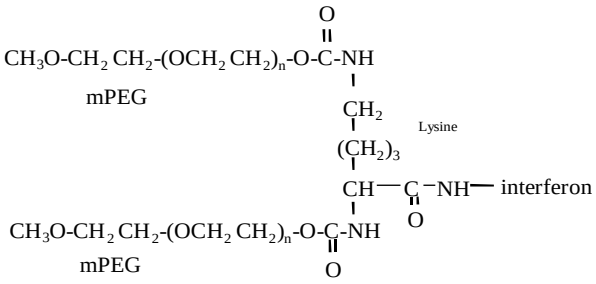
NAME OF THE MEDICINE

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 μg/0.5 mL and 180 μg/0.5 mL. The solution is clear and colourless to light yellow.

Each 0.5 mL pre-filled syringe contains 135 or 180 μg of peginterferon alfa-2a, expressed as the amount of interferon alfa-2a, with excipients sodium chloride, benzyl alcohol, sodium acetate, acetic acid, polysorbate 80 and water for injections.

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

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

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

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

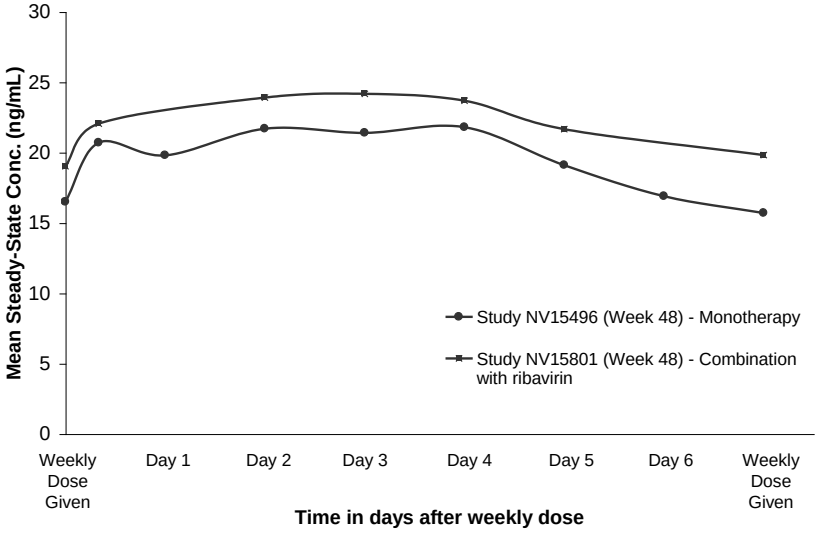
Pharmacokinetic Overview

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

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



Pharmacokinetics in Special Populations

Renal Impairment: A clinical trial evaluated 50 CHC patients with either moderate (creatinine clearance 30 to 50 mL/min) or severe (creatinine clearance less than 30 mL/min) renal impairment, or with end stage renal disease (ESRD) requiring chronic haemodialysis (HD). Patients with moderate renal impairment receiving Pegasys 180 mcg once weekly exhibited similar peginterferon alfa-2a plasma exposures compared to patients with normal renal function. Patients with severe renal impairment receiving Pegasys 180 mcg once weekly showed a 60% higher peginterferon alfa-2a exposure than patients with normal renal function, therefore a reduced dose of Pegasys 135 mcg once weekly is recommended in patients with severe renal impairment. In 18 patients with ESRD requiring chronic HD, administration of Pegasys 135 mcg

once weekly resulted in 34% lower peginterferon alfa-2a exposure than in patients with normal renal function. Despite the lower plasma peginterferon alfa-2a exposure, patients with ESRD experienced the highest frequency of serious adverse events among the other groups in the study, likely owing to the severity and complexity of comorbidities in this patient population. *Gender*: The pharmacokinetics of peginterferon alfa-2a were comparable between male and female healthy subjects.

