stimulating factors (which were administered to 24% of patients in the RBV 800 group and 23% in the RBV 1000/1200 group).

Table 10. Overview of neutropenia (Safety Population)

	PEG-IFN alfa-2a 180 µg RBV 800 mg (N = 135)	PEG-IFN alfa-2a 180 µg RBV 1000/1200 mg (N = 274)
No. of patients with neutrophil counts		
< 0.75 x 10^9/L	29 (21%)	59 (22%)
< 0.50 x 10^9/L	24 (18%)	24 (9%)
No. of patients with dose modification of study treatment for neutropenia[a]		
PEG-IFN alfa-2a	20 (15%)	34 (12%)
RBV	1 (<1%)	5 (2%)
No. of patients prematurely withdrawn from treatment for neutropenia		
PEG-IFN alfa-2a	-	1 (<1%)
RBV	-	1 (<1%)
No. of patients with neutropenia		
Clinical adverse event[c]	32 (24%)	62 (23%)
Serious adverse event[c]	-	-
No. of patients receiving growth factors for neutropenia	33 (24%)	64 (23%)

[a] Excludes patients with no dose modification of study treatment for neutropenia before premature withdrawal for neutropenia.
[b] Excludes patients prematurely withdrawn for neutropenia.
[c] Neutropenia that was serious, led to withdrawal from treatment, or resulted in treatment with a concomitant medication or modification of an ongoing concomitant medication.

Thrombocytopenia

Median platelet counts for patients in both groups who received 48 weeks of treatment, decreased during the first 8 weeks of study treatment to between 132 x 10^9 cells/L and 140 x 10^9 cells/L, and then stabilized at approximately 60% of their baseline values for the remainder of the treatment period. In both treatment groups, median platelet counts had increased and were close to their baseline levels by Week 52 (176.5 x 10^9 cells/L to 187 x 10^9 cells/L).

Most of the patients (97%) in both treatment groups had baseline platelet counts > 99 x 10^9 cells/L (ACTG grade 0). Baseline platelet counts in most of the remaining patients were between 75 and 99 x 10^9 cells/L (Grade 1). The percentage of patients who experienced a three-grade decrease from a normal baseline in platelet counts during the study was the same in both treatment groups (5%). In addition, one patient in the RBV 800 group and two patients in the RBV 1000/1200 group experienced a four-grade shift from a normal baseline in platelet counts. The percentage of patients with no change was 64% in the RBV 800 group and 70% of patients in the RBV 1000/1200 group.

Seven percent of both group had a lowest observed platelet count of < 50 x 10^9 cells/L. A decrease in platelet count to < 20 x 10^9 cells/L experienced two patients in each group was considered by the investigator as related to study treatment.

An overview of thrombocytopenia during the study is provided in Table 11. The majority of patients with thrombocytopenia in the two treatment groups were clinically managed by temporary or permanent reduction of either their PEG-IFN alfa-2a or the RBV doses. In the overall safety population, two patients in the RBV 800 group received platelet transfusions. Three patients were prematurely withdrawn from treatment for thrombocytopenia (two patients in the RBV 800 group and one patient in the RBV 1000/1200 group).

Thrombocytopenia considered to be serious and which led to withdrawal from treatment and resulted in treatment with a concomitant medication or modification of an ongoing concomitant medication occurred in the same percentage of patients in the two treatment groups. Three patients experienced serious thrombocytopenia, two of which had associated bleeding episodes (epitaxis and ecchymosis).

Table 11. Overview of thrombocytopenia (Safety Population)

	PEG-IFN alfa-2a 180 µg RBV 800 mg (N = 135)	PEG-IFN alfa-2a 180 µg RBV 1000/1200 mg (N = 274)
No. of patients with platelet counts		
<50 x 10^9/L	10 (7%)	18 (7%)
<20 x 10^9/L	2 (1%)	2 (<1%)
No. of patients with dose modification of study treatment for thrombocytopenia[a]		
PEG-INF-IFN alfa-2a	5 (4%)	5 (2%)
Ribavirin	0 (0%)	3 (1%)
No. of patients prematurely withdrawn from treatment for thrombocytopenia		
PEG-IFN alfa-2a	2 (1%)	1 (<1%)
Ribavirin	2 (1%)	1 (<1%)
No. of patients with thrombocytopenia		
Clinical adverse event	4 (3%)	1 (<1%)
Serious adverse event[b]	1 (<1%)	2 (<1%)
No. of patients receiving platelet transfusions for thrombocytopenia	2 (1%)	0 (0%)

[a]Excludes patients who did not have the dose of study drug modified for thrombocytopenia before being prematurely withdrawn for thrombocytopenia.
[b]Includes autoimmune thrombocytopenia

Anaemia and haemoglobin concentration

In both groups, median haemoglobin concentrations in patients who completed 48 weeks of treatment, declined within the first 4 weeks of treatment to between 13.4 g/dL and 12.7 g/dL and then stabilized at more than 80% of their baseline values during the remainder of the respective treatment periods. Median haemoglobin concentrations increased rapidly after the end of the scheduled treatment and returned to close to their baseline levels by Week 52 (13.9 g/dL to 13.5 g/dL).

All patients in both groups had baseline haemoglobin concentrations > 9.4 g/dL, (Grade 0). In patients treated with RBV 800 mg and RBV 1000/1200 mg, 7% and 14%, respectively, experienced a Grade 1 shift (8 - 9.4 g/dL) and 2% and 4%, respectively, experienced a Grade 2 shift (7 - 7.9 g/dL) from baseline in haemoglobin concentration during the study. Few patients in either treatment group experienced a Grade 3 or Grade 4 shift from baseline in haemoglobin concentration. Most patients (78% to 88%) in the two treatment groups had no change in grade from baseline in haemoglobin concentration during the study.

The percentage of patients whose lowest haemoglobin concentration was < 10 g/dL, and ≤ 8.5 g/dL at some time during treatment or follow-up, was lower in the 800 mg RBV group compared to the 1000/1200 mg RBV treatment group (10% and 4% versus 19% and 9%, respectively). Anaemia was reported in 24% of the RBF 800 group and 32% of the RBV 1000/1200 group. All anaemia events were assessed by the investigator as remotely, possibly, or probably related to treatment. (Table 12)

Few patients, 2% and 3% in the two treatment groups, had their PEG-IFN alfa-2a dose modified for AEs or laboratory abnormalities of anaemia. However, a larger percentage of patients with anaemia in the RBV 1000/1200 mg dose group had their ribavirin dose modified for AEs or laboratory abnormalities (10% and 18% in the RBV 800 mg and RBV 1000/1200 groups, respectively,).

Premature withdrawal from PEG-IFN alfa-2a treatment in patients with anaemia occurred in 1% and 3% of patients in the RBV 800 and RBV 1000/1200 groups, respectively. Premature withdrawal from ribavirin occurred in 2% of the RBV 800 group and 3% of the RBV 1000/1200 group. In the two treatment groups, patients with anaemia were clinically managed with the use of growth factors and transfusions (administered to 26% and 37% of patients in the RBV 800 and RBV 1000/1200 groups, respectively). Dose modification of either study treatment was used in 13% and 21% of patients, respectively (Table 12).

Table 12. Overview of Anaemia (Safety Population)

	PEG-IFN alfa-2a 180 µg RBV 800 mg (N = 135)	PEG-IFN alfa-2a 180 µg RBV 1000/1200 mg (N = 274)
No. of patients with anemia*		
Clinical adverse event*	33 (24%)	89 (32%)
Serious adverse event*	5 (4%)	10 (4%)
No. of patients with dose modification of study treatment for anemia		
PEG-INF alfa-2a	3 (2%)	7 (3%)
Ribavirin	14 (10%)	49 (18%)
No. of patients prematurely withdrawn from treatment for anemia		
PEG-IFN alfa-2a	2 (1%)	8 (3%)
Ribavirin	3 (2%)	8 (3%)
No. of patients receiving treatment for anemia		
Hematopoietic Stimulants	30 (22%)	85 (31%)
Transfusions	6 (4%)	17 (6%)
No. of patients with hemoglobin		
< 10 g/dL	13 (10%)	53 (19%)
< 8.50 g/L	6 (4%)	25 (9%)
< 6.5 g/dL	2 (1%)	4 (1%)

* Anemia events included hemolytic anemia, aplasia pure red cell, and pancytopenia.

Serum ALT

Mean serum ALT activity decreased rapidly from baseline during the first 4 weeks of study treatment in both treatment groups. Following the initial decrease, serum ALT activity stabilized for the remainder of the treatment and follow-up periods. At the Week 72 follow-up visit, mean serum ALT values in both groups were approximately 50% lower than baseline values.

ALT activity was examined using the ACTG grading system and assessing the worst change from baseline by grade at any time during treatment or follow-up. Approximately half of the patients (54% to 56%) in the treatment groups had baseline ALT levels that were Grade 1 (1.25 to 2.5 times upper limit of normal (ULN)) or Grade 2 (2.5 to 5 times ULN). None of the patients who experienced elevated ALT activity during treatment and follow-up required a dose modification of their study drug or premature withdrawal from treatment

Body weight

Decreases in body weight were noted more often than increases in both treatment groups. A decrease in body weight of ≥ 10% during treatment and follow-up was observed in 24% of patients in the RBV 1000/1200 group and 20% of subjects in the RBV 800 group. An increase ≥ 10% was observed in 5% and 2% of patients, respectively.

Vital signs

Very few patients (≤ 1%) in either treatment groups experienced abnormalities of potential clinical significance in blood pressure or pulse rate during the treatment period and follow-up. No patients were prematurely withdrawn from the study for vital sign abnormalities.

AIDS-defining events

The incidence of AIDS-defining events during treatment and follow-up was low: four patients, all in the RBV 1000/1200 group, experienced one event each. Three of the four AIDS-defining events that occurred were mild, with two considered possibly related and one unrelated to treatment. The fourth, a patient with Burkitt's lymphoma, was considered severe and unrelated to treatment. None of the patients who experienced AIDS-defining events had their doses adjusted or discontinued.

HIV-RNA

Mean changes from baseline in HIV-1 RNA titre were examined in patients who received 48 weeks of HCV treatment. In these patients, a decrease from baseline in mean HIV-1 RNA titres of between 0.2 to 0.3 log10 copies/mL was observed during the 48 weeks of HCV treatment in both RBV dose groups. At the end of treatment, mean HIV RNA titres increased to baseline levels in the RBV 1000/1200 group and remained close to baseline levels over the 24 week post-treatment period.

No mean increases from baseline in HIV RNA titres were seen in the two treatment groups. Thus, antiretroviral therapy continued to control HIV disease and HCV treatment appeared to have no apparent adverse effect on HIV status.

In the subgroup of patients who had detectable HIV-1 RNA titres at baseline and received 48 weeks of HCV treatment, a decrease from baseline in mean HIV-1 RNA titres of 0.6 to 1.09 log10 copies/mL was observed during the 48 weeks of HCV treatment in the RBV 800 group (n=17) and 0.4 to 0.9 log10 copies/mL in the RBV 1000/1200 group (n=32). At the end of 48 weeks treatment, mean HIV-1 RNA titres had increased to baseline levels in the RBV 1000/1200 group and remained close to mean baseline levels over the 24-week post-treatment period. However, in the RBV 800 group titres had increased toward baseline levels at Week 52 but then decreased over the rest of the post-treatment period.

In the subgroup of patients who had undetectable HIV-1 RNA titres at baseline and received 48 weeks of treatment, mean HIV-1 RNA titres increased very slightly over the 72 weeks of the study, with no meaningful differences between the treatment groups.

Total lymphocyte count

In patients who received 48 weeks of treatment, the median change from baseline in total lymphocyte counts decreased rapidly from baseline values during the first eight weeks of treatment but then decreased more slowly until approximately Week 24 in both treatment groups. After Week 24, the total lymphocyte counts stabilized and gradually returned to baseline levels after completion of the 48 weeks of treatment in both treatment groups. During treatment, a higher median decrease from baseline in total lymphocyte counts occurred in the RBV 1000/1200 group.

Few patients in either treatment group had a normal lymphocyte count during this study. Approximately 20% in both groups had severe lymphopaenia ($< 0.5 \times 10^9$ cells/L).

CD4+ cell counts

In patients who received 48 weeks of treatment, a rapid decrease from baseline in CD4+ cell counts occurred within the first 8 weeks of treatment in both treatment groups. CD4+

cell counts then continued to gradually decrease from baseline until approximately Week 24 but then gradually returned to baseline levels after completion of the 48 weeks of treatment in both treatment groups. As with the total lymphocyte counts, a greater decrease from baseline in CD4+ cell counts occurred during RBV 1000/1200 treatment than during RBV 800 treatment (in which the median change from baseline was similar).

Since approximately 92% of patients were receiving concomitant ART at baseline, median change from baseline in CD4+ cell counts for patients who received 48 weeks of treatment and were receiving ART at baseline resembled those changes observed in the overall population. The small number of patients who received 48 weeks of treatment who were not receiving ART at baseline made interpretation of data from this subgroup difficult.

Few patients in either treatment group had a normal lymphocyte count during this study. The largest percentage of patients in both groups had the lowest lymphocyte count between 0.5 to < 1.0 x 10^9 cells/L. Approximately 20% of patients in both groups had severe lymphopenia (< 0.5 x 10^9 cells/L).

An analysis of the CD4+% as a percentage of the total lymphocyte count during treatment and follow-up was performed in patients who received 48 weeks of treatment as well as in the subgroups of patients who received 48 weeks of treatment with or without ART at baseline. In the overall population, small median increases from baseline values in CD4+% were observed during the first 12 weeks of treatment in the two treatment groups (4.5 to 4.7). CD4+% in the two groups increased slightly to Week 24 and then stabilized until approximately Week 48, at which time they decreased to baseline levels. The median increase from baseline in CD4+% values was similar in both groups.

In the subgroup of patients who received 48 weeks of treatment and who were receiving ART at baseline, similar trends in median change of CD4+% from baseline were observed to those of the safety population. As only a small number of patients from each treatment group received 48 weeks of treatment and no ART at baseline, the interpretation of the data (change from baseline in CD4+%) for this subgroup was difficult if not impossible.

The ratio of CD4+ to CD8+ cell counts in patients who completed 48 weeks of treatment increased slowly from baseline to a maximum median change in ratio of 0.3 at Week 24 in RBV 800 group and at Week 36 in the RBV 1000/1200 group. Both ratios had returned to baseline at Week 52 and Week 48 in the two groups, respectively.

Similar increases from baseline in the ratio of CD4+ to CD8+ cell counts during treatment occurred in the subgroup of patients who completed 48 weeks of treatment and were receiving ART at baseline. Similar to the changes from baseline in CD4+ cell counts and CD4+%, results for the subgroup of patients that were not receiving ART at baseline and who completed 48 weeks of treatment were difficult to interpret due to the small number of patients available.

Fasting lipid profile - fasting triglyceride levels

Protease inhibitors (PIs) and interferon alfa have both been associated with an increase in triglyceride levels. PI use was reported in almost half of patients in both treatment groups at baseline and during the 48-week treatment and 24-week follow-up periods. Fasting lipid levels were examined in detail in order to assess the effect of concomitant use of PI and PEG-IFN alfa-2a in this patient population. Not all patients had available results.

Five percent of the patients in the RBV 800 group and 3% of patients in the RBV 1000/1200 group had a fasting triglyceride level at some time during treatment or follow-up that was > 750 mg/dL (ACTG Grades 3 and 4). Fasting triglyceride levels > 1200 mg/dL (ACTG Grade 4) were reported during the study in only one patient whose ART regimen during the study included fosamprenavir, lamivudine/zidovudine and ritonavir.

