PRODUCT INFORMATION

PEGATRON® Combination Therapy

PEG-INTRON® (PEGINTERFERON ALFA-2B) CLEARCLICK® INJECTOR + REBETOL® (RIBAVIRIN) CAPSULES

NAME OF DRUG

PEGATRON Combination Therapy is the brand name for composite packs containing peginterferon alfa-2b (rbe) for subcutaneous injection (PEG-INTRON) plus ribavirin capsules for oral administration (REBETOL).

DESCRIPTION

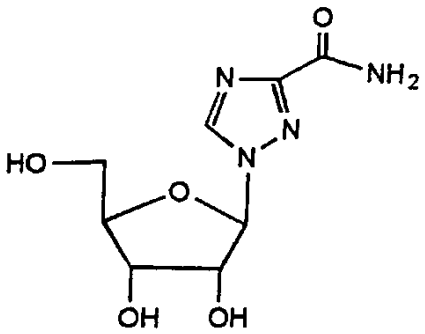
Peginterferon alfa-2b is a covalent conjugate of recombinant interferon alfa-2b with monomethoxy polyethylene glycol. The average molecular weight of the molecule is approximately 31,300 daltons.

Peginterferon alfa-2b is predominantly composed of monopegylated species (one PEG molecule is attached to one interferon molecule), with only a small amount of dipegylated species. Fourteen different PEG attachment sites on the interferon molecule have been identified.

CAS registry number: 215647-85-1.

Recombinant interferon alfa-2b is obtained from a clone of *E. coli*, which harbours a genetically engineered plasmid hybrid encompassing an interferon alfa-2b gene from human leukocytes.

Ribavirin is a nucleoside analogue with antiviral activity. It is a white, crystalline powder which is freely soluble in water and slightly soluble in dehydrated alcohol. Ribavirin is 1-β-D-ribofuranosyl-1*H*-1,2,4-triazole-3-carboxamide with the following structural formula:



CAS registry number: 36791-04-5 Mol. Wt: 244.21

PEGATRON Combination Therapy composite packs contain PEG-INTRON CLEARCLICK Injector and REBETOL Capsules.

PEG-INTRON CLEARCLICK Injector is a single use disposable injection pen. The PEG-INTRON Powder for Injection and solvent are contained in separate compartments of a two-chamber cartridge inside the CLEARCLICK Injector.

PEG-INTRON CLEARCLICK Injector is available in 5 different strengths:

- 50, 80, 100, 120 or 150 μg of peginterferon alfa-2b.

PEG-INTRON Powder for Injection also contains dibasic sodium phosphate, monobasic sodium phosphate, sucrose and polysorbate 80 as excipients. The solvent provided for parenteral use is sterile Water for Injections.

When reconstituted as recommended, each CLEARCLICK Injector is capable of delivering the labelled dose in 0.5 mL of PEG-INTRON solution (see DOSAGE AND ADMINISTRATION for the five dosage settings on the PEG-INTRON CLEARCLICK Injector).

REBETOL capsule contains ribavirin 200 mg in a white, opaque gelatin capsule. Inactive Ingredients: cellulose-microcrystalline, lactose, croscarmellose sodium and magnesium stearate. The capsule shell contains gelatin, titanium dioxide, sodium lauryl sulfate, silicon dioxide and TekPrint SB-6018 Blue Ink PI (2653).

PHARMACOLOGY

Peginterferon alfa-2b

In vitro and *in vivo* studies suggest that the biological activity of peginterferon alfa-2b is derived from its interferon alfa-2b moiety.

Interferons exert their cellular activities by binding to specific membrane receptors on the cell surface. Studies with other interferons have demonstrated species specificity. However, certain monkey species, e.g., Rhesus monkeys, are susceptible to pharmacodynamic stimulation upon exposure to human type 1 interferons.

Once bound to the cell membrane, interferon initiates a complex sequence of intracellular events that include the induction of certain enzymes. It is thought that this process, at least in part, is responsible for the various cellular responses to interferon, including inhibition of virus replication in virus-infected cells, suppression of cell proliferation and such immunomodulating activities as enhancement of the phagocytic activity of macrophages and augmentation of the specific cytotoxicity of lymphocytes for target cells. Any or all of these activities may contribute to interferon's therapeutic effects.

Recombinant interferon alfa-2b also inhibits viral replication *in vitro* and *in vivo*. Although the exact antiviral mode of action of recombinant interferon alfa-2b is unknown, it appears to alter the host cell metabolism. This action inhibits viral replication or if replication occurs, the progeny virions are unable to leave the cell.

Ribavirin

Ribavirin is a synthetic nucleoside analogue which has shown *in vitro* activity against some RNA and DNA viruses. Neither ribavirin nor its intracellular nucleotide metabolites at physiological concentrations has been shown to inhibit HCV-specific enzymes or HCV replication. Ribavirin monotherapy for chronic hepatitis C has been shown to have no effect on eliminating serum

HCV- RNA or improving hepatic histology after 6 to 12 months of therapy and 6 months of follow-up. However, when used in combination with peginterferon alfa-2b in the treatment of chronic hepatitis C, ribavirin has been shown to increase the efficacy of peginterferon alfa-2b used alone. The mechanism by which ribavirin in combination with peginterferon alfa-2b exerts its effects against HCV is unknown.

Pharmacokinetics

Peginterferon alfa-2b

Peginterferon alfa-2b is a well characterised polyethylene glycol-modified ("pegylated") derivative of interferon alfa-2b and is predominantly composed of monopegylated species. The plasma half-life of peginterferon alfa-2b is prolonged compared with that of interferon alfa-2b. Peginterferon alfa-2b has a potential to depegylate to free interferon alfa-2b. The biologic activity of pegylated isomers is qualitatively similar, but weaker than free interferon alfa-2b.

Following subcutaneous administration, maximal serum concentrations occur between 15-44 hours post-dose, and are sustained for up to 48-72 hours post-dose.

Peginterferon alfa-2b C_{max} and AUC measurements increase in a dose-related manner. Mean apparent volume of distribution is 0.99 L/kg.

Upon multiple dosing, there is an accumulation of immunoreactive interferons. There is, however, only a modest increase in biological activity as measured by a bioassay.