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

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

Non-cirrhotic and Cirrhotic Patients: The pharmacokinetics of peginterferon alfa-2a were similar between healthy subjects and patients with 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 μg SC once a week, or PEGASYS 180 μg 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 μg 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 ≥ 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 µg (*n* = 87)**	**ROFERON-A 6 MIU/3 MIU (*n* = 264)**	**PEGASYS 180 µg (*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 µg 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 µg 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 µg (*n* = 68)**	**ROFERON-A 6 MIU/3 MIU (*n* = 167)**	**PEGASYS 180 µg (*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 µg 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 / ≥ 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 µg SC once a week with placebo, PEGASYS 180 µg 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 µg with COPEGUS 800 mg (*n* = 207)	**PEGASYS 180 µg with COPEGUS 1000/1200 mg (*n* = 280)**	**PEGASYS 180 µg with COPEGUS 800 mg (*n* = 361)**	**PEGASYS 180 µg with COPEGUS 1000/1200 mg (*n* = 436)**	**PEGASYS 180 µg (*n* = 224)**	**PEGASYS 180 µg with COPEGUS 1000/1200 mg (*n* = 453) [A≥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 ≥ 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 μg 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 µg with COPEGUS 800 mg **24 weeks** **(*n* = 212)**	**PEGASYS 180 µg with COPEGUS 800 mg** **48 weeks** **(*n* = 210)** ***p*-values***	**Untreated Control** **48 weeks** **(*n* = 69)** ***p*-values****
All Genotypes **SVR (week 72)**	30% (63/212)	52% (109/210) $p \leq 0.001$	0% $p \leq 0.001$
Genotype 1 **SVR (week 72)**	13% (19/144)	40% (57/141) $p \leq 0.001$	0% $p \leq 0.001$
Genotype 2, 3 **SVR (week 72)**	72% (42/58)	78% (46/59) $p \leq 0.452$	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 µg 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 µg once a week and who achieved a SVR had an early virological response by week 12. In HIV-HCV co-infected patients treated with PEGASYS 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 ≥ 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 µg once a week for 12 weeks, followed by 180 µg once a week for a further 60 weeks; PEGASYS 360 µg once a week for 12 weeks, followed by 180 µg once a week for a further 36 weeks; PEGASYS 180 µg once a week for 72 weeks; or PEGASYS 180 µg once a week for 48 weeks. All patients received COPEGUS (1000 or 1200 mg daily) in combination with PEGASYS. The end-of-treatment (EOT) virological response and SVR following the 24 week treatment-free period comparing duration of therapy or PEGASYS induction dosing are summarised in Table 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 μg once a week and COPEGUS 1000/1200 mg daily. Patients who achieved undetectable levels of HCV RNA after 20 weeks of treatment remained on PEGASYS 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 µg once a week and weight-based COPEGUS daily. SVR was achieved in 51% of patients infected with genotype 1 and 64% of patients with genotype 2 or 3.

HIV-HCV Co-infection

In NR15961, 860 patients with 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 (≥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 $< 2 \times 10^4$ 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 $< 2 \times 10^4$ 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
In order to improve traceability of biological medicinal products, the trade name and batch number of the administered product should be clearly recorded in the patient medical record. Substitution by any other biological medicinal product requires the consent of the prescribing physician.

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.

Exercise caution and monitor for evidence of depression when administering PEGASYS to paediatric patients with a prior history of or concurrent psychiatric disorders.

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 alfa interferons, including PEGASYS, with or without ribavirin. 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)*.

Growth and Development (paediatric patients)
During the course of Pegasys plus ribavirin therapy lasting up to 48 weeks in patients aged 5 to 17 years, weight loss and growth inhibition were common.

At 2 years post-treatment, 16% of paediatric patients were more than 15 percentiles below their baseline weight curve and 11% were more than 15 percentiles below their baseline height curve.

At 5 to 6 years post-treatment, pediatric patients who were more than 15 percentiles below their baseline at 2 years post-treatment, either returned to baseline comparable height percentiles or a non-treatment related causative factor has been identified. The long term follow up data suggests that Pegasys treatment is unlikely to be associated with a sustained growth inhibition in children. The expected benefit of treatment should be carefully weighed against the safety findings observed for children and adolescents in the clinical trials on a case by case basis.

It is important to consider that the combination therapy induced a growth inhibition during treatment.

This risk should be weighed against the disease characteristics of the child, such as evidence of disease progression (notably fibrosis), co-morbidities that may negatively influence the disease progression, as well as prognostic factors of response (HCV genotype and viral load).

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 red blood cells, 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 $\leq$ 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
No dose adjustment is required for patients with mild to moderate renal impairment. A reduced dose of PEGASYS 135mcg once weekly is recommended in patients with severe renal impairment. In patients with end stage renal disease, a starting dose of PEGASYS 135mcg once weekly should be used. (*see PHARMACOLOGY, Pharmacokinetics in special populations*) Regardless of the starting dose or degree of renal impairment, patients should be monitored and appropriate dose reductions of PEGASYS during the course of therapy should be made in the event of adverse reactions (refer to *DOSAGE AND ADMINISTRATION, Special populations*). 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 (*refer also to PRECAUTIONS Growth and development (paediatric patients*)).

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 17β-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 μg 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 μg 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 μg SC once a week, indicates that the combination is associated with an increased risk for developing peripheral neuropathy. The mechanism behind these events is not known. Such an increased risk cannot be excluded for other interferons (pegylated or standard). Moreover, the benefit of the combination of telbivudine with interferon alfa (pegylated or standard) is not currently established.