Hypertriglyceridaemia was reported as a laboratory adverse event that required treatment in seven patients during the study, all in the RBV 1000/1200 group. The majority of these AEs were considered related to study treatment (4 of 7) and four of the seven had resolved by the time of the last contact with the patient.

Patients with cirrhosis

In general, the adverse event profile and treatment group differences in patients with frank cirrhosis and incomplete cirrhosis were similar to those seen in the overall population. The majority of cirrhotic patients in both groups reported at least one adverse event (93% to 100%). There were no unusual safety signals detected however, the numbers were small.

Child-Pugh score assessments

Of the 45 cirrhotic patients with Child-Pugh scores at baseline, there were 15 cirrhotic patients treated with RBV 800 mg, 13 had a Child-Pugh score of 5 and two patients had scores > 5 (1 patient each with a score of 6 or 7).

In the 30 cirrhotic patients treated with RBV 1000/1200 mg, there were 24 patients with a baseline Child-Pugh score of 5 and six patients with a score of > 5 (four patients with a score of 6 and two with a score of 7).

During the treatment, Child-Pugh scores ≥ 7 were seen in twelve patients (three in the RBV 800 group and nine patients in the RBV 1000/1200 group), as the scores were secondary to alterations in albumin and/or total bilirubin and without evidence of clinical hepatic decompensation, they were allowed to remain on treatment with increased monitoring.

Only one patient (treated with RBV 1000 mg) in the study developed clinical evidence of hepatic decompensation with bleeding oesophageal varices. The patient was cirrhotic and was on atazanavir. The patients baseline Child-Pugh score was 5, increased to 7 on Day 8 and remained at this level for one week, decreased again to 6 for approximately 28 weeks and then returned to baseline. This patient developed oesophageal varices on Day 299 determined to be unrelated to study drug and resolved without sequelae during the study. The patient's last Child-Pugh score was 5 on Day 238.

Thirty seven cirrhotic patients had a Child-Pugh score of 5 at baseline. In the RBV 800 group, 9/13 (69%) had either a shift in albumin, total bilirubin or both during treatment. In the RBV 1000/1200 group, 9/24 (38%) had either a shift in albumin, total bilirubin or both during treatment. In the two treatment groups of cirrhotic patients with a Child-Pugh score > 5, the summary of shifts from baseline in total bilirubin and albumin levels during treatment were similar except for a small number of patients treated with PEG-RBV 1000/1200 group.

In the RBV 800 group, 39/119 (33%) non cirrhotic patients had shifts from baseline in total bilirubin, albumin, or both during treatment. In the PEG-RBV 1000/1200 group, 96/244 (39%) non cirrhotic patients had shifts from baseline in total bilirubin, albumin, or both during treatment.

Neutropenia, thrombocytopenia and anaemia

Cirrhotic patients in both treatment groups had a similar risk of developing neutropenia as patients in the safety population, and the pattern of treatment differences among the groups was fairly similar to that seen in the safety population. However, no patients in the cirrhotic population had normal neutrophil counts at baseline, during treatment and 24 weeks post-treatment.

Cirrhotic patients were more likely to develop thrombocytopenia than patients in the safety population, although the pattern of treatment differences among the groups was similar to that seen in the safety population.

In general, cirrhotic patients had similar risk of developing anaemia as patients in the safety population, and in general the patterns seen in the cirrhotic population were similar.

Compared to the overall safety population, the mean maximum decrease from baseline in haemoglobin concentration was lower in the cirrhotic patients treated with RBV 800 mg (3.4 g/dL versus 3.9 g/dL, respectively) but the same in the cirrhotic patients treated with the higher dose of RBV 1000/1200 mg (3.9 g/dL). The maximum decrease from baseline in haemoglobin concentration in cirrhotic patients treated with the lower RBV dose of 800 mg was the same as in the safety population (9.0 g/dL) but lower in the cirrhotic patients treated with the high dose of RBV (1000/1200 mg) than in the safety population (7.8 g/dL versus 8.9 g/dL, respectively).

In the cirrhotic population, the percentage of patients whose lowest haemoglobin concentration was < 10 g/dL at some time during treatment or follow-up was lower in the RBV 800 group (4 patients or 25%) than in the RBV 1000/1200 group (12 patients or 40%). These percentages were higher than in the safety population. The percentage of cirrhotic patients whose lowest haemoglobin concentration was < 8.5 g/dL at some time during treatment or follow-up was also lower in the RBV 800 group (6%) than in the RBV 1000/1200 group (10%).

Post marketing experience

A search of Roche Drug Safety Database, ADVENT, was conducted by the sponsor, for reports of adverse events in patients with a medical history of HIV-HCV co-infection receiving PEG-IFN alfa-2a monotherapy or PEG-IFN alfa-2a in combination with ribavirin. The cut-off date for the cumulative data retrieval of this search was 21 October 2009.

The preferred terms used to define a medical history of HIV-HCV co-infection for this data search included the following: acquired immunodeficiency syndrome, AIDS encephalopathy, AIDS related complication, HIV infection, HIV infection CDC Category[6] B3, HIV infection CDC Group IV Subgroup C2[7], HIV peripheral neuropathy, HIV wasting syndrome, Blood HIV ribonucleic acid (RNA), HIV test positive, and Kaposi's sarcoma AIDS related.

It was estimated that approximately 85,000 HIV-HCV co-infected patients have received treatment with Pegasys. The search identified a total of 1,015 HIV-HCV cases reporting 1,996 adverse events. The 1,015 case reports included 695 (68%) males, 262 (26%) females. In 58 (6%) cases the gender was unknown. Of the 881 cases where age information was available (but excluding a one-year old patient), the median age was 43 years (range: 22 – 76 years).

Six hundred and twenty-two (61%) of the 1,015 cases were reported from clinical trials and 393 (39%) were from spontaneous or literature sources. Over two-thirds of the cases were reported from the following countries: United States (367), Spain (193), France (170), and Italy (63). The majority of the cases were treated for hepatitis C virus infection

[6] Centers for Disease Control and Prevention (CDC) classification system and the World Health Organization (WHO) Clinical Staging and Disease Classification System. The CDC disease staging system assesses the severity of HIV disease by CD4 cell counts and by the presence of specific HIV-related conditions. B3= Symptomatic Conditions with CD4+ cell count <200 cells/μL.

[7] C2= AIDS-Indicator Conditions and CD4+ cell count 200-499 cells/μL.

(920). Other indications included hepatitis B, hepatitis D and unknown type of viral hepatitis.

Adverse events

Of the total number of 1,996 AEs, the following system organ classes (SOC) have the most frequently reported AEs (> 5% of the total AEs): Blood and Lymphatic System Disorders (411 AEs), General Disorders (220 AEs), Infections and Infestations (207 AEs), Psychiatric Disorders (181 AEs), Investigations (169 AEs), Gastrointestinal Disorders (150 AEs), and Nervous System Disorders (122 AEs).

Serious adverse events

For the total of 892 cases 1,417 AEs (71%) were serious. Of the total number of serious AEs, the SOCs with the highest number of serious AEs were: Blood and Lymphatic System Disorders (362), Infections and Infestations (183), Psychiatric Disorders (128), Gastrointestinal Disorders (97), General Disorders (96), Investigations (88), and Nervous System Disorders (74). The most frequently reported serious AEs were anaemia (136) followed by neutropenia (100), thrombocytopenia (50), pneumonia (44), depression (37), pyrexia (22) , asthenia (20), pancytopenia (17), pancreatitis (14), suicidal ideation (13), suicide attempt (12), hyperbilirubinemia (12), hepatic failure (11), myocardial infarction (11), haemoglobin decreased (10), lactic acidosis (10) and convulsion (10).

Deaths

A total of 62 of the 1,015 case reports had a fatal outcome. Of the 56 cases where the cause of death was reported, regardless of treatment relationship, the number of cases with a fatal outcome sorted by SOC in which the primary fatal event was reported were as follows: Infection (15), Cardiac Disorders (11), Psychiatric Disorders (6), Injury, Poisoning and Procedural Conditions (5), Nervous System Disorders (4), Blood and Lymphatic System Disorders (3), Hepatobiliary Disorders (3), Neoplasm Benign, Malignant and Unspecified (2), Gastrointestinal Disorders (2), Metabolism and Nutrition Disorders (1), Vascular Disorders (1), Respiratory Disorders (1), Renal and Urinary Disorders (1) and Social Circumstances (1).

Based on preferred term level, the most frequent serious adverse event with a fatal outcome included: bacteraemia/sepsis/septic shock (7), myocardial infarction (5), completed suicide (5), death, cause unknown (5), pneumonia (4), drug overdose or toxicity (3), hepatitis C (3), hepatic failure (3) and cardiac or cardio-respiratory arrest (3). Other causes of death reported in one or two cases included: gastrointestinal haemorrhage, aspergillosis, coronary artery thrombosis, coronary artery arteriosclerosis, hypertensive heart disease, respiratory distress, lung adenocarcinoma, renal failure, AIDS, encephalopathy, cerebral haemorrhage, encephalitis, thrombotic thrombocytopenia purpura, autoimmune haemolytic anaemia, bone marrow failure, lymphoma, lactic acidosis, self injuries behaviour, victim of homicide, gunshot wound, road traffic accident and disease progression.

Of the 62 fatal cases, 47 patients were reported to be receiving antiretroviral therapy concomitantly with anti-hepatitis treatment. In addition to the patients' underlying co-infection, the presence of other confounding risk factors based on medical history or co-morbid conditions were identified in 46 of the cases, and included: hepatic cirrhosis, hepatic failure, liver transplant, myocardial infarction, atrioventricular block, deep vein thrombosis, cerebral haemorrhage, encephalopathy, haemophilia, thrombocytopenia, pneumonia, tuberculosis, asthma, COPD, fungal infection, lung adenocarcinoma, Stevens Johnson Syndrome, renal disorder, depression, illegal drug overdose, drug hypersensitivity, cachexia, syphilis as well as hyperlipidemia, hypertension, obesity,

diabetes, drug/alcohol abuse, smoking and concomitant use of immunosuppressive medications.

List of Questions

During 2010, the TGA began to change the way applications were evaluated. As part of this change, after an initial evaluation, a "list of questions" to the sponsor is generated.

TGA Question

A request was sent to the sponsor requiring details of the Good Clinical Practice audits done on the five sites involved in Study protocol NV18209, including the problems found, the actions taken, and the reason for including data from the sites, in particular the site with critical findings of non-compliance.

Sponsor response

Critical findings were noted during the audit for one of the clinical sites. Critical findings pertained to the lack of documented evidence that the Principle Investigator provided medical oversight of the patients. From the audit report for this site, it appears that six out of fourteen randomized patients at the site may have been affected.

The primary efficacy endpoint of the study was HCV RNA. Since this is assessed from serum taken during a standard blood draw and analysed according to a standardized and validated process and test, it is unaffected by the medical oversight of the patient. Since there was no potential impact on efficacy data as a result of the audit findings, HCV RNA data from the site was not excluded from the efficacy analyses.

For the safety assessments, additional training and increased monitoring through the end of study was instituted in accordance with Section 5.20.1 of the ICH Guideline for Good Clinical Practice[8] to ensure the medical oversight of the patients according to the delegation of responsibilities established at the site. In addition, the Pegasys Medical Monitor conducted a site visit to review all the source documents in order to ensure that all safety parameters had been captured appropriately. Although the proper documentation of medical oversight had been lacking at the beginning of the study, there was no evidence that the patients were not being medically managed by the Principle Investigator. In order to avoid not presenting all available safety information for the study, and since all data reported in the case report form was verified in the source documents, all safety data from the site were included in the analyses.

An audit finding regarding incomplete source documents was made in two out of four audits, while data inconsistencies between the source documents and the case report form were reported in the other two audits.

The number of records is not routinely counted. However, all the data inconsistencies were resolved with the help of the monitor, and missing data in the source documents (adverse event causality and clinical significance of abnormal laboratory values) were retrospectively documented by the principal Investigator via a Note to File, and appropriately reflected in the case report form.

Clinical Summary and Conclusions

In support of the application to alter the *Indication* for Pegasys and include patients with clinically stable HIV infection, the sponsor cited the APRICOT study, protocol number NR15961, which has previously been submitted to TGA for evaluation. This study was not re-evaluated. As the currently approved *Indication* did not exclude patients with HCV/HIV

[8] Note for Guidance on Good Clinical Practice CPMP/ICH/135/95. www.ema.europa.eu/pdfs/human/ich/013595en.pdf

co-infection, the proposed addition to the Product Information essentially narrows the indication by qualifying the relevant population of HCV/HIV co-infected patients included in the *Indication*. In addition, the Australian Drug Evaluation Committee (ADEC; now called the Advisory Committee for Prescription Medicines, ACPM) resolution dated 4 – 5 August 2005, states that there should be no objection to the approval of the submission from Roche Product Pty Ltd to register Pegasys pre-filled syringes containing peginterferon alfa-2a 180 µg/0.5 mL injection solution for the treatment of patients with chronic hepatitis C co-infected with human immunodeficiency virus with recommended dosage already included in the approved Product Information *Dosage and Administration* section.

In support of changes made to the *Contraindication* and *Precaution* sections of the Product Information, relating to patients with Child-Pugh staging of chronic liver disease, the sponsor submitted data relating to Study Protocol No. NV18209. This Phase IV study spanning three years between April 2006 and April 2009 involved 59 centres in the United States, Portugal and Spain. It was double-blind for ribavirin, randomised 2:1 to safety and efficacy study of PEG-IFN alfa-2a 180 µg plus ribavirin 1000 or 1200 mg compared to PEG-IFN alpha 2a 180 µg plus ribavirin 800 mg, in interferon-naive patients with chronic hepatitis C genotype 1 virus infection co-infected with HIV-1. The study design was decided in consultation with the United States Food and Drug Administration. The co-primary objectives were to compare efficacy of the two treatment regimens with regard to sustained viral response 24 weeks after the end of 48 weeks of treatment, and to compare safety.

The sample size was not based on a power calculation and in the assessment of efficacy the study was considerably underpowered. Based on the calculated Odds Ratio there was no statistical difference detected between treatment regimens. The sponsor has not requested changes to the Product Information based on the efficacy component of this study; specifically there is no change to the *Dosage and Administration* section.

The co-primary objective was to assess safety. No particular safety outcome was targeted. The adverse events in type and in frequency reported in the submission were in general consistent with those previously reported although study numbers precluded identification of uncommon or rare safety signals. In addition, the use of antiretroviral medications and the underlying viral diseases had the potential to confound safety results.

The frequency of anaemia in the submitted study was sufficiently high to merit inclusion in the Table 10 of the draft Product Information, which summarises adverse reactions occurring in at least 10% of patients in hepatitis C clinical trials. Currently this table does not include anaemia. In Study NV18209, the incidence of anaemia increased with increase in dose of ribavirin and it is not unreasonable to consider that ribavirin may have been implicated. It is recommended that the table is updated to include results from Study protocol NV18209.

It is recommended that the *Adverse Effects* section of the Product Information be updated to include at least some of the results from the current study, including the number of patients who withdrew for lack of efficacy, the number who withdrew for adverse events or abnormal laboratory results. To put the results into perspective it would be advisable to include a brief summary of the study methodology and patient demographics.