Mean peginterferon alfa-2b elimination half-life is approximately 40 hours, with apparent clearance of 22.0 mL/hr·kg. The mechanisms involved in clearance of interferons in man have not yet been fully elucidated. However, renal elimination may account for a minority (approximately 30%) of peginterferon alfa-2b apparent clearance.

Interferon neutralising factors: Interferon neutralising factor assays were performed on serum samples of patients who received peginterferon alfa-2b in combination with ribavirin in a Phase III clinical trial. Interferon neutralising factors are antibodies that neutralise the antiviral activity of interferon. The clinical incidence of neutralising factors in patients who received peginterferon alfa-2b 0.5 or 1.5 μg/kg were 2% to 3%.

Ribavirin (numbers in parenthesis indicate % coefficient of variation)

Single- and multiple-dose pharmacokinetic properties in adults with chronic hepatitis C and healthy volunteers are summarised in Table 1. Ribavirin was rapidly and extensively absorbed following oral administration. However, due to first-pass metabolism, the absolute bioavailability determined in healthy volunteers averaged 64% (44%). There was a linear relationship between dose and AUC_{tf} (AUC from time zero to last measurable concentration) following single doses of 200-1200 mg ribavirin. The relationship between dose and C_{max} was curvilinear, tending to asymptote above single doses of 400-600 mg.

Ribavirin has been shown to produce high inter- and intra-subject pharmacokinetic variability following single oral doses (intra-subject variability of approximately 30% for both AUC and C_{max}). This may be due to extensive first pass metabolism and transfer within and beyond the blood compartment.

Upon multiple oral dosing, based on AUC_{12hr}, a sixfold accumulation of ribavirin was observed in

plasma. Following oral dosing with 600 mg BID, steady-state was reached by approximately 4 weeks, with mean steady-state plasma concentrations of 2200 (37%) ng/mL. Upon discontinuation of dosing, the mean half-life was 298 (30%) hours, which probably reflects slow elimination from non-plasma compartments. Multiple dose ribavirin apparent clearance was 22.4 (34%) L/hr.

Table 1: Mean (% CV) pharmacokinetic parameters for REBETOL (ribavirin) when administered individually to adults with chronic hepatitis C and healthy volunteers

Parameter	REBETOL (n=12)	
	Single Dose 600 mg	**Multiple Dose 600 mg BID**
T_{max} (hr)	1.7 (46)*	3 (60)
C_{max} (ng/mL)	782 (37)	3680 (85)
AUC_{tf} (ng.hr/mL)	13400 (48)	228000 (25)
$T_{1/2}$ (hr)	43.6 (47)	298 (30)
Apparent Volume of Distribution (L)	2825 (9) §, †	-
Apparent Clearance (L/hr)	38.2 (40)	22.4 (34)
Absolute Bioavailability (%)	64 (44) §, ††	-

* n = 11
§ Data obtained from healthy volunteers
† Data obtained from a single-dose pharmacokinetic study using ^{14}C labelled ribavirin; N = 5
†† n = 6

Ribavirin transport into non-plasma compartments has been most extensively studied in red blood 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 extensive volume of distribution. The ratio of whole blood:plasma ribavirin concentrations is approximately 60:1; the excess of ribavirin in whole blood exists as ribavirin nucleotides sequestered in erythrocytes. Ribavirin does not bind to plasma proteins.

Ribavirin has two pathways of metabolism: (i) a reversible phosphorylation pathway in nucleated cells; and (ii) a degradative pathway involving deribosylation and amide hydrolysis to yield a triazole carboxylic acid metabolite. Ribavirin and its triazole carboxamide and triazole carboxylic acid metabolites are excreted renally. After oral administration of 600 mg of ^{14}C-ribavirin, approximately 61% and 12% of the radioactivity was eliminated in the urine and faeces, respectively, in 336 hours. Unchanged ribavirin accounted for 17% of the administered dose.

Results of *in vitro* studies using both human and rat liver microsome preparations indicated little or no cytochrome P450 enzyme-mediated metabolism of ribavirin, with minimal potential for P450 enzyme-based drug interactions.

Effect of Food on Absorption of Ribavirin: Both AUC_{tf} and C_{max} increased by 70% when REBETOL was administered with a high-fat meal (841 kcal, 53.8 g fat, 31.6 g protein and 57.4 g carbohydrate) in a single-dose pharmacokinetic study. It is possible that the increased bioavailability in this study was due to delayed transit of ribavirin or modified pH. There are insufficient data to address the clinical relevance of these results. In the pivotal clinical efficacy trial (see CLINICAL TRIALS), patients were instructed to take ribavirin with food to achieve the maximal plasma concentration of ribavirin.

Peginterferon alfa-2b and ribavirin

A ribavirin population pharmacokinetic analysis was conducted upon serum samples obtained at weeks 12, 24 and 48 during treatment with PEGATRON Combination Therapy. Based upon pharmacokinetic modelling, the recommended ribavirin dose of 800/1000/1200 mg/day based on body weights of <65/65-85/>85 kg (in combination with peginterferon alfa-2b 1.5 μg/kg), showed an overall 6.3% improved sustained response rate relative to a fixed dose of 800 mg/day. The improved sustained response rate was larger (+7.4%) in the patients with HCV Genotype 1 compared to patients with HCV Genotype non-1 (3.8%). The toxicity rate, defined as the percentage of patients with a haemoglobin below 105 g/L at week four of treatment was only minimally increased by 2.5% relative to a fixed dose of 800 mg/day. This increase in toxicity was considered mild and clinically manageable.

Peginterferon alfa-2b trough concentrations were obtained at weeks 12, 24 and 48 during treatment with PEGATRON Combination Therapy. The observed concentrations and the trend toward accumulation were similar to that observed previously with PEG-INTRON (peginterferon alfa-2b) monotherapy for chronic hepatitis C, supporting the lack of pharmacokinetic interaction between peginterferon alfa-2b and ribavirin.