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 ≥ 10% of Hepatitis C Patients with Normal ALT Levels

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

	PEGASYS 180 µg with COPEGUS 800 mg 24 weeks (*n* = 212) %	PEGASYS 180 µg with COPEGUS 800 mg 48 weeks (*n* = 210) %	Untreated Control 48 weeks (*n* = 69) %
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 ≥ 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 ≥ 10% of Patients in Clinical Trials

	HCV				**HIV-HCV**	**HBV**	**HCV Non-responders to prior Peginterferon alfa-2b therapy**
	PEGASYS 180 µg 48 weeks (*n* = 827) %	**PEGASYS 180 µg with COPEGUS 800 mg 24 weeks (*n* = 207) %**	**PEGASYS 180 µg with COPEGUS 1000 or 1200 mg 48 weeks (*n* = 887) %**	**Interferon alfa-2b with Ribavirin 1000 or 1200 mg 48 weeks (*n* = 443) %**	**PEGASYS 180 µg with COPEGUS 800 mg 48 weeks (*n* = 288) %**	**PEGASYS 180 µg† 48 weeks (*n* = 448) %**	**PEGASYS 180 µg 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

	HCV				HIV-HCV	HBV	HCV Non-responders to prior Peginterferon alfa-2b therapy
	PEGASYS 180 µg 48 weeks (*n* = 827) %	PEGASYS 180 µg with COPEGUS 800 mg 24 weeks (*n* = 207) %	PEGASYS 180 µg with COPEGUS 1000 or 1200 mg 48 weeks (*n* = 887) %	Interferon alfa-2b with Ribavirin 1000 or 1200 mg 48 weeks (*n* = 443) %	PEGASYS 180 µg with COPEGUS 800 mg 48 weeks (*n* = 288) %	PEGASYS 180 µg† 48 weeks (*n* = 448) %	PEGASYS 180 µg with COPEGUS 1000 or 1200 mg 72 weeks (*n* = 156) %
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							

	HCV				HIV-HCV	HBV	HCV Non-responders to prior Peginterferon alfa-2b therapy
	PEGASYS 180 µg 48 weeks (*n* = 827) %	PEGASYS 180 µg with COPEGUS 800 mg 24 weeks (*n* = 207) %	PEGASYS 180 µg with COPEGUS 1000 or 1200 mg 48 weeks (*n* = 887) %	Interferon alfa-2b with Ribavirin 1000 or 1200 mg 48 weeks (*n* = 443) %	PEGASYS 180 µg with COPEGUS 800 mg 48 weeks (*n* = 288) %	PEGASYS 180 µg† 48 weeks (*n* = 448) %	PEGASYS 180 µg with COPEGUS 1000 or 1200 mg 72 weeks (*n* = 156) %
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.

Tongue pigmentation has been reported in a post marketing setting.

Facial palsy has been reported with PEGASYS.

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 μg 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 μg	< 75 kg = 1000 mg	2 morning	3 evening	48 weeks
		≥ 75 kg = 1200 mg	3 morning	3 evening	48 weeks
Genotype 2, 3	180 μg	800 mg	2 morning	2 evening	24 weeks

† Data on genotypes 5 and 6 are too few to make definitive 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 μg once a week by subcutaneous administration in the abdomen or thigh. For patients < 75 kg and ≥ 75 kg, 1000 mg and 1200 mg of COPEGUS respectively, should be administered daily. COPEGUS should be administered in divided doses (morning and evening) with food.

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

HIV-HCV Co-infection
The recommended dose of PEGASYS, 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 μg is generally adequate. However, in some cases, dose reduction to 90 μg or 45 μg is necessary. Dose increases to, or toward, the original dose may be considered when the adverse 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 μg	< 500 cells/mm^3, treatment should be suspended until ANC values return to more than 1000 cells/mm^3 Initially reinstitute at 90 μg and monitor ANC
Platelet Count	< 50 000 cells/mm^3, reduce to 90 μg	< 25 000 cells/mm^3

Table 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 μg 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***:** No dose adjustment is required for adult patients with mild or moderate renal impairment A reduced dose of 135 mcg once weekly PEGASYS is recommended in adult patients with severe renal impairment. In adult patients with end stage renal disease, a starting dose of PEGASYS 135 mcg once weekly should be used (*see PHARMACOLOGY, Pharmacokinetics in Special Populations*).

Regardless of the starting dose or degree of renal impairment, patients should be monitored and appropriate dose reductions of PEGASYS during the course of therapy should be made in the event of adverse reactions.

No data is available for paediatric patients with renal impairment.

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) SI unit (μmol/l)	< 2 2 - 3 > 3 < 34 34 - 51 > 51	1 2 3 1 2 3
S-Albumin (g/L)	> 35 35 - 28 < 28	1 2 3
INR	< 1.7 1.7-2.3 > 2.3	1 2 3

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

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 μg/week) have been reported. None of these patients experienced unusual, serious or treatment-limiting events. Weekly doses of up to 540 and 630 μg have been administered in renal cell carcinoma and chronic myelogenous leukaemia clinical trials, respectively. Dose-limiting toxicities were fatigue, elevated liver enzymes, neutropenia and thrombocytopenia consistent with interferon therapy.

Treatment of overdose should consist of general supportive measures.

For information on the management of overdose, contact the Poison Information Centre (in Australia call 13 11 26; in New Zealand call 0800 764 766).

PRESENTATION AND STORAGE CONDITONS

PEGASYS pre-filled syringe:

PEGASYS is available as a sterile, ready-to-use solution for subcutaneous injection in pre-filled syringes in two strengths, 135 μg/0.5 mL* and 180 μg/0.5 mL.

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.

** Presentations not available in New Zealand*

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.

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