In discussion with the FDA, fourteen months after commencement of the study the protocol was altered to allow patients with Child-Pugh score greater than 5 to enter the study if the increase was due to raised unconjugated bilirubin due to concomitant administration of medication such as atazanavir or indinavir, or to a medical condition such as Gilberts' syndrome. The protocol was also amended to allow continuation of study

treatment when reported increase in Child-Pugh score considered due to change in albumin level which was not thought to be due to worsening liver function. However, a Child-Pugh score greater than 5, secondary to decreased albumin, was not acceptable at inclusion. While a patient with increased score due to low albumin was at times allowed to continue treatment, the FDA mandated strict risk management of those patients.

The sponsor included a post-hoc analysis of albumin levels in patients without cirrhosis to support the contention that decrease in albumin is not always due to worsening liver disease as measured by the Child-Pugh Score. Inclusion of text in the Product Information based on post-hoc analyses is not recommended. The clinical evaluator considers that while there may be reasonable to conclude that an elevation of unconjugated serum bilirubin is due to a specific drug effect or specific clinical diagnosis unrelated to liver impairment, it is less possible to be sure that a decrease in albumin may be entirely due to malnutrition in a patient with pre-existing cirrhosis and compromised liver function. Thus it is not recommended that the proposed warning in the *Precautions* section regarding monitoring of patients for signs and symptoms of hepatic decompensation is qualified by suggesting that "The Child-Pugh scoring may be affected by factors related to treatment ..."

The large number of trial centres and the protracted period over which the trial was run are testament to the determination and perseverance of the investigators. Only five sites were audited for GMP and problems were found in all five, critical matters of non-compliance were found at one study centre. The problems with documentation were dealt with in some respects retrospectively and thus it considered not possible to be wholly reliant on the results.

Benefit

Chronic hepatitis C infection is associated with the risk of development in the long term of liver fibrosis, cirrhosis with attendant problems related to portal hypertension, liver failure and hepatocellular carcinoma. In Australian it is calculated that over one quarter of liver transplants are due to chronic hepatitis C infection[9]. Current evidence suggests that HIV worsens hepatitis C-related liver disease and can fasten the progression to cirrhosis and decompensated liver disease and lead to earlier development of hepatocellular carcinoma. It is unclear what impact hepatitis C infection has on HIV progression.

Hepatitis C is more common in people with HIV than in the general population because of shared risk factors for viral transmission. In Australia, it is estimated that about 13% of people with HIV also have hepatitis C. In 2008, the estimated number of people living with HIV infection in Australia was 17 444 including 12,053 individuals aged 15 – 49 years. The most recently available figures of estimated HIV prevalence in Australia are for 2008. The estimate at that time was 123 per 100 000 population aged 15 – 49 years.

Currently there is no cure for hepatitis C and the only available treatment option is pegylated interferon alfa and ribavirin. Therefore, even the limited success rate documented in the submitted study, is to be valued.

Risk

In the submitted study, while 19 – 22% of patients were reported to have sustained viral response, 96 – 98% number reported adverse events regardless of relationship and 94% - 96% reported adverse events considered at least possibly related to study drug treatment. Between 6 – 8% of patients reported at least possibly related serious adverse events, 12% withdrew due to safety concern and 21 – 27% required dose modification.

[9] http://www.nchecr.unsw.edu.au/NCHECRweb.nsf/resources/SurvReports_3/$file/ASR2009-updated-2.pdf

The numbers in the subgroup with cirrhosis were insufficient to confidently assess the safety profile in the subgroup and in particular it was not possible to assess the safety of continuing treatment in the face of cirrhosis and falling serum albumin levels.

In this study, nearly one quarter of all patients were reported to have at least one episode of neutropenia and the same proportions were given at least one treatment with colony stimulating factors (23 – 24%). The proportion of patients reporting at least one episode of anaemia and the proportion given at least one treatment with haematopoietic stimulants were 22% (RBV 800) and 31% (RBV1000/1200). Use of these bone marrow stimulants added another layer of potential harm for between one fifth and one third of patients in the study under evaluation. Although it would appear that colony stimulating factors are considered safe enough to use in healthy individuals donating stem cells, cautionary literature exists. [10]

Transfusions were administered to 26% and 37% of patients. It was noted that 10 study patients were in their present dilemma because of transfusion. Transfusions are potentially hazardous.

The effect of treatment of hepatitis C infection on the outcome of HIV infection has not been the primary objective of investigation.

Balance

Despite the considerable risk of drug related adverse events and the relatively low chance of success based on the surrogate marker of sustained virologic response, the balance is considered to remain on the side of benefit for HCV-HIV co-infected patients treated with Pegasys-RBV.

Recommendation

The application to include mention of HIV infected patients in INDICATIONS is recommended. In making this endorsement it is further recommended that:

- Continuing cumulative data relating to HCV-HIV co-infected patients treated with Pegasys-RBV is collected in future post marketing safety reports to be made available to the TGA on request.

V. Pharmacovigilance Findings

There was no Risk Management Plan (RMP) submitted with this application. The sponsor provided a justification for not submitting an RMP which was accepted by the TGA. Routine pharmacovigilance as per guidelines was considered to be sufficient.

VI. Overall Conclusion and Risk/Benefit Assessment

The submission was summarised in the following Delegate's overview and recommendations:

Quality

There was no requirement for a quality evaluation in a submission of this type.

Nonclinical

There was no requirement for a nonclinical evaluation in a submission of this type.

[10] Tigue CC, J M McKoy JM *et al* (2007). *Bone Marrow Transplantation* 40, 185–192

Clinical

The dossier consisted of clinical data only comprising one clinical study (NV18209). The clinical evaluation report (CER) is considered comprehensive and objective review of the submitted data and should be referred to. The clinical evaluator recommends that the current indication does not need modification as it does not exclude treatment of HIV-HCV co-infected patients. In fact, the proposed indication may appear to restrict the use to HIV-HCV co-infected patients.

The sponsor's main reasoning for updating the indication is to bring it in line with its overseas approved form in the EU and the USA. Note that the supporting clinical trial for the indication update is NR15961 which was reviewed as part of a previous submission to TGA. The use of combination therapy in HIV-HCV co-infection was recommended for approval at a meeting of the ADEC held in April 2005. A description of NR15961 (APRICOT trial) was included in the Australian PI but the wording of the therapeutic indication was not modified at that time.

Study NV18209 submitted with the current Australian submission was conducted as a post-approval regulatory commitment in the USA and Europe. The objective was to obtain further evidence of efficacy and safety in HCV genotype 1 patients, patients of African American descent as well as assess the use of high dose ribavirin 1000/1200mg daily dose compared to the current fixed daily dose of 800mg. A summary is presented below:

The trial population consisted of adult patients with HCV genotype 1 infection, stable HIV-1 disease, CD4+ count≥ 100/μL and ch ronic liver disease consistent with HCV on biopsy. Up to 20% patients with cirrhosis or incomplete cirrhosis were allowed but were required to have Child Pugh (C-P) score of 5. A subsequent protocol amendment allowed C-P score ≥ 6 if it was a consequence of a concomitant medication or a clinical condition. Patients with C-P score ≥ 6 were not allowed to enrol if was secondary to albumin, INR, ascites or hepatic encephalopathy. Decompensated liver disease was an exclusion criterion as was previous treatment with pegylated interferon.

The trial was randomised and double-blind with respect to the ribavirin treatment: 800mg (Group A) versus 1000/1200mg (Group B). The cut-off for 1000/1200mg dosing in Group B was body weight ≥ 75kg.

All patients received peginterferon in the same manner (180μg SC per week). The treatment duration was 48 weeks. The assessment of SVR (undetectable viral RNA; below assay threshold) occurred 24 weeks after completion of treatment.

The median age of the sample population was 46 years, nearly 80% were males and about 30% were of African American origin.

A total of 415 eligible patients were randomised to the two comparator groups. Consistent with the stratified randomisation, the results were reported adjusted for geographical region, African American ethnicity and cirrhosis status. The response rate (SVR) was small (19% versus 22%) and the comparison between the two groups was not significant as shown below (Table 13).

Table 13. Response rate (SVR).

	Rx	randomised	completed	SVR (%)	Odds Ratio (OR)	p-value	OR 95% CI
Group A	ribavirin 800mg	138	55/138 (40%)	26/138 (19%)	1.17	0.56	0.69, 1.98
Group B	ribavirin 1000/1200mg	277	119/277 (43%)	60/27 (22%)			

The results were similar using per protocol population. For secondary efficacy variables please see CER.

The safety outcomes have been discussed in the CER. Nearly all patients (98% & 96% in Groups A & B respectively) experienced at least one adverse event (AE), of which 16% and 17% respectively were serious AEs. The adverse effects profile was similar between the two Groups. Noteworthy differential outcomes were anaemia (24% versus 32%, respectively) and depression (22% versus 27%, respectively), that is, higher in the high ribavirin group. Two deaths were reported in Group B; one during the treatment period and one during follow up. For changes in bilirubin and albumin in cirrhotic patients with C-P score equal to 5, C-P score > 5 and non-cirrhotic patients see the CER.

The supporting clinical trial for the proposed extension of indication has been reviewed in the past by the ADEC and the TGA. For reference the efficacy results, reported in the approved Australian PI, are reproduced below:

Table 8. SVR in HIV-HCV Co-infected Patients

	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

Note that the trial population in this case was unrestricted with respect to HCV genotype or ethnicity.

Risk Management Plan (RMP)

There was no RMP submitted with this application.

Risk-Benefit Analysis

Delegate Considerations

Based on two available trials in HIV-HCV co-infected patients, consideration and recommendation for approval in the past by the ADEC, overseas approval status and the

currently approved indication(s) for the comparator alfa-2b analogue, the Delegate supported the change in indication to include treatment of HIV-HCV co-infected patients. For clarity this should be stated separate from the current indication in the PI and should also reflect the trial population with respect to interferon treatment naive status. Furthermore, a description of the Study NV18209 should be added to the Clinical Trials section of the PI.

Please note that use in HIV-HCV co-infection has been approved overseas, but the current trial NV18209 appears not to have yet been reviewed. This study failed to show improved efficacy or safety of weight-based higher dose ribavirin regimen compared to fixed 800 mg daily divided dosing regimen. A limiting factor in interpreting the utility of findings in this trial was high premature rate of withdrawals which was > 50% in both arms.

The combination therapy is relatively less efficacious in HCV genotype 1. The SVR was 29% in Study NR15961 compared to 19% in the current study (NV18209) and could presumably be attributed to differences in the baseline characteristics of the participating populations in the two trials. The NR15961 trial population is probably better reflection of composition of overall Australian population and similar response rates may be expected, although true effect in non-Caucasian population can only be speculated.

In the Delegate's view, the proposed change in the Contraindications was not supported as (1) the trial does not provide sufficient data to reliably assess its safety, (2) the risk of hepatic injury from interferon cannot be assumed to remain stable if the decompensation was caused by a concomitant factor and (3) the contraindication in its current form correctly reflects the overall inclusion/exclusion criteria, that is, use in adult patients with compensated liver disease. Furthermore, the intensive clinical monitoring mandated in the clinical trial setting may not be practical in clinical practice. Consequently, the proposed precautionary statement is also not appropriate.

The same course of action is proposed for Pegasys and Copegus product information documents as well.

As a related matter, the therapeutic indication in the Pegasys PI gives the impression that treatment-naive HCV patients (single infection) should receive interferon monotherapy. It was therefore recommended that an appropriate statement should be added to the effect that preferred treatment in HCV in combination therapy. Monotherapy is mainly indicated in case of intolerance or contraindication to ribavirin.

Delegate's Proposed Action

The Delegate proposes the therapeutic indication as follows:

> *(Pegylated interferon & ribavirin) combination therapy is indicated for the treatment of chronic hepatitis C in treatment-naive patients and patients who have failed previous treatment with interferon alfa (pegylated or non-pegylated) alone or in combination therapy with ribavirin. Patients must be 18 years or older and have compensated liver disease.*
> *(Pegylated interferon & ribavirin) combination therapy is also indicated for the treatment of chronic hepatitis C with stable HIV co-infection who have previously not received interferon treatment. Patients must be 18 years or older and have compensated liver disease.*

The proposal to modify contraindications and precautions is not supported. Further recommendations include addition of description of Study NV18209 including its efficacy and safety results in the Australian PI. Additional recommendations were detailed by the clinical evaluator and these were supported by the Delegate.

Summary of the Response from Sponsor

The sponsor has agreed with the delegate for a separate indication for HCV/HIV coinfected patients.
The sponsor has incorporated a statement in the *Dosage and Administration* section relating to treatment of chronic hepatitis C in treatment-naive patients " PEGASYS and COPEGUS combination treatment is recommended unless intolerance or contraindication to ribavirin."

The sponsor does not agree to remove the proposed modification of *Contraindications* and *Precautions* based on the data in clinical trials NV18209 and NR15961. It is argued that deterioration in the Child-Pugh score when solely due to fall in serum albumin or increase in serum bilirubin without signs and symptoms of hepatic decompensation such as ascites may not be appropriate for discontinuing treatment in HCV/HIV coinfected patients. The sponsor notes that if sole dependence on the Child-Pugh score in the original protocol had been rigidly maintained, nearly half of the cirrhotic patients enrolled in NV18209 either would have not been allowed entry into the study or would have been prematurely discontinued from treatment. In the opinion of the sponsor this would have been an unfortunate outcome as cirrhotic HIV-HCV co-infected patients are an especially high-risk group and are in most need of treatment for their HCV infection.

Advisory Committee Considerations

The Advisory Committee on Prescription Medicines (ACPM) (which has succeeded ADEC), having considered the evaluations and the Delegate's overview, as well as the sponsor's response to these documents, agreed with the Delegate's proposal.

Outcome

Based on a review of quality, safety and efficacy, TGA approved the registration of

Pegasys-RBV containing peginterferon alfa-2a 0.5mL injection pre-filled syringe and ribavirin tablet for the **new indication**:

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

Based on a review of quality, safety and efficacy, TGA approved the registration of Pegasys containing peginterferon alfa-2a 0.5mL injection pre-filled syringe for the **new indication**:

> *The combination of Pegasys and Copegus is also indicated for the treatment of chronic hepatitis C in patients with clinically stable human immunodeficiency virus (HIV) co-infection who have previously not received interferon therapy.*

Based on a review of quality, safety and efficacy, TGA approved the registration of Copegus containing ribavirin 200mg tablets for the **new indication**:

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

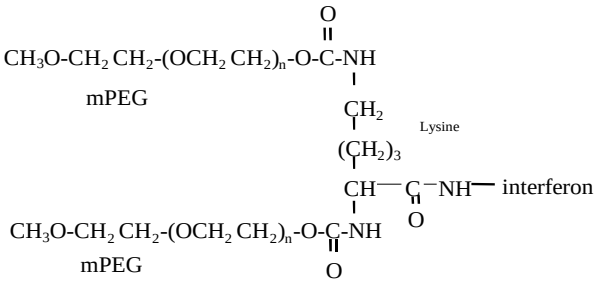
Attachment 1. Product Information

The following Product Information was approved at the time this AusPAR was published. For the current Product Information please refer to the TGA website at www.tga.gov.au.