Special Populations

Renal dysfunction: Renal clearance appears to account for 30% of total clearance of peginterferon alfa-2b. In a single dose study (1.0 μg/kg) in patients with impaired renal function, C_{max}, AUC, and half-life increased in relation to the degree of renal impairment. The pharmacokinetics of ribavirin were assessed after administration of a single oral dose (400 mg) of ribavirin to subjects with varying degrees of renal dysfunction. The mean AUC_{tf} value was threefold greater in subjects with creatinine clearance values between 10 to 30 mL/min when compared to control subjects (creatinine clearance >90 mL/min). This appears to be due to a reduction of apparent clearance in these patients. Ribavirin was not removed by haemodialysis.

It is recommended that renal function be evaluated in all patients prior to initiation of PEGATRON Combination Therapy and that patients be monitored closely during treatment (see PRECAUTIONS, DOSAGE AND ADMINISTRATION).

Patients with severe renal dysfunction or creatinine clearance <50 mL/min must not be treated with PEGATRON Combination Therapy (see CONTRAINDICATIONS). Patients with impaired renal function and/or those above the age of 50 should be more carefully monitored with respect to the development of anaemia.

Hepatic dysfunction: The pharmacokinetics of peginterferon alfa-2b has not been evaluated in patients with severe hepatic dysfunction. Therefore, PEGATRON Combination Therapy must not be used in these patients.

The effect of hepatic dysfunction was assessed after a single oral dose of ribavirin (600 mg). The mean AUC_{tf} values were not significantly different in subjects with mild, moderate or severe hepatic dysfunction (Child-Pugh Classification A, B or C), when compared to control subjects. However, the mean C_{max} values increased with severity of hepatic dysfunction and was twofold greater in subjects with severe hepatic dysfunction when compared to control subjects (see also PRECAUTIONS, DOSAGE AND ADMINISTRATION).

Children and Adolescents: PEGATRON Combination Therapy can be used for the treatment of chronic hepatitis C in children and adolescents ≥ 27 kg bodyweight.

Multiple-dose pharmacokinetic properties for PEG-INTRON and REBETOL (capsules and oral solution) were evaluated in paediatric patients with chronic hepatitis C between 3 and 17 years of age. In children and adolescent patients receiving body surface area-adjusted dosing of PEG-INTRON at 60 µg/m^2/week, the log transformed ratio estimate of exposure during the dosing interval is predicted to be 58% (90% CI: 141-177%) higher than observed in adults receiving 1.5 µg/kg/week. The pharmacokinetics of REBETOL (dose-normalised) in this trial were similar to those reported in adult subjects.

The use of PEGATRON Combination Therapy has not been studied in children under 3 years of age.

Elderly patients ≥ 65 years of age: There does not appear to be a significant age-related effect on the pharmacokinetics of PEG-INTRON Injection or REBETOL Capsules. However, as in younger patients, renal function must be determined prior to the administration of PEGATRON Combination Therapy (see PRECAUTIONS, DOSAGE AND ADMINISTRATION).

Patients co-infected with HCV/HIV: Patients taking Nucleoside Reverse Transcriptase Inhibitors (NRTI) treatment in association with ribavirin and interferon alfa-2b or peginterferon alfa-2b may be at increased risk of mitochondrial toxicity, lactic acidosis and hepatic decompensation.

Patients treated with PEG-INTRON and ribavirin combination therapy and zidovudine are at increased risk of developing anaemia and therefore the concomitant use of this combination with zidovudine is not recommended (see PRECAUTIONS).

The two trials conducted in HCV/HIV co-infection were limited to patients with CD4 cell count above 200/mL. Caution is therefore warranted in the treatment of patients with low CD4 counts.

Please refer to the respective product information of the antiretroviral medicinal products that are to be taken concurrently with HCV therapy for awareness and management of toxicities specific for each product and the potential for overlapping toxicities with PEGATRON Combination Therapy.

CLINICAL TRIALS

Naïve patients

A Phase III clinical study was conducted to compare the efficacy and safety of two PEGATRON [PEG-INTRON (peginterferon alfa-2b) Injection plus REBETOL (ribavirin) Capsules] regimens with standard therapy of REBETRON [INTRON A (interferon alfa-2b) Injection plus REBETOL Capsules].

Patients with confirmed chronic hepatitis C (HCV-RNA >100 copies/mL by polymerase chain reaction assay or PCR), a liver biopsy consistent with a histological diagnosis of chronic hepatitis, abnormal serum ALT and not previously treated with an alfa interferon, peginterferon or alfa interferon plus ribavirin were randomised into three treatment groups.

A total of 1530 patients were treated for one year with one of the following combination

regimens:

- P1.5/R: PEG-INTRON Injection (1.5 µg/kg/week) + REBETOL Capsules (800 mg/day), (n = 511)
- P 0.5/R: PEG-INTRON Injection (1.5 µg/kg/week for one month followed by 0.5 µg/kg/week for 11 months) + REBETOL Capsules (1,000/1,200 mg/day), (n = 514)
- I/R: INTRON A Injection (3 MIU TIW) + REBETOL Capsules (1,000/1,200 mg/day), (n = 505).

Sustained virological response was defined as undetectable HCV-RNA in serum at 6 months after cessation of treatment. In this study, the sustained response rate was significantly higher in the higher dose PEGATRON Combination Therapy (P 1.5/R) group than the REBETRON combination (I/R) group, overall and in patients infected with Genotype 1 (Table 2).

Hepatitis C virus (HCV) genotype and baseline virus load are prognostic factors that are known to affect response rates. However, response rates in this trial were shown to be dependent also on the dose of ribavirin administered in the combination. Response rates in those patients who received >10.6 mg/kg ribavirin (800 mg dose in typical 75 kg patient), regardless of genotype or viral load, were significantly higher than in those patients who received ≤10.6 mg/kg ribavirin (Table 2).

In patients who received >10.6 mg/kg ribavirin, the benefit of high dose PEGATRON Combination Therapy was more evident for both patients with developing cirrhosis, cirrhosis or fibrosis (55%) and for those with minimal fibrosis (61%). In patients with developing cirrhosis, cirrhosis or fibrosis, the sustained virological response rate was higher for patients treated with PEGATRON Combination Therapy (i.e. PEG-INTRON 1.5 µg/kg and >10.6 mg/kg ribavirin) than for those given the combination of interferon alfa-2b with ribavirin (55% vs. 43%).