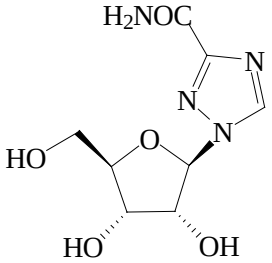
NAME OF THE MEDICINE

PEGASYS RBV® Combination Therapy

PEGASYS®
peginterferon alfa-2a
CAS -198153-51-4



COPEGUS®
ribavirin
CAS 36791-04-05



The chemical name for ribavirin is 1-β-D-ribofuranosyl-1H-1,2,4-triazole-3-carboxamide with the molecular formula $C_8H_{12}N_4O_5$ and the molecular weight is 244.21

DESCRIPTION

PEGASYS RBV is a combination pack containing PEGASYS (peginterferon alfa-2a) 135 or 180 micrograms (mg) injection (0.5 mL) and COPEGUS (ribavirin) 200 mg tablets.

PEGASYS
PEGASYS is made by conjugating a single branched polyethylene glycol chain (PEG) of approximate molecular weight of 40 kilodaltons (kD) to interferon alfa-2a (20 kD) via a stable amide bond. The combination of PEG and interferon alfa-2a forms an intact active molecule known as peginterferon alfa-2a, having an approximate molecular weight of 60 kD. Chemically, it is a bis-(N-monomethoxypolyethylene-glycol-urethanyl) lysyl interferon alfa-2a.

PEGASYS is a sterile ready-to-use solution for subcutaneous injection. It is available as pre-filled syringes in two strengths, 135 and 180 mg. The solution is clear and colourless to light yellow.

Each pre-filled syringe contains 135 or 180 mg 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.

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 mg 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 mg. 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.

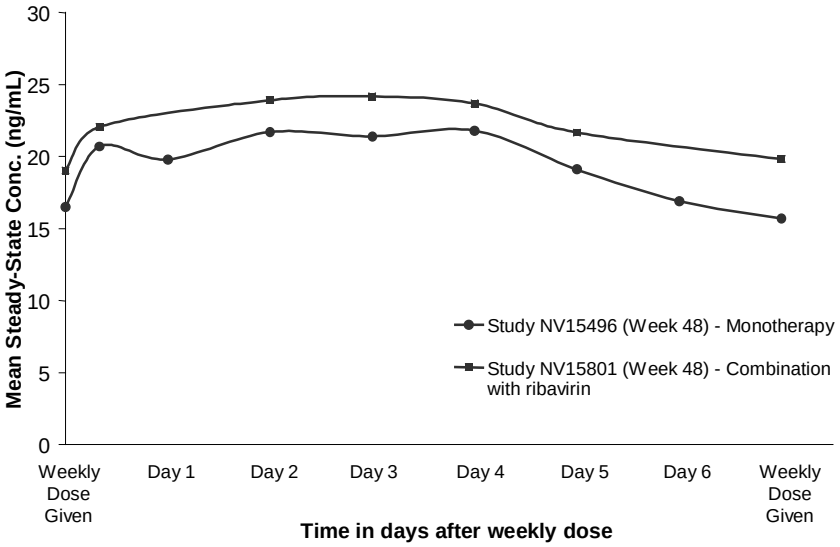
Elimination: After iv administration, the terminal half-life of peginterferon alfa-2a in healthy subjects is approximately 60 h compared to 3 – 4 h for standard interferon. A mean elimination half-life of 160 h (84 – 353 h) at primary elimination phase was observed in patients after subcutaneous (sc) 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 mg

Pharmacokinetic Parameter	Healthy Subjects PEGASYS 180 mg (*n* = 50)	CHC Patients in NV15496 PEGASYS 180 mg (*n* = 16)	
	Single Dose Mean ± SD [Range]	Single Dose Mean ± SD [Range]	Week 48 Dose Mean ± SD [Range]
C_{max} (ng/mL)	14 ± 5 [6 - 26]	15 ± 4 [7 - 23]	26 ± 9 [10 - 40]
T_{max} (h)	92 ± 27 [48 - 168]	80 ± 28 [23 - 119]	45 ± 36 [0 - 97]
$AUC_{1\text{-}168\ h}$ (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 mg 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 mg, 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_{tf} 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 carboxyacid 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 mg 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 / ³ 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 mg sc once a week with placebo, PEGASYS 180 mg sc once a week with COPEGUS 1000 mg (body weight < 75kg) or 1200 mg (body weight ≥ 75kg) daily, or INTRON Aâ 3 MIU sc three times a week with REBETOLâ 1000 mg or 1200 mg daily (REBETRONâ) 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 mg with COPEGUS 800 mg (*n* = 207)	**PEGASYS 180 mg with COPEGUS 1000/1200 mg (*n* = 280)**	**PEGASYS 180 mg with COPEGUS 800 mg (*n* = 361)**	**PEGASYS 180 mg with COPEGUS 1000/1200 mg (*n* = 436)**	**PEGASYS 180 mg (*n* = 224)**	**PEGASYS 180 mg with COPEGUS 1000/1200 mg (*n* = 453) [A³ 80%]**	**INTRON A 3 MIU with REBETOL 1000/1200 mg (*n* = 444) *p*-values***
All Genotypes	55% (114/207)	64% (179/280)	52% (187/361)	63% (275/436)	29% (66/224)	56% (255/453) [75%]	45% (200/444) *p* = 0.001
Genotype 1	29% (29/101)	42% (49/118)	41% (102/250)	52% (142/271)	21% (30/145)	46% (138/298) [67%]	36% (104/285) *p* = 0.016
Genotype non-1†	80% (85/106)	80% (130/162)	77% (85/111)	81% (133/165)	45% (31/69)	76% (106/140) [88%]	61% (89/145) *p* = 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 ³ 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 mg 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 mg with COPEGUS 800 mg 24 weeks (*n* = 212)	**PEGASYS 180 mg 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 mg 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 mg 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 ³ 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 mg once a week for 12 weeks, followed by 180 mg once a week for a further 60 weeks; PEGASYS 360 mg once a week for 12 weeks, followed by 180 mg once a week for a further 36 weeks; PEGASYS 180 mg once a week for 72 weeks; or PEGASYS 180 mg 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 **PEGASYS 360 µg 12 wk then 180 µg 60 wk COPEGUS 1000/1200 mg 72 wk (*n* = 317)**	**B** **PEGASYS 360 µg 12 wk then 180 µg 36 wk COPEGUS 1000/1200 mg 48 wk (*n* = 156)**	**C** **PEGASYS 180 µg 72 wk COPEGUS 1000/1200 mg 72 wk (*n* = 156)**	**D** **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 (360 µg 12 wk then 180 µg 60 wk + 180 µg 72 wk) (*n* = 473)	**48 wk Groups (360 µg 12 wk then 180 µg 36 ek + 180 µg 48 wk) (*n* = 469)**	**360 µg Groups (360 µg 12 wk then 180 µg 60 wk + 360 µg 12 wk then 180 µg 36 wk) (*n* = 473)**	**180 µg Groups (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 % SVR (responders/total)	Peginterferon alfa-2b/ribavirin Non-responders re-treated for 72 weeks % 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 mg 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)**	**Pegyinterferon** **% 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 mg 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 (³ 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 clinically 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/mm^3, with baseline platelet count < 90,000 cells/mm^3 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/mm^3
- absolute neutrophil count (ANC) $\geq$ 1500 cells/mm^3
- thyroid stimulating hormone (TSH) and T_4 within normal limits or adequately controlled thyroid function
- HIV-HCV co-infection: $CD_{4+} \geq 200/\mu L$ or $CD_{4+} \geq 100/\mu L$ to $< 200/\mu L$ 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/mm^3 (refer to *Dosage and Administration*). For patients with ANC values below 500 cells/mm^3 treatment should be suspended until ANC values return to more than 1000 cells/mm^3. 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/mm^3, and cessation of therapy is recommended when platelet count decreases to levels below 25,000 cells/mm^3 (refer to *Dosage and Administration*).

Anaemia (haemoglobin≤ 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 17b-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 spermatogensis 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 mg 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 mg 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_{tf} 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-methyl-thioinosine 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 ³ 10% of Hepatitis C patients with Normal ALT Levels

	PEGASYS 180 mg with COPEGUS 800 mg 24 weeks (*n* = 212) %	PEGASYS 180 mg 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 andconnective 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/mm^3 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/mm^3, 30%; and platelet < 50 000/mm^3, 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 ³ 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 ³ 10% of Patients in Hepatitis C Clinical Trials

	HCV			HIV-HCV	HCV Peginterferon alfa-2b Non-responders
	PEGASYS 180 mg with COPEGUS 800 mg 24 weeks (*n* = 207) %	PEGASYS 180 mg 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 mg with COPEGUS 800 mg 48 weeks (*n* = 288) %	PEGASYS 180 mg 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 medistinal 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/mm^3 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/mm^3.

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/mm^3 mostly in patients with cirrhosis and who entered the trial with baseline platelet counts as low as 75 000 cells/mm^3. In HIV-HCV co-infected patients, 8% of patients receiving PEGASYS RBV had decreases in platelets below 50 000 cells/mm^3.

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 mg 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 mg	< 75 kg = 1000 mg	2 morning	3 evening	48 weeks
		³ 75 kg = 1200 mg	3 morning	3 evening	48 weeks
Genotype 2, 3	180 mg	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 mg once a week by subcutaneous administration in the abdomen or thigh. For patients < 75 kg and ³ 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 mg is generally adequate. However, in some cases, dose reduction to 90 mg or 45 mg 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 mg	< 500 cells/mm^3, treatment should be suspended until ANC values return to more than 1000 cells/mm^3 Initially reinstitute at 90 mg and monitor ANC
Platelet Count	< 50 000 cells/mm^3, reduce to 90 mg	< 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 mg 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 Grade 1-2 Grade 3-4*	1 2 3
Ascites	Absent Slight Moderate	1 2 3
S-Bilirubin (mg/dL)	< 2 2 - 3 > 3	1 2 3
SI unit = (mmol/l)	< 34 34 - 51 > 51	1 2 3
S-Albumin (g/L)	> 35 35 - 28 < 28	1 2 3
INR	< 1.7 1.7 - 2.3 > 2.3	1 2 3

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

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, pharmcodynamic, 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 mg/week) have been reported. None of these patients experienced unusual, serious or treatment-limiting events. Weekly doses of up to 540 and 630 mg 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 overdosage.

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 mg pre-filled syringe x 4 + COPEGUS 112, 140 or 168 tablets
- PEGASYS 135 mg pre-filled syringe x 4 + COPEGUS 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.

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

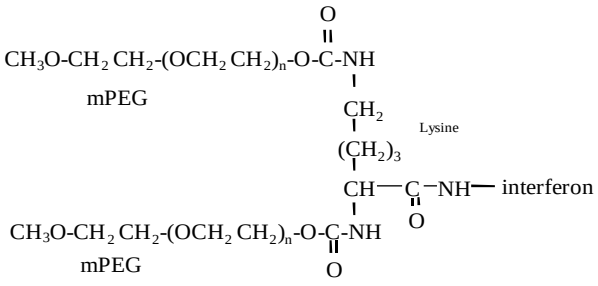
TGA Approval Date: 13 May 2011

NAME OF THE MEDICINE

PEGASYS®

peginterferon alfa-2a

CAS -198153-51-4



DESCRIPTION

PEGASYS (peginterferon alfa-2a) is made by conjugating a single branched polyethylene glycol chain (PEG) of approximate molecular weight of 40 kilodaltons (kD) to interferon alfa-2a (20 kD) via a stable amide bond. The combination of PEG and interferon alfa-2a forms an intact active molecule known as peginterferon alfa-2a, having an approximate molecular weight of 60 kD. Chemically, it is a bis-(N-monomethoxypolyethylene-glycol-urethanyl) lysyl interferon alfa-2a.

PEGASYS is a sterile ready-to-use solution for subcutaneous injection. It is available as pre-filled syringes in two strengths, 135 and 180 micrograms (mg). The solution is clear and colourless to light yellow.

Each 0.5 mL pre-filled syringe contains 135 or 180 mg 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.

PHARMACOLOGY

PHARMACODYNAMICS

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 mg and stays maximal throughout the 1 week dosing interval. The magnitude and duration of peginterferon alfa-2a induced 2',5'-OAS activity were reduced in subjects older than 62 and in subjects with significant renal impairment (creatinine clearance 20 – 40 mL/min).

PHARMACOKINETICS

The pharmacokinetics of peginterferon alfa-2a were studied in healthy subjects and patients infected with hepatitis C. The results for patients with chronic hepatitis B (CHB) were similar to those for patients with chronic hepatitis C (CHC).

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 mg. 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.

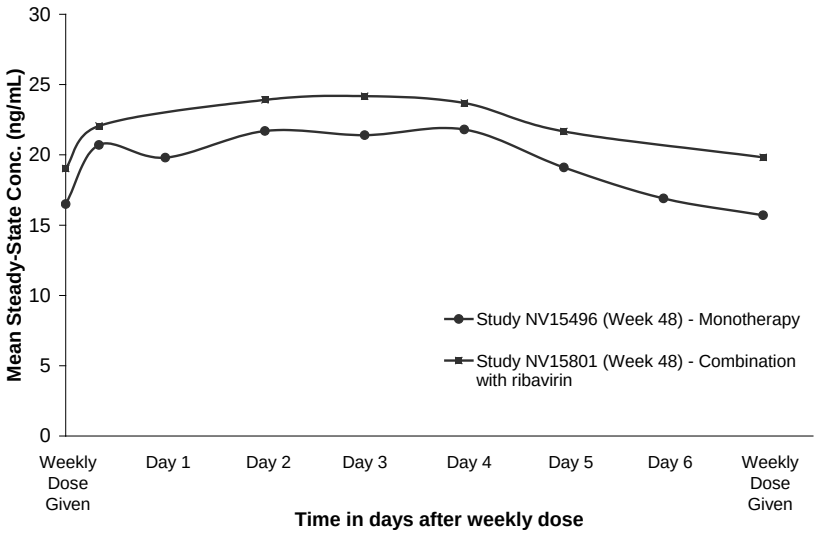
Pharmacokinetic Overview

In patients with CHC, steady-state serum concentrations increase 2 – 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. 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 mg

Pharmacokinetic Parameter	Healthy Subjects PEGASYS 180 mg (*n* = 50) Single Dose Mean ± SD [Range]	CHC Patients in NV15496 PEGASYS 180 mg (*n* = 16) Single Dose Mean ± SD [Range]	CHC Patients in NV15496 PEGASYS 180 mg (*n* = 16) Week 48 Dose Mean ± SD [Range]
C_{max} (ng/mL)	14 ± 5 [6 - 26]	15 ± 4 [7 - 23]	26 ± 9 [10 - 40]
T_{max} (h)	92 ± 27 [48 - 168]	80 ± 28 [23 - 119]	45 ± 36 [0 - 97]
$AUC_{1\text{-}168\ h}$ (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 mg Monotherapy and in Combination with COPEGUS



Pharmacokinetics in Special Populations

Renal Impairment: No significant relationship between the pharmacokinetics of peginterferon alfa-2a 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 mg resulted in similar exposure as 180 mg 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 should be made during the course of therapy in the event of adverse reactions.

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 mg, 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 CHC or CHB. Comparable exposure and pharmacokinetic profiles were seen in patients with cirrhosis with compensated liver disease and patients without cirrhosis.

CLINICAL TRIALS

Clinical trials have demonstrated that PEGASYS alone or in combination with COPEGUS (ribavirin) is effective in the treatment of patients with CHC or CHB, including cirrhotic patients with compensated liver disease and in patients with HIV-HCV co-infection.

Chronic Hepatitis C (CHC)

Monotherapy in Treatment-Naïve Patients

The safety and effectiveness of PEGASYS for the treatment of hepatitis C were assessed in randomised, open-label, active-controlled clinical trials (NV15495 and NV15497). All patients were adults with compensated CHC, detectable HCV RNA, persistently abnormal ALT levels, a histological diagnosis consistent with CHC, and previously untreated with interferon therapy.