Response rates in this trial were increased if patients were able to maintain compliance. Regardless of genotype, patients who received the recommended combination regimen and received ≥80% of their treatment with PEGATRON Combination Therapy had a higher sustained response 6 months after 1 year of treatment than those who took <80% of their treatment (72% vs. 46%).

Table 2: Sustained Virological Response rates (by ribavirin dose [mg/kg])

Ribavirin dose (mg/kg)	P 1.5/R (n=511)	P 0.5/R (n=514)	I/R (n=505)	p values	
				P 1.5/R *vs* I/R	P 0.5/R *vs* I/R
All HCV Genotypes:					
All	**54%** (274/511)	**47%** (244/514)	**47%** (235/505)	0.01	0.73
≤10.6	50% (160/323)	41% (13/32)	27% (6/22)		
>10.6	61% (114/188)	48% (231/482)	47% (229/483)		
HCV Genotype 1:					
All	**42%** (145/348)	**34%** (118/349)	**33%** (114/343)	0.02	0.94
≤10.6	38% (87/226)	25% (5/20)	20% (3/15)		
>10.6	48% (58/122)	34% (113/329)	34% (111/328)		
HCV Genotype 1 ≤2 million copies/mL*:*					
All	**73%** (67/92)	**51%** (52/102)	**45%** (43/96)	<0.01	0.38
≤10.6	74% (40/54)	25% (1/4)	33% (1/3)		
>10.6	71% (27/38)	52% (51/98)	45% (42/93)		
HCV Genotype 1 >2 million copies/mL*:*					
All	**30%** (78/256)	**27%** (66/247)	**29%** (71/247)	0.67	0.35
≤10.6	27% (47/172)	25% (4/16)	17% (2/12)		
>10.6	37% (31/84)	27% (62/231)	29% (69/235)		
HCV Genotypes 2/3:					
All	**82%** (121/147)	**80%** (122/153)	**79%** (115/146)	0.46	0.89
≤10.6	79% (70/89)	73% (8/11)	50% (3/6)		
>10.6	88% (51/58)	80% (114/142)	80% (112/140)		

P 1.5/R: PEGATRON Combination Therapy (peginterferon alfa-2b 1.5 micrograms/kg + ribavirin 800 mg)

P 0.5/R: PEGATRON Combination Therapy (peginterferon alfa-2b 1.5 to 0.5 microgram/kg + ribavirin 1,000/1,200 mg)
I/R: REBETRON (Interferon alfa-2b 3 MIU + ribavirin 1,000/1,200 mg)

A retrospective analysis of results from the P1.5/R >10.6 mg/kg dose group in this study demonstrated that quantitative testing of HCV-RNA at Week 12 was the optimum early test for assessment of probability of developing a sustained viral response. 80% of patients who were either HCV-RNA negative or with a ≥2 $\log_{10}$ reduction in HCV-RNA at Week 12 developed a sustained viral response. No patients who were HCV-RNA positive with <2 $\log_{10}$ reduction in HCV- RNA at Week 12 developed a sustained viral response.

Table 3: Sustained Viral Response by early viral response (EVR) for the P1.5/R >10.6 mg/kg/day dose group.

Ribavirin dose	**Patient numbers assessed for EVR**	**EVR+**	**PPV**	**NPV**
>10.6 mg/kg/day	**174**	**82%**	**80%**	**100%**
Genotype 1	110	75%	71%	100%
Genotype 2/3	56	100%	91%	N/A

EVR+= HCV-RNA negative or a ≥ 2 $\log_{10}$ reduction in HCV-RNA at Week 12 PPV= positive predictive value
NPV= negative predictive value

A large randomised, parallel group, double-blind trial compared the safety and efficacy of treatment for 48 weeks with two PEG-INTRON/ribavirin regimens [PEG-INTRON 1.5 µg/kg and 1 µg/kg subcutaneously once weekly both in combination with ribavirin 800 to 1,400 mg p.o. daily (in two divided doses)] and the open label active comparator of peginterferon alfa- 2a 180 µg subcutaneously once weekly with ribavirin 1,000 to 1,200 mg p.o daily (in two divided doses) in 3,070 treatment-naïve adults with chronic hepatitis C genotype 1. Response to the treatment was defined as undetectable HCV-RNA at 24 weeks post treatment **(See Table 4).**

Table 4: Virologic Response at Treatment Week 12, End of Treatment (EOT), Sustained Virologic Response (SVR) and Relapse Rate[*a]

Treatment group	% (number) of patients								
	PEG-INTRON 1.5 µg/kg + ribavirin (Arm 1)	PEG-INTRON 1 µg/kg + ribavirin (Arm 2)	peginterferon alfa-2a 180 µg+ ribavirin (Arm 3)	Arm 1 vs Arm 3		Arm 1 vs Arm 2		Arm 2 vs Arm 3	
				P value	Adj Diff %[b] (95% CI)	P value	Adj Diff %[b] (95% CI)	P value	Adj Diff %[b] (95% CI)
Undetectable HCV- RNA at Treatment Week 12	40 (407/1,019)	36 (366/1,016)	45 (466/1,035)	-	-	-	-	-	-
EOT response[a]	53 (542/1,019)	49 (500/1,016)	64 (667/1,035)	<0.001	-11.5 (-15.6, -7.4)	0.035	3.9 (-0.3, 8.1)	<0.001	-15.5 (-19.6, - 11.4)
SVR	40 (406/1,019)	38 (386/1,016)	41 (423/1,035)	0.567	-1.1 (-5.3, 3.0)	0.195	1.8 (-2.3, 6.0)	0.151	-3.0 (-7.2, 1.1)
SVR in patients with undetectable HCV- RNA at treatment Week 12	81 (328/407)	83 (303/366)	74 (344/466)	-	-	-	-	-	-
Relapse [a,c]	24 (123/523)	20 (95/475)	32 (193/612)	0.012	-8.0 (-13.2, -2.8)	0.236	3.5 (-1.6, 8.6)	<0.001	-11.5 (-16.7, -6.4)

*[a] (HCV-RNA PCR assay, with lower limit of quantitation of 27 IU/mL).
In this trial, lack of early virologic response by treatment Week 12 (undetectable HCV-RNA or ≥2 $\log_{10}$ reduction from baseline) was the criteria for discontinuation of treatment.