Patients with cirrhosis: In NV15495, patients received either interferon alfa-2a (ROFERON-A) 3 MIU subcutaneous (sc) three times a week, PEGASYS 90 mg sc once a week, or PEGASYS 180 mg sc once a week for 48 weeks of therapy followed by 24 weeks of treatment-free follow-up. The study enrolled 271 patients whose baseline characteristics were 72% male, 88% Caucasian, 78% with cirrhosis and 21% with bridging fibrosis, and 56% genotype 1.

Patients with or without cirrhosis: In NV15497, patients received either ROFERON-A 6 MIU sc three times a week for 12 weeks followed by 3 MIU sc three times a week for 36 weeks or PEGASYS 180 mg sc once a week for 48 weeks, both arms were followed by 24 weeks of treatment-free follow-up. The study enrolled 531 patients whose baseline characteristics were 67% male, 85% Caucasian, 13% with cirrhosis or bridging fibrosis, a mean Knodell HAI score of 9, and 62% genotype 1.

Sustained virological response (SVR) was defined as a single undetectable HCV RNA measurement at the end of treatment-free follow-up period, measured by the qualitative COBAS AMPLICOR HCV Test, version 2.0 (limit of detection 100 copies/mL equivalent to 50 IU/mL) (refer to Table 2). Histological improvement was measured as ³ 2 point decrease in total Knodell HAI score at end of follow-up as compared to pre-treatment values (refer to Table 3).

Table 2. Virological Responses to Monotherapy Treatment*

	NV15495 (with cirrhosis)		NV15497 (without cirrhosis)	
	ROFERON-A 3 MIU (*n* = 88)	**PEGASYS 180 mg (*n* = 87)**	**ROFERON-A 6 MIU/3 MIU (*n* = 264)**	**PEGASYS 180 mg (*n* = 267)**
All Genotypes SVR (week 72)	8% (7/88)	30% (26/87) *p* = 0.001	19% (50/264)	39% (103/267) *p* = 0.001
Genotype 1 SVR (week 72)*	2% (1/47)	13% (6/48) *p* = 0.1†	7% (12/161)	28% (47/168) *p* < 0.0001‡
Genotype non-1 SVR (week 72)*	15% (6/40)	53% (19/36) *p* = 0.001‡	37% (37/101)	56% (55/98) *p* = 0.009‡

*Patients in the ITT population of unknown genotype are not included

Note: *p*-values assessed by Cochran-Mantel-Haenszel test stratified by center, except for † Fisher's exact test and ‡ Pearson's chi-square test with Yates' continuity correction

Patients treated with PEGASYS 180 mg had overall SVRs of 30% in patients with cirrhosis and 39% in patients without cirrhosis. In the dose finding study, NV15489, a SVR was achieved in 6/20 (30%) patients given PEGASYS 90 mg for 48 weeks.

Table 3. Histological Responses to Monotherapy Treatment, Patients with Paired Biopsies

	NV15495 (with cirrhosis)		NV15497 (without cirrhosis)	
	ROFERON-A 3 MIU (*n* = 55)	**PEGASYS 180 mg (*n* = 68)**	**ROFERON-A 6 MIU/3 MIU (*n* = 167)**	**PEGASYS 180 mg (*n* = 184)**
Histological Response (week 72)	31% (17/55)	54% (37/68)*	55% (92/167)	63% (116/184)
Median baseline HAI	13	14	10	9
Median change from baseline	0.0	-3.0	-2.0	-2.0
Histological Response in Virological Non-responders	26% (13/50)	35% (15/43)	44% (55/124)	47% (47/100)

* $p < 0.025$, assessed by Cochran-Mantel-Haenszel test stratified by center

In all trials, most patients treated with PEGASYS have normalisation or improvement of serum ALT during therapy. However, ALT may not normalise, even in patients in whom HCV RNA has become undetectable, until after PEGASYS treatment has been completed. Whether or not ALT normalises, virological determination provides a more reliable means of determining the effectiveness of PEGASYS treatment.

Quality of Life Assessment

During treatment with ROFERON-A, patients commonly experience shaking chills, body aches, headache, loss of concentration, fatigue, anxiety, and insomnia. Such complaints reflect the significant quality of life reductions associated with standard interferon alfa-2a therapy.

In NV15497, patients treated with PEGASYS experienced superior quality of life during the first 12 weeks of therapy than those receiving standard interferon alfa-2a. Most of these differences were statistically and clinically significant in terms of physical health, mental health and fatigue severity.

Combination Therapy in Treatment-Naïve Patients

Patients with Elevated Alanine Transferase (ALT) Levels
The safety and effectiveness of PEGASYS in combination with ribavirin (COPEGUS) 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 mg sc once a week and randomised to treatment for either 24 or 48 weeks and to a COPEGUS daily dose of 800 mg or 1000/1200 mg (for body weight < 75 kg / ³ 75 kg). Assignment to the 4 treatment arms was stratified by viral genotype and baseline HCV viral titer.

In NV15801, a prospective, randomised controlled, multinational clinical trial, 1121 patients received either PEGASYS 180 mg sc once a week with placebo, PEGASYS 180 mg sc once a week with COPEGUS 1000 mg (body weight < 75 kg) or 1200 mg (body weight ≥ 75 kg), 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.

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 4. SVR to Combination Treatment in CHC Patients (Elevated ALT Levels)

	NV15942				NV15801		
	24 weeks		48 weeks		48 weeks		
	PEGASYS 180 mg with COPEGUS 800 mg (*n* = 207)	**PEGASYS 180 mg with COPEGUS 1000/1200 mg (*n* = 280)**	**PEGASYS 180 mg with COPEGUS 800 mg (*n* = 361)**	**PEGASYS 180 mg with COPEGUS 1000/1200 mg (*n* = 436)**	**PEGASYS 180 mg (*n* = 224)**	**PEGASYS 180 mg with COPEGUS 1000/1200 mg (*n* = 453) [A³ 80%]**	**INTRON A 3 MIU with REBETOL 1000/1200 mg (*n* = 444) *p*-values***
All Genotypes	55% (114/207)	64% (179/280)	52% (187/361)	63% (275/436)	29% (66/224)	56% (255/453) [75%]	45% (200/444) *p* = 0.001
Genotype 1	29% (29/101)	42% (49/118)	41% (102/250)	52% (142/271)	21% (30/145)	46% (138/298) [67%]	36% (104/285) *p* = 0.016
Genotype non-1†	80% (85/106)	80% (130/162)	77% (85/111)	81% (133/165)	45% (31/69)	76% (106/140) [88%]	61% (89/145) *p* = 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 4). 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 in combination with COPEGUS 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 in combination with COPEGUS 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 ³ 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 in combination with COPEGUS 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 to 600 IU/mL and approximately 26% had no evidence of fibrotic liver disease.

In NR16071, 514 patients were randomised to receive PEGASYS 180 mg 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 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 5).

Table 5. SVR to Combination Treatment in CHC Patients (Normal ALT Levels)

	PEGASYS 180 mg with COPEGUS 800 mg 24 weeks (*n* = 212)	PEGASYS 180 mg 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) $p \leq 0.452$	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 mg sc once a week and COPEGUS 1000/1200 mg daily than when treated with COPEGUS 800 mg 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 mg 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 in combination with COPEGUS 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 ³ 80%) of the planned PEGASYS in combination with COPEGUS 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 of prior treatment), were randomised to 4 different treatments: PEGASYS 360 mg once a week for 12 weeks, followed by 180 mg once a week for a further 60 weeks; PEGASYS 360 mg once a week for 12 weeks, followed by 180 mg once a week for a further 36 weeks; PEGASYS 180 mg

once a week for 72 weeks; or PEGASYS 180 mg 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 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				
	A **PEGASYS 360 µg 12 wk then 180 µg 60 wk COPEGUS 1000/1200 mg 72 wk** **(*n* = 317)**	**B** **PEGASYS 360 µg 12 wk then 180 µg 36 wk COPEGUS 1000/1200 mg 48 wk** **(*n* = 156)**	**C** **PEGASYS 180 µg 72 wk** **COPEGUS 1000/1200 mg 72 wk** **(*n* = 156)**	**D** **PEGASYS 180 µg 48 wk** **COPEGUS 1000/1200 mg 48 wk** **(*n* = 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; 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 7. SVR in Previous Peginterferon alfa-2b/Ribavirin Non-responders: Pooled Treatment Comparisons

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

Table 8. SVR Rates After Treatment with PEGASYS and COPEGUS Combination Therapy 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	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 mg 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 plus COPEGUS 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 9). There was no difference in disease progression/cirrhosis with or without treatment (33% versus 34%).

Table 9. 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, 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 mg 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 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 10.

Table 10. 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 in combination with COPEGUS achieved higher SVRs 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 (³ 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 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

Chronic Hepatitis B (CHB)

Clinical trials have demonstrated that PEGASYS is effective in the treatment of patients with CHB, in both HBeAg-positive patients and HBeAg-negative/anti-HBe-positive patients.

The safety and effectiveness of PEGASYS for the treatment of CHB were assessed in two randomised, partially double-blinded clinical trials in HBeAg-positive patients (WV16240) and HBeAg-negative patients (WV16241). Both trials recruited patients with CHB who had active viral replication measured by HBV DNA, elevated levels of ALT and a liver biopsy consistent with chronic hepatitis. No HBV-HIV co-infected patients were included in these clinical trials.

In both trials, patients received either PEGASYS 180 µg sc once a week with placebo, PEGASYS 180 µg sc once a week with lamivudine 100 mg daily or lamivudine 100 mg daily for 48 weeks of therapy followed by 24 weeks of treatment-free follow-up.

In WV16240, the primary measures were HBeAg seroconversion and suppression of HBV DNA to < 10^5 copies/mL. HBV DNA was measured by the COBAS AMPLICOR HBV MONITOR Assay (limit of detection 200 copies/mL). Response rates at the end of follow-up are presented in Table 11.

Table 12. Virological and Biochemical Responses in HBeAg-Positive CHB Patients

	Study WV16240		
	PEGASYS 180 µg with placebo (*n* = 271)	**PEGASYS 180 µg with lamivudine 100 mg (*n* = 271)**	**Lamivudine 100 mg (*n* = 272)**
HBeAg Seroconversion	32% [1] (87/271)	27% (74/271)	19% (52/272)
HBV DNA*	32% [2] (86/271)	34% (91/271)	22% (60/272)
ALT Normalisation**	41% [3] (111/271)	39% (106/271)	28% (76/272)
HBsAg Seroconversion	3% [4] (8/271)	3% (8/271)	0% (0/272)

* HBV DNA < 10^5 copies/mL; mean baseline viral titres ~10^{10} copies/mL

** ALT level < 30 U/L; mean baseline ALT 111 U/L

1 Odds Ratio (95% CI) vs lamivudine = 2.00 (1.34 – 2.97); *p*-value (stratified Cochran-Mantel-Haenszel test) < 0.001

2 Odds Ratio (95% CI) vs lamivudine = 1.64 (1.12 – 2.42); *p*-value (stratified Cochran-Mantel-Haenszel test) = 0.012

3 Odds Ratio (95% CI) vs lamivudine = 1.77 (1.23 – 2.54); *p*-value (stratified Cochran-Mantel-Haenszel test) = 0.002

4 Odds Ratio not definable; *p*-value (stratified Cochran-Mantel-Haenszel test) = 0.004

In WV16241, the primary measures were normalised ALT and suppression of HBV DNA to < 2 x 10^4 copies/mL. Response rates at the end of follow-up are presented in Table 13.

Table 13. Virological and Biochemical Responses in HBeAg-Negative / anti-HBe-Positive CHB Patients

	Study WV16241		
	PEGASYS 180 µg with placebo (*n* = 177)	**PEGASYS 180 µg with lamivudine 100 mg (*n* = 179)**	**Lamivudine 100 mg (*n* = 181)**
HBV DNA*	43% [1] (76/177)	44% (79/179)	29% (53/181)
ALT Normalisation**	59% [2] (105/177)	60% (107/179)	44% (80/181)
HBsAg Seroconversion	3% (5/177)	2% (3/179)	0% (0/181)

* HBV DNA < 2 x 10^4 copies/mL; mean baseline viral titres ~10^7 copies/mL

** ALT level < 30 U/L; mean baseline ALT 97 U/L

1 Odds Ratio (95% CI) vs lamivudine = 1.84 (1.17 – 2.89); *p*-value (stratified Cochran-Mantel-Haenszel test) = 0.007

2 Odds Ratio (95% CI) vs lamivudine = 1.86 (1.22 – 2.85); *p*-value (stratified Cochran-Mantel-Haenszel test) = 0.004

INDICATIONS

Chronic Hepatitis C (CHC)

The combination of PEGASYS and COPEGUS 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.

The combination of PEGASYS and COPEGUS is also indicated for the treatment of chronic hepatitis C patients with clinically stable human immunodeficiency virus (HIV) co-infection who have previously not received interferon therapy.

PEGASYS monotherapy is indicated for the treatment of chronic hepatitis C in treatment-naïve patients (see *Dosage and Administration; Chronic Hepatitis C: Treatment-Naive Patients*).

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

Chronic Hepatitis B (CHB)
PEGASYS is indicated for the treatment of chronic hepatitis B in adult patients with evidence of viral replication and liver inflammation and compensated liver disease.

CONTRAINDICATIONS

PEGASYS is contraindicated in patients with:

- known hypersensitivity to alfa interferons, to *E. coli*-derived products, to polyethylene glycol or to any component of the product
- autoimmune hepatitis
- decompensated cirrhosis
- 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.
- neonates and infants up to the age of 3 years, because of the excipient benzyl alcohol

PEGASYS in combination with COPEGUS is contraindicated in:

- 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 pregnant or breast-feeding
- men whose female partners are pregnant or are not using adequate contraception

For full product information on PEGASYS in combination with COPEGUS please refer to the PEGASYS RBV Product Information.

PRECAUTIONS

General
Treatment with PEGASYS 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*).

The optimal treatment for CHC is considered to be the administration of combination interferon alfa based therapies with ribavirin, including PEGASYS RBV combination therapy. For PEGASYS in combination with COPEGUS therapy, please refer to the PEGASYS RBV Product Information.

The use of PEGASYS and COPEGUS combination therapy 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.

Neuropsychiatric
Severe psychiatric adverse reactions may manifest in patients receiving therapy with interferons, including PEGASYS. Depression, suicidal ideation, suicide, relapse of drug dependence and drug overdose may occur in patients with or without previous psychiatric illness. PEGASYS 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 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.

HCV: 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. 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.

HBV: Disease exacerbations during therapy are not uncommon and are characterised by transient and potentially significant increases in serum ALT. In clinical trials with PEGASYS in HBV, marked transaminase flares have been accompanied by mild changes in other measures of hepatic function and without evidence of hepatic decompensation. ALT elevation > 10-fold higher than the upper limit of normal (ULN) were reported in 12% and 18% during PEGASYS treatment and 7% and 12% post-treatment in HBeAg-negative and HBeAg-positive patients, respectively. In approximately half the cases of flares exceeding 10 x ULN, PEGASYS dosing was reduced or withheld until the transaminase elevations subsided, while in the rest, therapy was continued unchanged. More frequent monitoring of hepatic function was recommended in all instances. If ALT increases are severe and progressive despite reduction of PEGASYS dose or are accompanied by increase in bilirubin or evidence of hepatic decompensation, PEGASYS should

be immediately discontinued (refer to *Adverse Effects*: *Laboratory Values-ALT elevations* and *Dosage and Administration, Dose Modification-Hepatic Function)*.