[b] The adjusted differences between treatment arms and associated 95% CIs are based on Cochran-Mantel-Haenszel proportions adjusting for baseline viral load (≤600,000 IU/mL vs >600,000 IU/mL, measured by the SP laboratory) and race (Black vs non-Black).

[C] The p values for relapse are based on a final multiple logistic regression model developed using a stepwise procedure to select variables (significance level of 0.05 for variables to both enter and stay in the final model) from a set of potential factors that included treatment and various baseline demographic and disease characteristics.
Note: Sensitivity analysis was conducted to include subjects with undetectable HCV-RNA at EOT with missing Follow-up Week (FW) 12 and FW 24 HCV-RNA levels, but who had FW 4 HCV-RNA results. Those with detectable HCV-RNA levels at FW 4 and the expected number of relapsers in those with undetectable HCV-RNA levels at FW 4 was estimated using proportional imputation for each treatment arm. These data were incorporated in the relapse rate calculation resulting in 'adjusted' relapse rates of 23.3% in the PEG2b 1.5/R arm, 20.2% in the PEG2b 1.0/R arm and 32.0% in the PEG2a/R arm.

In all three treatment groups, sustained virologic response rates were similar. In the majority of patients with poor prognostic factors treatment with PEG-INTRON (1.5 µg/kg)/ribavirin combination therapy resulted in higher sustained virologic response rate compared to PEG-INTRON 1 µg/kg. At the PEG-INTRON 1.5 µg/kg plus ribavirin dose, sustained virologic response rates were lower in patients with cirrhosis, in patients with normal ALT levels, in patients with a baseline viral load > 600, 000 IU/mL, and in patients > 40 years old. Caucasian patients had a higher sustained virologic response rate compared to the African Americans. Among patients with undetectable HCV-RNA at the end of treatment, the relapse rate was 24%.

Predictability of sustained virological response- Naive patients

Virological response by week 12 is defined as at least 2 log_{10} viral load decrease or undetectable levels of HCV-RNA. Virological response by week 4, is defined as at least 1 log_{10} viral load decrease or undetectable levels of HCV-RNA. These time points (Treatment Week 4 and Treatment Week 12) have been shown to be predictive for sustained response **(Table 5).**

Table 5: Predictive Value of In-Treatment Virologic Response while on PEG-INTRON 1.5 µg/kg/ribavirin 800-1,400 mg Combination Therapy

	Negative			**Positive**		
	No response at Treatment Week	No sustained Response	Negative Predictive Value	Response at Treatment Week	Sustained response	Positive Predictive Value
Genotype 1* **By Week 4 *** (n=950)**						
HCV-RNA negative	834	539	**65%** (539/834)	116	107	**92%** (107/116)
HCV-RNA negative or ≥ 1 log_{10} decrease in viral load	220	210	**95%** (210/220)	730	392	**54%** (392/730)
By week 12* (n=915)**						
HCV-RNA negative	508	433	**85%** (433/508)	407	328	**81%** (328/407)
HCV-RNA negative or 2 log_{10} decrease in viral load	206	205	N/A+	709	402	57% (402/709)
Genotype 2,3 By Week 12 (n=215)**						
HCV-RNA negative or ≥ 2 log_{10} decrease in viral load	2	1	**50% (1/2)**	213	177	**83% (177/213)**

* Genotype 1 receive 48 weeks treatment
** Genotype 2,3 receive 24 weeks treatment
*** The presented results are from a single point of time. A patient may be missing or have had a different result for Week 4 or Week 12.
+These criteria were used in the protocol. If Week 12 HCV-RNA is positive and ≤2 log_{10} decrease from baseline, patients to stop therapy. If Week 12 HCV-RNA is positive and decreased ≥2 log_{10} baseline then retest HCV-RNA at Week 24 and if positive, patients to stop therapy.

HCV/HIV co-infected patients

Two trials have been conducted in patients co-infected with HCV and stable HIV disease and a CD4 cell count above 200/mL. The response to treatment in both of these trials is presented in Table 6. Study 1 (RIBAVIC; P01017) was a randomised, multicentre study, which enrolled 412

previously untreated adult patients with chronic hepatitis C who were co-infected with HIV. Patients were randomised to receive either peginterferon alfa-2b (1.5 µg/kg/week) plus ribavirin (800 mg/day) or interferon alfa-2b (3 MIU TIW) plus ribavirin (800 mg/day) for 48 weeks with a follow up period of 6 months. Study 2 (P02080) was a randomised, single centre study that enrolled 95 previously untreated adult patients with chronic hepatitis C who were co-infected with HIV. Patients were randomised to receive either peginterferon alfa-2b (100 or 150 µg/week based on weight) plus ribavirin (800-1200 mg/day based on weight) or interferon alfa-2b (3 MIU TIW) plus ribavirin (800-1200 mg/day based on weight). The duration of therapy was 48 weeks with a follow up period of 6 months except for patients infected with genotypes 2 or 3 and viral load <800,000 IU/mL (Amplicor) who were treated for 24 weeks with a 6 month follow up period.

Table 6: Sustained virological response based on genotype after peginterferon alfa-2b in combination with ribavirin in HCV/HIV co-infected patients

	Study 1[1]			**Study 2[2]**		
	Peginterferon alfa-2b (1.5 µg/kg/wk) + ribavirin (800 mg)	Interferon alfa-2b (3 MIU TIW) + ribavirin (800 mg)	Treatment Difference	Peginterferon alfa-2b (100 or 150[c] µg/wk) + ribavirin (800-1200 mg)[d]	Interferon alfa-2b (3 MIU TIW) + ribavirin (800-1200 mg)[d]	Treatment Difference[b]
All	27% (56/205)	20% (41/205)	7.5% (95% CI: -0.7 to 5.7%, p=0.047[a])	44% (23/52)	21% (9/43)	23% (95% CI: 4 to40%, p=0.017b)
Genotype 1, 4	17% (21/125)	6% (8/129)		38% (12/32)	7% (2/27)	
Genotype 2, 3	44% (35/80)	43% (33/76)		53% (10/19)	47% (7/15)	

MIU = million international units; TIW = three times a week.
a: p value based on Cochran-Mantel Haenszel Chi square test.
b: p value based on chi-square test.
c: subjects <75 kg received 100 µg/week peginterferon alfa-2b and subjects ≥75 kg received 150 µg/week peginterferon alfa-2b.
d: ribavirin dosing was 800 mg for patients <60 kg, 1000 mg for patients 60-75 kg, and 1200 mg for patients >75 kg.

[1]Carrato F, Bani-Sadir F, Pol S et al. JAMA 2004; 292(23): 2839-2848.

[2] Laguno M, Murillas J, Blanco J et al. AIDS 2004; 18(13): F27-F36.

Histological response

Liver biopsies were obtained before and after treatment in Study 1 and were available for 210 of the 412 subjects (51%). The changes in activity scores and fibrosis scores for these subjects are shown in Table 7. Shift of >1 point indicates clinically meaningful improvement (decrease) or deterioration (increase).

Table 7: Changes in activity scores and fibrosis scores

Characteristic	Peginterferon alfa-2b/ribavirin (n=103)		Interferon alfa-2b/ribavirin (n=107)	
	Patients With SVR	Patients Without SVR	Patients With SVR	Patients Without SVR
Number of subjects	37	66	27	80
Activity				
METAVIR score (mean change)	-0.3 ± 0.5	-0.1 ± 0.6	-0.3 ± 0.6	0.1 ± 0.5
Ishak grade (mean change)	-1.2 ± 1.5	-0.2 ± 0.5	-1.1 ± 1.4	0 ± 1.4
Fibrosis				
METAVIR score (mean change)	0.0 ± 0.6	0.1 ± 0.7	0.0± 0.7	0.3 ± 0.9
Ishak stage (mean change)	0.1 ± 0.9	0.3 ± 1.4	-0.1 ± 1.0	0.6 ± 1.2

HCV = Hepatitis C Virus; SVR = sustained virologic response.

Predictability of response and non-response in HCV/HIV co-infection

Early virological response by Week 12, defined as a 2 $\log_{10}$ viral load decrease or undetectable levels of HCV-RNA, has been shown to be predictive for sustained response. The negative predictive value for sustained response in HCV/HIV co-infected patients treated with peginterferon alfa-2b/ribavirin was 99% (67/68; Study 1) (see CLINICAL TRIALS).

In an open label, single arm, non-comparative trial, 235 patients with HCV genotype 1 and low viral load (≤ 2,000,000 copies/mL; a value of 2,000,000 copies/mL is approximately equivalent to 600,000 IU/mL) and 224 patients with HCV genotype 2 or 3 received 24 weeks of treatment with PEG-INTRON, 1.5 microgram/kg subcutaneously, once weekly, in combination with oral ribavirin 800 mg – 1400 mg.

Table 8: Virologic response in HCV genotype 1 subjects with low viral load (n=235)

	Peginterferon alfa-2b in combination with ribavirin		
HCV Subjects	End of treatment response	Sustained virological response	Relapse
HCV1 subjects with low viral load	80% (188/235)	50% (117/235)	37% (68/184)

In patients infected with HCV genotype 1, the overall sustained response rate after a 24-week treatment was 50%. In the subgroup of patients who became HCV-RNA negative at treatment week 4 and remained HCV-RNA negative at treatment week 24, a high sustained virological response rate (over 90%) was observed following 24 weeks of therapy. Limited historical data in this subgroup showed that the 48 weeks therapy may be associated with a higher sustained

response rate [100% (11/11)] and a lower risk of relapse.

In patients infected with HCV genotype 2 or genotype 3, the overall sustained response rate after a 24-week treatment was 81%. Patients with genotype 2 had a higher response rate (93%) than patients with genotype 3 (79%). The 24 weeks of treatment in this trial was better tolerated than the 48 weeks of treatment in the pivotal trial; for discontinuation 5% vs. 14%, for dose modification 18% vs. 49%.

Table 9: Virologic response in HCV genotype 2 and 3 subjects (n=224)

	Peginterferon alfa-2b in combination with ribavirin		
HCV subjects	End of treatment response	Sustained virological response	Relapse
HCV2 and HCV3	94% (211/224)	81% (182/224)	12% (27/224)
HCV2	100% (42/42)	93% (39/42)	7% (3/42)
HCV3	93% (169/182)	79% (143/182)	14% (24/166)

In a large scale, prospective, multi-center, open-label, randomised study conducted in the United States, the efficacy and safety of peginterferon alfa-2b in combination with 2 different ribavirin regimens was compared in subjects with chronic hepatitis C. The efficacy of 24 weeks versus 48 weeks of therapy was also compared in subjects with HCV genotype 2 and 3. A total of 1552 genotype 2 and 3 patients were included in the primary efficacy population and randomised to either 24 weeks or 48 weeks treatment. No additional treatment benefit was observed with the longer duration.

PEGATRON retreatment of prior treatment failures

In an uncontrolled prospective trial, 1336 chronic hepatitis C patients with moderate to severe fibrosis who failed (relapsed or non-responders) previous treatment with interferon alfa were retreated with peginterferon/ribavirin combination.

The majority (80%) of the patients were infected with HCV Genotype 1. The previous treatment consisted of nonpegylated alfa interferon (77%), peginterferon alfa-2a (7%) and peginterferon alfa-2b (16%) with ribavirin, at least 6 months prior to retreatment. No patients had received interferon monotherapy.

These patients were retreated with peginterferon alfa-2b 1.5 µg/kg subcutaneously, once weekly, in combination with weight-adjusted ribavirin. The patients who achieved response at 12 weeks (undetectable HCV-RNA) continued the treatment for a total of 48 weeks. Response to treatment was defined as undetectable HCV-RNA at 24 weeks post-treatment (Table 10).