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

Endocrine
As with other interferons, PEGASYS 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 can not be effectively controlled by medication should not begin PEGASYS therapy. Patients who develop these conditions during treatment and can not be controlled with medication should discontinue PEGASYS therapy.

Autoimmune
Exacerbation of autoimmune disease has been reported in patients receiving alfa interferon therapy. PEGASYS should be used with caution in patients with autoimmune disorders. Use of alfa interferons has been associated with exacerbation or provocation of psoriasis. PEGASYS 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. urticara, angioedema, bronchoconstriction, anaphylaxis) have been rarely observed during alfa interferon therapy. If such a reaction develops during treatment with PEGASYS, 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. 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 should be used with caution in patients with baseline neutrophil counts < 1500 cells/mm^3, with baseline platelet count $< 90\,000$ cells/mm^3 or baseline haemoglobin < 120 g/L (refer to *Dosage and Administration*). As with other interferons, caution should be exercised when administering PEGASYS 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. 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 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. Appropriate anti-infective therapy should be started immediately and discontinuation of therapy should be considered.

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

Effects on Laboratory Tests
Before beginning PEGASYS, standard haematological and biochemical laboratory tests are recommended for all patients. 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.

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

- platelet count $\geq$ 90 000 cells/mm^3
- absolute neutrophil count (ANC) $\geq$ 1500 cells/mm^3
- thyroid stimulating hormone (TSH) and T_4 within normal limits or adequately controlled thyroid function
- HIV-HCV co-infection: CD4+ $\geq$ 200/µL or $CD_{4+} \geq$ 100/µL to < 200/µL and HIV-1 RNA < 5000 copies/mL using Amplicor HIV-1 Monitor test, version 1.5.

For PEGASYS in combination with COPEGUS, please refer also to the PEGASYS RBV Product Information for the effects on laboratory parameters.

PEGASYS treatment 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/mm^3 (refer to *Dosage and Administration*). For patients with ANC values below 500 cells/mm^3 treatment should be suspended until ANC values return to more than 1000 cells/mm^3. In clinical trials with PEGASYS, 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 treatment 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 below 50 000 cells/mm^3, and cessation of therapy is recommended when platelet count decreases to below 25 000 cells/mm^3 (refer to *Dosage and Administration*).

Anaemia (haemoglobin≤ 100 g/L) was observed in 13% and 3% of patients in clinical trials treated with PEGASYS with COPEGUS for 48 weeks and 24 weeks, respectively (refer to *Adverse Effects*: *Laboratory Test Values – Haemoglobin and Haematocrit*). The risk of developing anaemia is higher in the female population. The maximum drop in haemoglobin occurred within 4 weeks of initiation of ribavirin 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. Prior to initiation of PEGASYS therapy, evaluate thyroid stimulating hormone (TSH) levels. PEGASYS treatment may be initiated if TSH levels can be maintained in the normal range by medication. If the patient develops clinical symptoms consistent with possible thyroid dysfunction, determine TSH levels during the course of therapy. In the presence of thyroid dysfunction, 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*). Caution should be exercised in prescribing PEGASYS to patients with severe renal impairment.

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

This product contains 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 effects may occur in neonates or infants is not known (refer to *Contraindications*).

Use in the Elderly
No special dosage modification is required for elderly patients based on pharmacokinetic, pharmacodynamic, tolerability, and safety data from clinical trials (refer to *Pharmacokinetics*).

Carcinogenesis and Mutagenesis
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.

Effects on Fertility
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 17b-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.

Use in Pregnancy: Category B3
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 in humans. 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

For PEGASYS in combination with COPEGUS, please refer also to the PEGASYS RBV Product Information.

Use in Lactation
It is not known whether peginterferon alfa-2a or its metabolites 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, a decision should be made either to discontinue nursing or PEGASYS 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, or 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 HCV clinical trials. Similarly, lamivudine had no effect on PEGASYS pharmacokinetics during HBV clinical trials.

Treatment with PEGASYS 180 mg 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 AUC of theophylline was observed in the same study. Comparable effects on the pharmacokinetics of theophylline 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 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 – 150 mg), treatment with PEGASYS 180 mg sc once a week 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.

Azathioprine
COPEGUS, by having an inhibitory effect on inosine monophosphate dehydrogenase, may interfere with azathioprine metabolism possibly leading to an accumulation of 6-methyl-thioinosine 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*).

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 (NRTIs, i.e. 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 hyperlactacidaemia/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.

Telbivudine: A clinical trial investigating the combination of telbivudine 600 mg daily, with PEGASYS 180 mg 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.

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

ADVERSE EFFECTS

The adverse reactions observed with other alfa interferons, alone or in combination with ribavirin, may also be expected with PEGASYS alone or in combination with COPEGUS.

Experience from Clinical Trials

The frequency and severity of the most commonly reported adverse reactions are similar in patients treated with PEGASYS and interferon alfa-2a as well as in patients treated with PEGASYS or interferon alfa in combination with COPEGUS.

The most frequently reported adverse reactions with PEGASYS alone and in combination with COPEGUS were mostly mild to moderate in severity and were manageable without the need for discontinuation of therapy.

Chronic Hepatitis C (CHC)

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 and 13% for PEGASYS in combination with COPEGUS 1000/1200 mg given for 48 weeks. Discontinuation of treatment due to laboratory abnormalities occurred in only 1% and 3% of patients on PEGASYS alone or in combination, respectively. The withdrawal rates for patients with cirrhosis were similar to those of the overall population.

In comparison to 48 weeks of treatment with PEGASYS and COPEGUS 1000/1200 mg, reducing treatment exposure to 24 weeks and daily dose of COPEGUS to 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 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 14 below).

Table 14. Adverse Reactions Occurring in ³ 10% of Hepatitis C Patients with Normal ALT Levels

	PEGASYS 180 mg with COPEGUS 800 mg 24 weeks (*n* = 212) %	PEGASYS 180 mg 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/mm^3 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 counts (ANC) < 750/mm^3, 30%; and platelet < 50 000/mm^3, 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, the adverse reactions reported with PEGASYS, alone or in combination with COPEGUS, were similar to those observed in HCV infected patients. The incidence of withdrawal from treatment for adverse reactions, laboratory abnormalities or AIDS-defining events was 16% for PEGASYS alone and 15% for PEGASYS in combination with COPEGUS 800 mg, given for 48 weeks. Respectively, 4% and 3% of patients required discontinuation of PEGASYS alone or in combination with COPEGUS, due to blood and lymphatic system disorder adverse events. Serious adverse reactions were reported in 21% and 17% of those receiving PEGASYS alone or in combination with COPEGUS, 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 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 ³ 10% of patients in study NV18209 were similar to those within Table 14 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*).

Chronic Hepatitis B (CHB)

In CHB patients, adverse reactions reported with PEGASYS were similar to that seen in CHC, although the frequency of reported adverse reactions was notably less in hepatitis B (refer to Table 15). Serious adverse reactions were reported in 6% of patients receiving PEGASYS and

4% of patients receiving lamivudine. The incidence of withdrawal due to adverse reactions or laboratory abnormalities was 5% for PEGASYS. The withdrawal rates for patients with cirrhosis were similar to those of the overall population. The addition of lamivudine did not adversely affect the safety profile of PEGASYS.

Table 15 shows those adverse reactions occurring in ≥ 10% of HCV patients receiving PEGASYS alone or combination with COPEGUS, HIV-HCV patients receiving PEGASYS in combination with COPEGUS, HBV patients receiving PEGASYS alone and HCV patients who did not respond to previous peginterferon alfa-2b treatment receiving PEGASYS in combination with COPEGUS.

Table 15. Adverse Reactions Occurring in ³ 10% of Patients in Clinical Trials

	HCV				**HIV-HCV**	**HBV**	**HCV Peginterferon alfa-2b Non-responders**
	PEGASYS 180 mg 48 weeks (*n* = 827) %	**PEGASYS 180 mg with COPEGUS 800 mg 24 weeks (*n* = 207) %**	**PEGASYS 180 mg 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 mg with COPEGUS 800 mg 48 weeks (*n* = 288) %**	**PEGASYS 180 mg† 48 weeks (*n* = 448) %**	**PEGASYS 180 mg with COPEGUS 1000 or 1200 mg 72 weeks (*n* = 156) %**
General disorders and administration site conditions							
Fatigue	49	45	49	53	40	21	36
Rigors*	30	30	25	34	16	6	12
Pyrexia*	35	37	39	54	41	52	20
Injection Site Reaction	22	28	21	16	10	7	12
Pain	11	9	10	9	6	1	6
Asthenia	7	18	15	16	26	11	30
Psychiatric disorders							
Depression*	18	17	21	28	22	4	16
Irritability	17	28	24	27	15	3	17
Anxiety	6	8	8	12	8	3	6
Musculoskeletal and connective tissue disorders							
Myalgia	37	42	38	49	32	25	22
Arthralgia	26	20	22	23	16	10	15
Nervous system disorders							
Headache	52	48	47	49	35	23	32
Insomnia	20	30	32	37	19	6	29

Dizziness	15	13	15	14	7	6	10
Concentration Impairment	9	8	10	13	2	2	5
Skin and subcutaneous tissue disorders							
Alopecia*	23	25	24	33	10	17	18
Pruritus	13	25	21	18	5	6	22
Dermatitis	9	15	16	13	1	<1	1
Dry Skin	5	13	12	13	4	1	17
Gastrointestinal disorders							
Nausea	24	29	28	28	24	6	24
Diarrhoea	16	15	14	10	16	6	13
Abdominal pain	15	9	10	9	7	4	9
Respiratory, thoracic and mediastinal disorders							
Dyspnoea	5	11	13	14	7	1	11
Cough	4	8	13	7	3	2	17
Metabolism and nutrition disorders							
Anorexia	16	20	27	26	23	13	15
Weight Decrease	5	2	7	10	16	4	9

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

† In HBV clinical trials, 450 patients received PEGASYS in combination with lamivudine. The addition of lamivudine had no effect on the safety profile of PEGASYS

Patients with normal ALT levels

The safety profile of PEGASYS and COPEGUS combination therapy 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 15).

Commonly reported adverse reactions (1 – 10%) in patients treated with PEGASYS in combination with COPEGUS or PEGASYS monotherapy during clinical trials 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, peripheral oedema, 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 in combination with COPEGUS 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 in combination with COPEGUS or PEGASYS monotherapy 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, hallucination

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 combination therapy of PEGASYS and COPEGUS.

Dehydration has been reported rarely with combination therapy of PEGASYS and COPEGUS.

As with other alfa interferons, serous retinal detachment has been reported with PEGASYS and COPEGUS 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, used in combination with COPEGUS, may be associated with pancytopenia, and very rarely, aplastic anaemia has been reported. .

Laboratory Test Values

Haematology
As with other interferons, treatment with PEGASYS alone or in combination therapy were 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 (refer to *Precautions*: *Effects on Laboratory Tests* and *Dosage and Administration*). 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
Although treatment with PEGASYS alone 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 (refer to *Precautions*: *Effects on Laboratory Tests* and *Dosage and Administration*). Anaemia (haemoglobin < 100 g/L) was reported in 7% ,14% and 28% of HIV-HCV co-infected patients treated with PEGASYS, alone or in combination with COPEGUS 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 HCV/HBV patients on PEGASYS monotherapy and 5% of HCV patients receiving PEGASYS combination therapy had transient decreases in ANC to levels below 500 cells/mm^3 at some time during therapy. In HIV-HCV co-infected patients, 13% and 11% of those receiving PEGASYS, alone or in combination with COPEGUS, respectively, had decreases in ANC < 500 cells/mm^3.

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 50 000 cells/mm^3 mostly in patients with cirrhosis and who entered the trial with baseline platelet counts as low as 75 000 cells/mm^3. In clinical trials for HBV, 14% of patients had decreases in platelet counts to below 50 000 cells/mm^3, mostly in patients who entered the study with low baseline platelet counts. In HIV-HCV co-infected patients, 10% and 8% of those receiving PEGASYS, alone or in combination with COPEGUS, respectively, had decreases in platelets below 50 000 cells/mm^3.

Thyroid Function
PEGASYS treatment 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 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.

ALT Elevations
HBV: Transient ALT elevations were observed with Hepatitis B therapy with PEGASYS. ALT elevation > 10-fold higher than the ULN were reported in 12% and 18% during PEGASYS treatment and 7% and 12% post-treatment in HBeAg-negative and HBeAg-positive patients, respectively (refer to *Precautions*: *Hepatic Function, HBV* and *Dosage and Administration*: *Dose Modification-Hepatic Function).*

Anti-interferon Antibodies
Two percent of HCV patients receiving PEGASYS monotherapy or in combination with COPEGUS 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, standard haematological and biochemical laboratory tests are recommended for all patients (refer to *Precautions*: *Effects on Laboratory Tests*).

For use of COPEGUS in combination with PEGASYS, please refer to the PEGASYS RBV Product Information**.**

Chronic Hepatitis C: Treatment-Naïve Patients

PEGASYS and COPEGUS combination treatment is recommended unless intolerance or contraindication to ribavirin.

The recommended dose of PEGASYS, alone or in combination with oral COPEGUS is 180 mg once a week by subcutaneous administration in the abdomen or thigh. COPEGUS should be administered in divided doses (morning and evening) with food. The recommended duration of PEGASYS monotherapy is 48 weeks. The duration of combination therapy and the daily dose of COPEGUS should be individualised based on the patient's viral genotype (refer to Table 16).

Table 16. Dosing Recommendation for CHC Combination Therapy

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

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

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

Chronic Hepatitis C: Prior Treatment Non-responder and Relapser Patients
The recommended dosage of PEGASYS and COPEGUS combination therapy is PEGASYS 180 mg once a week by subcutaneous administration in the abdomen or thigh. For patients < 75 kg and ³ 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, alone or in combination with oral COPEGUS 800 mg daily, is 180 µg once a week by subcutaneous administration in the abdomen or thigh. 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.

Chronic Hepatitis B
The recommended dose of PEGASYS is 180 µg once a week by subcutaneous administration in the abdomen or thigh. The recommended duration of therapy is 48 weeks.

Dose Modification

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

Haematological

Table 17. 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 mg	< 500 cells/mm^3, treatment should be suspended until ANC values return to more than 1000 cells/mm^3 Initially reinstitute at 90 mg and monitor ANC
Platelet Count	< 50 000 cells/mm^3, reduce to 90 mg	< 25 000 cells/mm^3

Table 18. 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, 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 ribavirin, PEGASYS monotherapy may be continued.

Hepatic Function
Fluctuations in abnormalities of hepatic function tests are common in patients with chronic hepatitis. 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. For HCV patients, the dose should be reduced initially to 135 mg 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.

For use of COPEGUS in combination with PEGASYS, please refer also to the PEGASYS RBV Product Information.

For HBV patients, transient flares of ALT levels sometimes exceeding 10 times the ULN are not uncommon, and may reflect immune clearance. Consideration should be given to continuing treatment with more frequent monitoring of hepatic function during ALT flares (> 5 x ULN). If ALT increases are severe (> 10 x ULN) and persistent then consideration should be given to discontinuation of treatment. If ALT increases are severe and progressive despite reduction of PEGASYS dose or are accompanied by increase in bilirubin or evidence of hepatic decompensation, PEGASYS should be immediately discontinued (refer to *Adverse Effects*: *Laboratory Values-ALT elevations* and *Precautions*: *Hepatic Function-HBV)*.