Table 10: Rates of Response to Retreatment in Prior Treatment Failures

	Interferon alfa-2b/Ribavirin		Peginterferon alfa-2b/Ribavirin	
	SVR% (n)	**99% CI**	**SVR% (n)**	**99% CI**
Overall	25 (255/1030)	21, 28	16 (48/299)	11, 22
Prior Relapsers	45 (95/213)	36, 53	36 (40/112)	24, 47
Genotype 1/4	34 (52/154)	24, 44	29 (24/83)	16,42
Genotype 2/3	73 (41/56)	58, 89	55 (16/29)	-
Prior Non-responders*	17 (117/673)	14, 21	4 (7/172)	0, 8
Genotype 1/4	13 (75/592)	9, 16	4 (6/160)	0, 8
Genotype 2/3	51 (40/78)	37, 66	10 (1/10)	-
Genotype				
1	17 (138/825)	13, 20	12 (28/243)	6, 17
2/3	62 (103/166)	52, 72	44 (17/39)	23, 64
4	31 (10/32)	10, 52	20 (3/15)	-
METAVIR fibrosis Score				
F2	32 (92/289)	25, 39	23 (15/66)	9, 36
F3	27 (86/323)	20, 33	17 (16/92)	7, 28
F4	19 (77/416)	14, 23	12 (17/141)	5, 19
Baseline Viral Load				
HVL (≥600,000 IU/mL)	21 (128/622)	16, 25	9 (17/192)	4, 14
LVL (<600,000 IU/mL)	31 (127/406)	25, 37	29 (30/105)	17, 40

*Non-responders were defined as patients with detectable HCV-RNA at the end of 12 weeks of treatment in previous interferon/ribavirin combination therapy. Serum HCV-RNA is measured with a research-based quantitative polymerase chain reaction assay by a central laboratory.

Approximately 37% of subjects had undetectable plasma HCV-RNA levels at Week 12 of therapy. In this subgroup, there was a 57% (282/499) sustained virological response rate. The predictors of response in this subgroup were fibrosis score and genotype. Patients with lower fibrosis scores or who were genotype 2 or 3 were more likely to achieve a sustained response.

After one retreatment attempt, the response in patients who relapsed after treatment with peginterferon/ribavirin combination was 36% (40/112) compared with 45% (95/213) in patients who relapsed after treatment with non-pegylated interferon/ribavirin combination. The response rate in patients who were non-responders to peginterferon/ribavirin combination was 4% (7/172) compared with 17% (117/673) in patients who were non-responders to non-pegylated interferon/ribavirin combination.

Long-term efficacy data

A long-term follow-up study enrolled 567 patients after treatment in a prior study with peginterferon alfa-2b (with or without ribavirin). The purpose of the study was to evaluate the durability of sustained virologic response (SVR) and assess the impact of continued viral negativity on clinical outcomes. 327 patients completed at least 5 years of long-term follow-up. Overall, 18 patients out of the 366 sustained responders relapsed during this period of 5 years. However 14 of these 18 subjects had detectable, though not quantifiable, HCV-RNA at some point during the long term follow-up, and they did not receive any antiviral/immunomodulatory therapy, and subsequently had undetectable virus. The majority of these subjects had multiple undetectable HCV-RNA tests that followed the single positive results. As such it was determined that these patients were unlikely to be relapsers, so that only 4/18 patients were considered to be possible and/or definite relapsers.

The Kaplan-Meier estimate for continued SVR over 5 years was thus estimated to be 99% (95% CI: 97 – 100%). SVR after treatment of chronic HCV with peginterferon alfa-2b (with or without ribavirin) results in long-term clearance of the virus. However, this does not preclude the occurrence of hepatic events in patients with cirrhosis (including hepatocarcinoma).

Children and Adolescents

Chronic Hepatitis C

Previously untreated children and adolescent subjects 3 to 17 years of age with compensated chronic hepatitis C and detectable HCV-RNA were treated with REBETOL 15 mg/kg/day plus PEG- INTRON 60 µg/m^2 once weekly for 24 or 48 weeks based on HCV genotype and baseline viral load. All subjects were to be followed for 24 weeks post-treatment. A total of 107 subjects received treatment of whom 52% were female, 89% were Caucasian, and 67% were infected with HCV Genotype 1. Subjects infected with Genotype 1, 4 or Genotype 3 with HCV-RNA ≥ 600,000 IU/mL received 48 weeks of therapy while those infected with Genotype 2 or Genotype 3 with HCV-RNA < 600,000 IU/mL received 24 weeks of therapy. The study results are summarized in Table 11.

Table 11: Sustained Virologic Response Rates (%/n) by Genotype and Treatment Duration in previously untreated Children and Adolescents

Genotype	All Subjects (n=107)	
	24 Weeks	48 Weeks
	Virologic Response % (n * †)	Virologic Response % (n * †)
All	96 (26/27)	55 (44/80)
1	-	53 (38/72)
2	93 (14/15)	-
3^	100 (12/12)	67 (2/3)
4	-	80 (4/5)

* Response to treatment was defined as undetectable HCV-RNA at 24 weeks post-treatment.
† n = number of responders/number of subjects with given genotype, and assigned treatment duration.
^ Subjects with genotype 3 low viral load (< 600,000 IU/mL) were to receive 24 weeks of treatment while those with genotype 3 and high viral load (≥ 600,000 IU/ml) were to receive 48 weeks of treatment.

INDICATIONS

PEGATRON Combination Therapy is indicated for the treatment of chronic hepatitis C in adult patients with compensated liver disease who are either treatment naïve or who had failed previous therapy with interferon alfa (pegylated or nonpegylated) and ribavirin combination therapy or interferon monotherapy (see CLINICAL TRIALS*).*

Combination Therapy is also indicated for the treatment of chronic hepatitis C in adult patients with compensated liver disease and with stable HIV co-infection, who have not previously received interferon treatment.

PEGATRON Combination Therapy is also indicated for the treatment of chronic hepatitis C in children and adolescents with a bodyweight of ≥ 27 kg with compensated liver disease and who have not received previous interferon treatment.

Interferon alfa monotherapy (including PEG-INTRON) is indicated mainly in case of intolerance or contraindication to ribavirin. REBETOL capsules must not be used alone because ribavirin is not effective as monotherapy in the treatment of hepatitis C.