After PEGASYS dose reduction or withholding, therapy can be restored once the flare subsides.

Special Populations

*Renal Impairment***:** In patients with end stage renal disease (creatinine clearance 20 to 40 mL/minute), a starting dose of PEGASYS 135 mg once a week should be used (refer to *Precautions*). The pharmacokinetics of COPEGUS are altered in patients with renal impairment due to reductions 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 creatinine clearance < 50 mL/min must not be treated with COPEGUS. 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)*.

For use of COPEGUS in combination with PEGASYS, please refer also to the PEGASYS RBV Product Information.

*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*).

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 (refer to Table 19).

Table 19. Modified Assessment

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

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

Children: Safety and effectiveness have not been established in patients below the age of 18. In addition, PEGASYS injection 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 special dosage modification is required for elderly patients based upon pharmacokinetic, pharmacodynamic, tolerability, and safety data from clinical trials.

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 mg/week) have been reported. None of these patients experienced unusual, serious or treatment-limiting events. Weekly doses of up to 540 and 630 mg 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.

Treatment of overdose should consist of general supportive measures.

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

PRESENTATION AND STORAGE CONDITONS

PEGASYS is available as a sterile, ready-to-use solution for subcutaneous injection in pre-filled syringes in two strengths, 135 and 180 mg.

Each single use, graduated, glass pre-filled syringe contains 0.5 mL solution for injection. Available in packs of 4 with corresponding number of injection needles.

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

Store in the refrigerator at 2 to 8 °C. Do not freeze or shake. Protect from light.

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

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

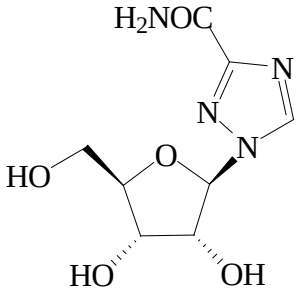
TGA Approval Date: 13 May 2011

NAME OF THE MEDICINE

COPEGUS®

ribavirin

CAS 36791-04-05



The chemical name for ribavirin is 1-β-D-ribofuranosyl-1*H*-1,2,4-triazole-3-carboxamide with the molecular formula $C_8H_{12}N_4O_5$ and the molecular weight is 244.21.

DESCRIPTION

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

COPEGUS is supplied as light pink, flat, oval shaped film-coated tablets 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

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 hepatitis C virus (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 hepatitis C virus (HCV RNA) or improving hepatic histology after 6 – 12 months of therapy and 6 months follow-up.

PHARMACOKINETICS

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 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 the dose and AUC_{tf} 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 carboxyacid metabolite. 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 $AUC_{(0\text{-}192h)}$ 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 ribavirin. In order to achieve the optimal ribavirin plasma concentrations, it is recommended that COPEGUS is taken with food.

Pharmacokinetics of HCV genotype 1 infected patients (Study NP17534)
Multiple dose ribavirin pharmacokinetic data are available for HCV genotype 1 infected adult patients who received ribavirin in combination with peginterferon alfa-2a. This study in 42 subjects demonstrated that there is no clinically significant difference in ribavirin pharmacokinetics among Black, Hispanic and Caucasian subjects. The inter-patient variability in ribavirin pharmacokinetics data ranged from 30% – 50% and was similar between groups. Table 1 includes the pharmacokinetic data for the Caucasian subjects on administration of 1000 mg/day (< 75 kg) or 1200 mg/day (≥ 75 kg) with food for 8 weeks mean ± SD (*n* = 15).

Table 1: Summary of Ribavirin Pharmacokinetic Results for HCV Genotype 1 Infected Caucasian Subjects at Week 8

	***n* = 15**	
	Mean ± SD	**CV (%)**
T_{max} h	2.6 ±-2.1	52.2
Dose-normalised C_{max} ng/mL	3821± 1188	47.6
AUC $_{0-12}$ hr ng.hr/mL	35803 ± 10918	30.5
C_{ss} min ng/mL	2184 ± 643	29.4
CL/F (L/h)	18.4 ± 6.3	34.0

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 (≥ 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.

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. A list of pharmacokinetic data from Caucasian subjects in included in Table 1.

CLINICAL TRIALS

In combination with PEGASYS.

Chronic Hepatitis C: Treatment-Naïve Patients

Patients with Elevated Alanine Transaminase (ALT) Levels:
The safety and effectiveness of COPEGUS in combination with PEGASYS (peginterferon alfa-2a) 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 mg subcutaneous (sc) once a week and were 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/³ 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 mg sc once a week with placebo, PEGASYS 180 mg sc once a week with COPEGUS 1000 mg (body weight < 75kg) or 1200 mg (body weight ≥ 75kg) daily, or interferon alfa-2b 3 MIU sc three times a week with ribavirin 1000 mg or 1200 mg daily (REBETRON^{â}) 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 mg with COPEGUS 800 mg (*n* = 207)	**PEGASYS 180 mg with COPEGUS 1000/1200 mg (*n* = 280)**	**PEGASYS 180 mg with COPEGUS 800 mg (*n* = 361)**	**PEGASYS 180 mg with COPEGUS 1000/1200 mg (*n* = 436)**	**PEGASYS 180 mg (*n* = 224)**	**PEGASYS 180 mg with COPEGUS 1000/1200 mg (*n* = 453) [A³ 80%]**	**Interferon alfa-2b with Ribavirin (REBETOL) 1000/1200 mg (*n* = 444) *p*-values***
All Genotypes	55% (114/207)	64% (179/280)	52% (187/361)	63% (275/436)	29% (66/224)	56% (255/453) [75%]	45% (200/444) *p* = 0.001
Genotype 1	29% (29/101)	42% (49/118)	41% (102/250)	52% (142/271)	21% (30/145)	46% (138/298) [67%]	36% (104/285) *p* = 0.016
Genotype non-1†	80% (85/106)	80% (130/162)	77% (85/111)	81% (133/165)	45% (31/69)	76% (106/140) [88%]	61% (89/145) *p* = 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 NV1580, the SVR was 43% in cirrhotic patients treated with PEGASYS combination with COPEGUS therapy compared to 33% in the interferon alfa-2b with ribavirin treatment group**.** At the end of follow-up, 80% of patients who had a paired biopsy and were treated with PEGASYS combination with COPEGUS 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 ³ 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 COPEGUS in combination with PEGASYS 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 three occasions, a minimum of 4 weeks apart. The patient population across the three 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 mg 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 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 SVRs 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 numerically, but 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 mg with COPEGUS 800 mg **24 weeks** **(*n* = 212)**	**PEGASYS 180 mg 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) $p < 0.001$	0% $p < 0.001$
Genotype 1 SVR (week 72)	13% (19/144)	40% (57/141) $p < 0.001$	0% $p < 0.001$
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% $p < 0.001$

† 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 mg sc once a week and COPEGUS 1000/1200 mg daily than when treated with COPEGUS 800 mg 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 $\log_{10}$ 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 mg once a week and who achieved a SVR had an early virological response by week 12. In HIV-HCV co-infected patients treated with COPEGUS in combination with PEGASYS and who achieved a SVR, 98% achieved an early virological response.

In the NV15801 trial, patients who had an early virological response by week 12 and adhered to at least 80% (A ³ 80%) of the planned PEGASYS with COPEGUS 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

treatment), were randomised to four different treatments: PEGASYS 360 mg once a week for 12 weeks, followed by 180 mg once a week for a further 60 weeks; PEGASYS 360 mg once a week for 12 weeks, followed by 180 mg once a week for a further 36 weeks; PEGASYS 180 mg once a week for 72 weeks; or PEGASYS 180 mg once a 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 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 **PEGASYS 360 µg 12 wk then 180 µg 60 wk COPEGUS 1000/1200 mg 72 wk** **(*n* = 317)**	**B** **PEGASYS 360 µg 12 wk then 180 µg 36 wk COPEGUS 1000/1200 mg 48 wk** **(*n* = 156)**	**C** **PEGASYS 180 µg 72 wk COPEGUS 1000/1200 mg 72 wk** **(*n* = 156)**	**D** **PEGASYS 180 µg 48 wk COPEGUS 1000/1200 mg 48 wk** **(*n* = 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; 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 Rates in Previous Peginterferon alfa-2b/Ribavirin Non-responders: Pooled Treatment Comparisons

Study MV17150 **(pooled groups)**				
	72 wk Groups **(360 µg 12 wk then 180 µg 60 wk + 180 µg 72 wk)** **(*n* = 473)**	**48 wk Groups** **(360 µg 12 wk then 180 µg 36 wk + 180 µg 48 wk)** **(*n* = 469)**	**360 µg Groups** **(360 µg 12 wk then 180 µg 60 wk + 360 µg 12 wk then 180 µg 36 wk)** **(*n* = 473)**	**180 µg Groups** **(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 and COPEGUS Combination Therapy 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	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 mg 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 plus COPEGUS 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 mg 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 and treated with either PEGASYS 180 µg once a week with placebo, PEGASYS 180 µg once a weekl 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. All patients were adults with compensated liver disease, detectable hepatitis C virus, 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. The SVRs for the three 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 - 4.32), *p*-value (stratified Cochran-Mantel-Haenszel test) < 0.0001

Patients treated with COPEGUS in combination with PEGASYS achieved higher SVR rates irrespective of HCV genotype or baseline viral titre than patients treated with conventional COPEGUS with ROFORON-A 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 (³ 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.

In combination with ROFERON-A.

Treatment-Naive Patients

A randomised, controlled trial was conducted to investigate the sustained efficacy of combining COPEGUS with ROFERON-A^{O} (interferon alfa-2a) compared to ROFERON-A alone. Sixty non-cirrhotic patients with CHC participated in this trial for 24 weeks treatment with a 72 week treatment-free follow-up period. Patients were followed up at 4 week intervals for the initial 24 weeks and every 8 weeks thereafter for a total of 96 weeks.

Patients were randomised to 1 of 3 treatment regimens: COPEGUS 1200 mg daily with ROFERON-A 3 MIU sc three times a week (*n* = 21); ROFERON-A 3 MIU sc three times a week (*n* = 19); or no treatment (*n* = 20).

Virological response, defined as negative HCV RNA (determined by Polymerase Chain Reaction using the COBAS-AMPLICOR^{Ò} version 2.0, sensitivity to 100 copies/mL) was measured at the end of treatment and during the treatment-free follow-up period to determine the SVR rates (refer to Table 10).

Virological response was reported more frequently in patients treated with COPEGUS in combination with ROFERON-A therapy than those treated with ROFERON-A alone. Patients receiving COPEGUS with ROFERON-A combination therapy maintained a significantly higher rate of SVR for up to 2 years.

Table 10. Virological Responses*

	COPEGUS + ROFERON-A (*n* = 21)	**ROFERON-A (*n* = 19)**	***p*-value (Fisher's Exact Test)**
SVR (week 48)	48%	11%	0.016
SVR (week 72)	43%	6%	0.009
SVR (week 96)	43%	6%	0.009
Virological Response, End of treatment (week 24)	90%	42%	0.002

*Intent to treat population

Histological response was measured in 28 out of 60 patients by the Knodell Histology Activity Index (HAI). Histological improvements were defined as a decrease in the inflammation score of at least 2 points. Histology changes indicated that there was no significant difference between combination and interferon treatment groups.

Relapsed Patients

COPEGUS in combination with ROFERON-A has been investigated in CHC patients who had relapsed after treatment with interferon alfa monotherapy. In a placebo controlled, double-blind trial 99 patients were randomised into two treatment groups; 49 patients received oral COPEGUS 1000 mg daily in two divided doses with ROFERON-A 4.5 MIU sc three times a week and 50 patients received ROFERON-A 4.5 MIU sc three times a week with placebo. The treatment duration was 24 weeks with a 24 week treatment-free follow-up period.

Virological response, as defined for previously untreated patients, was measured at the end of treatment and during the treatment-free follow-up period to determine sustained responses (refer to Table 11).

SVRs were significantly higher for COPEGUS with ROFERON-A combination treated patients compared to ROFERON-A with placebo.

Table 11. Virological Responses*

	COPEGUS with ROFERON-A (*n* = 49)	ROFERON-A with placebo (*n* = 50)	*p*-value (Fischer's exact test)
SVR (week 48) All Genotypes	43% (21/49)	4% (2/50)	$p < 0.01$
SVR (week 48) Genotype 1	28% (7/25)	0% (0/24)	$p < 0.01$
SVR (week 48) Genotype non-1	28% (14/24)	8% (2/26)	$p < 0.01$
Virological Response (week 24) All Genotypes	88% (43/49)	46% (23/50)	$p < 0.01$

*Intent to treat population

Liver biopsies were conducted post-treatment to determine any improvements in histology. Histological improvements were defined as a decrease in the inflammation score of at least 2 points using the Knodell HAI (refer to Table 12). Fibrosis was graded according to the Metavir system in which a score of 0 indicated the absence of fibrosis and a score of 4 the presence of cirrhosis. Fibrosis was usually moderate, mild or absent in patients treated with COPEGUS with ROFERON-A combination therapy but usually severe, moderate or mild in patients treated with ROFERON-A alone.

Table 12. Overall Histological Response

	COPEGUS with ROFERON-A (*n* = 38)	ROFERON-A with placebo (*n* = 42)	*p*-value (Wilcoxon test)
Knodell HAI*			
Improvement	68%	45%	
Stabilisation	18%	29%	
Deterioration	13%	26%	$p = 0.03$
Metavir fibrosis score			
F0	8%	0%	
F1	61%	49%	
F2	26%	37%	
F3	3%	12%	
F4	3%	2%	$p < 0.05$

* based on the first 3 items: necroinflammatory score

INDICATIONS

COPEGUS is indicated in combination with PEGASYS (peginterferon alfa-2a) or other interferon alfa agents for the treatment of chronic hepatitis C in previously untreated (treatment-naïve) patients. COPEGUS in combination with PEGASYS is also indicated for the treatment of patients who have failed previous treatment with interferon alfa (pegylated or non-pegylated) alone or in combination therapy with ribavirin.

COPEGUS is also indicated in combination with PEGASYS for the treatment of chronic hepatitis C in patients with clinically 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 counseled 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.

COPEGUS is also contraindicated in patients with:

- known hypersensitivity to ribavirin or to any of the component of the product
- haemoglobinopathies (e.g. thalassaemia, sickle-cell anaemia)

PEGASYS and COPEGUS combination therapy is contraindicated in patients with hepatic decompensation.

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

For combination therapy with PEGASYS please also refer to the PEGASYS RBV (peginterferon alfa-2a + ribavirin) Product Information or PEGASYS (peginterferon alfa-2a) Product Information.

For combination therapy with ROFERON-A (interferon alfa-2a) please also refer to the ROFERON-A(interferon alfa-2a) Product Information.

PRECAUTIONS

General

COPEGUS used in combination with PEGASYS or ROFERON-A may lead to moderate to severe adverse experiences requiring dose reduction, temporary dose cessation or discontinuation of further 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 precautions listed in this section refer to the administration of COPEGUS only. For combination therapy please also refer to the PEGASYS RBV (peginterferon alfa-2a + ribavirin) Product Information, PEGASYS (peginterferon alfa-2a) Product Information or ROFERON-A (interferon alfa-2a) Product Information as appropriate.

Haemolysis
A decrease in haemoglobin levels to <100 g/L was observed in 13 % and 3% of patients in clinical trials treated with PEGASYS with COPEGUS combination therapy for 48 weeks and 24 weeks, respectively and up to 19% of patients treated with COPEGUS in combination with ROFERON-A in clinical trials. Anaemia occurred within 1 – 2 weeks of initiation of COPEGUS therapy. The risk of developing anaemia is higher in the female population. Complete blood counts should be obtained pre-treatment and at least at week 2 and week 4 of therapy and periodically thereafter. Patients should then be followed as clinically appropriate. Patients with haemoglobinopathies (e.g. thalassaemia major, sickle-cell anaemia) should not be treated with COPEGUS.

The use of COPEGUS and PEGASYS combination therapy 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 -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*).

Cardiovascular
Fatal and nonfatal myocardial infarctions have been reported in patients with patients with anaemia caused by ribavirin. Because cardiac disease may be worsened by ribavirin-induced anaemia, patients with a history of significant or unstable cardiac disease in the previous six months should not use COPEGUS. 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 electrogram prior to initiation, and during the course of COPEGUS therapy.

Hypersensitivity
If an acute hypersensitivity reaction, e.g. urticaria, angioedema, bronchoconstriction, anaphylaxis, develops, COPEGUS must be discontinued and appropriate medical therapy instituted immediately. Transient rashes do not necessitate the interruption of treatment.

Renal Impairment
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 modifications 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.

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*).

Hepatic Impairment
In patients who develop evidence of hepatic decompensation during treatment with COPEGUS in combination with PEGASYS or ROFERON-A, treatment should be discontinued.

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 $\geq$ 7). Combined treatment with COPGEUS and PEGASYS or ROFERON-A 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.

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

Effect on Ability to Drive or Operate Machinery
COPEGUS has no or negligible influence on the ability to drive or operate machinery. Any patients who develops fatigue, somnolence, or confusion during treatment must be cautioned to avoid driving or operating machinery.

Effects on Laboratory Tests
Before beginning COPEGUS therapy, standard haematological tests and blood chemistries: complete blood count and differential platelet count, electrolytes, serum creatinine, liver function tests, uric acid must be conducted in all patients prior to initiating therapy. After initiation of therapy, laboratory evaluations should be performed at week 2 and week 4 of therapy and biochemical tests should be performed at week 4. Additional testing should be performed periodically thereafter as clinically appropriate. Acceptable baseline values that may be considered as a guideline prior to initiation of COPEGUS in combination with peginterferon alfa-2a or interferon alfa-2a are:

- Haemoglobin ≥ 120 g/L (females); ≥ 130 g/L (males)
- Platelet count ≥ 90 000 cells/mm^3
- Absolute neutrophil count (ANC) ≥ 1500 cells/mm^3.
- For HIV-HCV co-infected patients: CD4+ ≥ 200/µL or CD4+ ≥ 100/µL to < 200/µL and HIV-1 RNA < 5000 copies/mL using Amplicor HIV-1 Monitor Test, version 1.5

Pregnancy screening and monthly pregnancy testing should be conducted for all women of child bearing potential while receiving COPEGUS therapy. HIV-HCV co-infected patients treated COPEGUS in combination with PEGASYS have increased frequency of haematological adverse events and should be monitored carefully. Female partners of male patients must have a routine pregnancy test performed monthly during treatment and for six months after treatment.

Paediatric Use
Safety and efficacy have not been established in children less than 18 years. It is therefore not recommended to give COPEGUS to children less than 18 years of age.

Use in the Elderly
No dosage adjustment is required for elderly patients. However, as in younger patients, renal function must be determined prior to administration of COPEGUS.

Carcinogenesis and Mutagenesis
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
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 spermatogensis cycles ie. 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) be must counselled to use effective contraception during therapy and for 6 months after therapy.

Use in Pregnancy – Category X

Ribavirin should not under any circumstances be administered to pregnant women or to men whose female partners are pregnant (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 ribavirin is excreted in human milk. Because of the potential for adverse reactions in nursing infants, nursing must be discontinued prior to initiation of treatment.

Interactions with Other Medicines
Interaction studies have been conducted with COPEGUS in combination with PEGASYS, interferon alfa agents and antacids. COPEGUS concentrations are similar when given concomitantly with PEGASYS or interferon alfa agents.

Any potential for 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. 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_{tf} 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 *Haemolysis*).

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 substudy to examine the effect of ribavirin on the intracellular phosphorylation of some nucleoside reverse transcriptase inhibitors (NRTIs; 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/latic 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 COPEGUS and PEGASYS developed severe neutropaenia (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

The types and frequency of adverse events with combination therapy are consistent with the known safety profile of PEGASYS and ROFERON-A.

Experience from Clinical Trials

<u>In combination with PEGASYS.</u>

Chronic Hepatitis C (CHC)

Treatment-naïve patients

Patients with elevated ALT levels: In comparison to 48 weeks of treatment with COPEGUS 1000/1200 mg and PEGASYS, 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 ribavirin dose modification (39% vs. 19%).

Patients with normal ALT levels: The safety profile of COPEGUS 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 13).

Table 13. Adverse reactions occurring in ³ 10% of patients with normal ALT levels (PEGASYS combination therapy)

	PEGASYS 180 mg with COPEGUS 800 mg 24 weeks (*n* = 212) %	PEGASYS 180 mg 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/mm^3 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/mm^3, 30%; and platelet < 50 000/mm^3, 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 COPEGUS in combination with PEGASYS, were similar to those observed in HCV infected patients.

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 ³ 10% of patients in study NV18209 were similar to those within Table 14 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 14 shows those adverse reactions occurring in ≥ 10% of patients receiving COPEGUS 1000/1200 mg in combination with PEGASYS for 48 weeks (*n* = 887) and 72 weeks (*n* = 156), COPEGUS 800 mg in combination with PEGASYS for 24 weeks (*n* = 207) and comparator (*n* = 443) for 48 weeks.

Table 14. Adverse Reactions occurring in ³ 10% of patients with elevated ALT levels (PEGASYS combination therapy)

	HCV			HIV-HCV	HCV Peginterferon alfa-2b Non-responder
	PEGASYS 180 mg with COPEGUS 800 mg 24 weeks (*n* = 207) %	PEGASYS 180 mg with COPEGUS 1000 or 1200 mg 48 weeks (*n* = 887) %	Interferon alfa-2b with Ribavirin 1000 or 1200 mg (REBETOL) 48 weeks (*n* = 443) %	PEGASYS 180 mg with COPEGUS 800 mg 48 weeks (*n* = 288) %	PEGASYS 180 mg 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		
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

* For HCV trials, statistically significant difference between PEGASYS/COPEGUS and Interferon alfa-2b/ribavirin treatments

Commonly reported adverse reactions, 1 – 10% of patients on COPEGUS in combination with PEGASYS:

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

Ear and labyrinth disorders: vertigo, earache

Vascular disorders: flushing

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

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, chelitis, 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, epitaxis

Skin and subcutaneous tissue disorders: rash, photosensitivity reaction, eczema, skin disorder, psoriasis, urticara, 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 COPEGUS in combination with PEGASYS 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 events have been reported in patients receiving PEGASYS alone or in combination with ribavirin 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, hallucination

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-Johnsons Syndrome, toxic epidermal necrolysis, pure red cell aplasia (PRCA) and homicidal ideation have been reported very rarely with combination therapy of COPEGUS and PEGASYS.

Dehydration has been reported rarely with combination therapy of COPEGUS with PEGASYS.

As with other alfa interferons, serous retinal detachment has been reported with PEGASYS and COPEGUS 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 used in combination with COPEGUS, may be associated with pancytopenia, and very rarely, aplastic anaemia has been reported.

In combination with ROFERON-A

The following adverse reactions are based on clinical experience of COPEGUS in combination with ROFERON-A in CHC patients.

Table 15. Adverse Reactions Occurring in ³ 4% of Patients on COPEGUS with ROFERON-A Combination Therapy

	Relapsed patients		Previously untreated patients		
	COPEGUS + ROFERON-A (*n* = 49) (%)	**ROFERON-A (*n* = 50) (%)**	**COPEGUS + ROFERON-A (*n* = 21) (%)**	**ROFERON-A (*n* = 19) (%)**	**Placebo (*n* = 20) (%)**
General disorders and administration site conditions					
Asthenia	73	68	71	53	50
Influenza-like symptoms	35	34	-	-	-
Fever	8	6	-	-	-
Psychiatric disorders					
Insomnia	27	14	43	47	15
Irritability	24	10	29	42	35
Depression	14	14	29	42	35
Anorexia	8	4	+	+	+
Nervous system disorders					
Headache	22	18	-	-	-
Dizziness	8	8	-	-	-
Paraesthesia	4	2	-	-	-
Tremor	4	0	-	-	-
Respiratory, thoracic and mediastinal disorders					
Dyspnoea	18	6	-	-	-
Cough	6	0	-	-	-
Skin and subcutaneous tissue disorder					
Alopecia	18	20	62·	58·	20·
Pruritus	16	4	-	-	-
Skin dry	8	2	-	-	-
Rash erythematous	4	4	0	11	0
Eczema	4	0	-	-	-
Gastrointestinal disorders					

Nausea	16	6	24+	26+	10+
Dyspepsia	10	0	-	-	-
Vomiting	8	2	-	-	-
Dry mouth	6	2	-	-	-
Abdominal pain	4	6	-	-	-
Diarrhoea	4	4	14	16	5
Metabolism and nutritional disorders					
Weight decrease	8	6	24	47	10
Musculoskeletal and connective tissue disorders					
Arthralgia	6	8	38	53	10
Myalgia	6	12	-	-	-
Blood					
Epistaxis	6	2	-	-	-
Special senses					
Taste perversion	4	0	-	-	-
Cardiac disorders					
Palpitations	0	4	-	-	-

+ listed as anorexia and nausea, · listed as mild hair loss.

Laboratory Test Values

In clinical trials of COPEGUS in combination with PEGASYS or ROFERON-A, the majority of cases of abnormal laboratory values were managed with dose modifications.

Haemolytic Anaemia

Haemolysis is the defining toxicity of COPEGUS therapy. A decrease in haemoglobin levels to < 100 g/L was observed in up to 13% and 3% of patients in clinical trials treated with COPEGUS 1000/1200 mg in combination with PEGASYS for 48 weeks and 24 weeks, respectively and up to 19% of patients in combination with ROFERON-A. It is not expected that patients will need to discontinue therapy because of a 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.

In study NR16071, patients with normal ALT levels treated with COPEGUS in combination with PEGASYS for 24 and 48 weeks, haemoglobin < 100 g/L was seen in 6% and 12%, while dosage modification was required in 8% and 21% respectively. The higher incidence of anaemia in the normal ALT study is mainly due to the predominance of females (60% vs. 33% in the elevated ALT study).

Most cases of anaemia, leukopenia and thrombocytopenia were mild (WHO grade 1). Laboratory changes reported for haemoglobin (4%), leukocytes (24%), and thrombocytes (2%) of patients were moderate (WHO grade 2). Moderate absolute neutrophil count (ANC) and severe neutropenia was observed in 24% and 5% of patients receiving 48 weeks of COPEGUS 1000/1200 mg in combination with PEGASYS.

An increase in uric acid and indirect bilirubin values associated with haemolysis were observed in some patients treated with COPEGUS used in combination with PEGASYS or ROFERON-A and values returned to baseline levels within 4 weeks after the end of therapy. In rare cases this was associated with clinical manifestations.

HIV-HCV co-infection

Although neutropenia, thrombocytopenia and anaemia occurred more frequently in HIV-HCV co-infected patients, the majority could be managed by dose modification, the use of growth factors and, infrequently, required premature discontinuation of treatment. Decrease in ANC levels below 500 cells/mm^3 was observed in 11% of patients receiving COPEGUS in combination with PEGASYS. Decrease in platelets below 50 000/mm^3 was observed in 8% of patients receiving COPEGUS in combination with PEGASYS. Anaemia (haemoglobin < 100

g/L) was reported in 14% and 28% of patients treated with COPEGUS in combination with PEGASYS 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.

DOSAGE AND ADMINISTRATION

Before beginning COPEGUS therapy, standard haematological tests and blood chemistries must be conducted in all patients (refer to *Precautions*: *Effects on Laboratory Tests*).

The recommended dose and duration of COPEGUS is dependent on the interferon therapy used.

In combination with PEGASYS

Chronic Hepatitis C: Treatment-Naïve Patients
The daily dose and duration of COPEGUS given in combination with PEGASYS should be individualised based on the patient's viral genotype and body weight (refer to Table 16). The daily dose of COPEGUS is administered orally in 2 divided doses (morning and evening) with food.

Table 16. COPEGUS Dosing Recommendation in Combination with PEGASYS

Genotype	COPEGUS daily dose	Number of 200 mg tablets to be taken		Duration or treatment
Genotype 1, 4	<75 kg = 1000 mg	2 morning	3 evening	48 weeks
	³ 75 kg = 1200 mg	3 morning	3 evening	48 weeks
Genotype 2, 3	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 and COPEGUS combination therapy is PEGASYS 180 mg once a week by subcutaneous administration in the abdomen or thigh. For patients < 75 kg and ³ 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 COPEGUS in combination with PEGASYS 180 µg once a week is 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.

In combination with ROFERON-A .

The recommended dose of COPEGUS in combination with ROFERON-A is dependent on the patient's body weight (refer to Table 17). The recommended treatment duration is 24 weeks.

Table 17. COPEGUS Dosing Recommendation in Combination with ROFERON-A

Patient weight	COPEGUS daily dose	Number of 200 mg tablets to be taken		Duration or treatment
< 75 kg	1000 mg	2 morning	3 evening	24 weeks
≥ 75 kg	1200 mg	3 morning	3 evening	24 weeks

Dosage Modification for Adverse Reactions

If severe adverse reactions or laboratory abnormalities develop during COPEGUS combination therapy with PEGASYS or ROFERON-A modify the dosages of each component as appropriate until the adverse reactions abate (refer to Table 18). If intolerance persists after dose adjustment, discontinuation of COPEGUS or both COPEGUS and PEGASYS or ROFERON-A may be necessary.

For combination therapy please refer to the PEGASYS or ROFERON-A Product Information for appropriate Dosage and Administration guidelines.

Table 18. Dosage Modification Guidelines

Laboratory Values	Reduce COPEGUS dose to 600mg /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 (permanent dose reduction)	< 120 g/L after 4 weeks of dose reductions

*Patients whose dose of ribavirin is reduced to 600 mg daily receive 200 mg in the morning and 400mg in the evening.
** If the abnormality is reversed, COPEGUS may be restarted at 600 mg daily, and further increased to 800 mg daily at the discretion of the treating physician. However, a return to higher doses is not recommended.

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 treating physician. However, a return to the original dose is not recommended.

Special Populations

Renal Impairment: 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*).

OVERDOSAGE

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 overdosage should consist of general supportive measures.

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

PRESENTATION AND STORAGE CONDITIONS

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

The tablets are available in bottles containing 112, 140 and 168 tablets.

COPEGUS tablets are not available as individual bottles.

COPEGUS tablets are only available in PEGASYS RBV combination packs [i.e. in combination with PEGASYS (*peginterferon alfa-2a*) pre-filled syringes].

COPEGUS tablet should be stored below 30°C. COPEGUS tablets should not be taken after the expiry date.

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

TGA Approval Date: 13 May 2011

Therapeutic Goods Administration

PO Box 100 Woden ACT 2606 Australia
Email: info@tga.gov.au Phone: 1800 020 653 Fax: 02 6232 8605
www.tga.gov.au

Reference/Publication #