CONTRAINDICATIONS

- a history of hypersensitivity to ribavirin or any component of REBETOL Capsules, or to peginterferon alfa-2b or any component of PEG-INTRON Powder for Injection or to any alfa interferon.
- PEGATRON Combination Therapy must not be used by women who are pregnant or men whose partners are pregnant and in both men and women when pregnancy is planned or could occur (see PRECAUTIONS). Extreme care must be taken to avoid pregnancy in female patients and in partners of male patients taking REBETOL Capsules. REBETOL Capsules must not be initiated until a report of a negative pregnancy test has been obtained immediately prior to initiation of therapy. Women of childbearing potential and men must use two forms of effective contraception during treatment and during the 6 months after treatment has been concluded. Significant teratogenic and/or embryocidal effects have been demonstrated for ribavirin in all animal species in which adequate studies have been conducted. These effects occurred at doses as low as one twentieth of the recommended human dose of ribavirin (see PRECAUTIONS).
- breast-feeding
- a history of severe pre-existing cardiac disease, including unstable or uncontrolled cardiac disease, in the previous six months (see PRECAUTIONS)
- haemoglobinopathies (e.g. thalassaemia, sickle-cell anaemia)
- patients who are being treated or who have been treated recently with immunosuppressive agents, excluding short-term corticosteroid withdrawal
- autoimmune hepatitis; or history of autoimmune disease
- immunosuppressed transplant recipients

- pre-existing thyroid disease unless it can be controlled with conventional treatment
- severe, debilitating medical conditions
- severe hepatic impairment (Child-Pugh Classification B or C) or decompensated cirrhosis of the liver
- epilepsy and/or compromised CNS function
- HCV/HIV patients with cirrhosis and a Child-Pugh score ≥6
- paediatric patients: existence of, or history of severe psychiatric conditions, particularly severe depression, suicidal ideation or suicidal attempt
- patients with chronic renal failure, patients with creatinine clearance <50 mL/min and/or on haemodialysis

PRECAUTIONS

Psychiatric and Central Nervous System (CNS): Patients with pre-existing severe psychiatric condition or a history of severe psychiatric disorder should not be treated with PEGATRON Combination Therapy.

Severe CNS effects, particularly depression, homicidal ideation, suicide, suicidal ideation and attempted suicide, have been observed in some patients during PEGATRON Combination Therapy. Among children and adolescents treated with interferon alfa-2b in combination with ribavirin, suicidal ideation or attempts were reported more frequently compared to adult patients (2.4% vs 1%) during treatment and during the 6-month follow-up after treatment. As in adult patients, children and adolescents experienced other psychiatric adverse events (e.g. depression, emotional lability, and somnolence). Other CNS effects including aggressive behaviour, sometimes directed towards others, psychosis including hallucinations, confusion and alteration of mental status have been observed with alfa interferon. Severe psychiatric effects may occur even after treatment is discontinued, mainly during the 6 month follow-up period.

More significant obtundation and coma, including cases of encephalopathy, have been observed in some patients, usually elderly, treated at higher doses of interferon alfa-2b. While these effects are generally reversible, in a few patients full resolution took up to three weeks. Very rarely, seizures have occurred with high doses of PEGATRON. Patients should be advised to report immediately any symptoms of depression and/or suicidal ideation to their prescribing physicians.

Treatment with interferons may be associated with exacerbated symptoms of psychiatric disorders in HCV infected patients with co-occurring psychiatric and substance use disorders. If treatment with interferons is judged necessary in patients with prior history or existence of psychiatric condition or with substance use disorders, in order to reach successful adherence to treatment with interferons, adequate management of psychiatric symptoms and substance use requires individualized screening strategies and frequent psychiatric symptom monitoring. Early intervention for re-emergence or development of neuropsychiatric symptoms and substance use is recommended.

If patients develop psychiatric or CNS problems, including clinical depression, it is recommended that the patient be carefully monitored by the prescribing physician during treatment and in the 6 month follow-up period, due to the potential seriousness of these undesirable effects. If such symptoms appear, the potential seriousness of

these undesirable effects must be born in mind by the prescribing physician. If psychiatric symptoms persist or worsen, or suicidal or homicidal ideation or aggressive behaviour towards others is identified, it is recommended that PEGATRON Combination Therapy be discontinued, and the patient followed with psychiatric intervention as appropriate.

REBETOL alone

Based on results of clinical studies, the use of ribavirin as monotherapy is not effective and REBETOL Capsules must not be used alone. There is no information regarding the use of REBETOL brand of ribavirin with other interferons. The safety and efficacy of combination therapy have been established only when REBETOL is administered together with peginterferon alfa-2b (PEG-INTRON) or interferon alfa-2b (INTRON A). Variations in dosage, routes of administration and adverse reactions exist among different brands of interferon.

Teratogenic Risk

There are no studies in pregnant women. Significant teratogenic and/or embryocidal potential has been demonstrated for ribavirin in all animal species in which adequate studies have been conducted, occurring at doses as low as one-twentieth of the recommended human dose (see Use In Pregnancy). The incidence and severity of teratogenic effects increased with escalation of the ribavirin dose. Survival of foetuses and offspring was reduced. It should be assumed that the teratogenic effects of ribavirin will also be caused by the drug combination.

Female patients: PEGATRON Combination Therapy must not be used by women who are pregnant or men whose partners are pregnant (see CONTRAINDICATIONS; Use In Pregnancy). Extreme care must be taken to avoid pregnancy in female patients taking REBETOL Capsules. PEGATRON Combination Therapy must not be initiated until a report of a negative pregnancy test has been obtained immediately prior to initiation of therapy. Women of childbearing potential and their partners must use two forms of effective contraception during treatment and for 6 months after treatment has been concluded (15 half-lives for clearance of ribavirin from the body); routine monthly pregnancy tests must be performed during this time. If pregnancy does occur during treatment or during 6 months post-treatment, the patient must be advised of the significant teratogenic risk of ribavirin to the foetus.

Male patients and their female partners: PEGATRON Combination Therapy must not be used by women who are pregnant or men whose partners are pregnant (see CONTRAINDICATIONS; Use In Pregnancy). Extreme care must be taken to avoid pregnancy in partners of male patients taking REBETOL Capsules. Ribavirin accumulates intracellularly and is cleared from the body very slowly. It is unknown whether the ribavirin that is contained in sperm will exert its known teratogenic effects upon fertilisation of the ova. In animal studies, ribavirin produced changes in sperm at doses below the clinical dose. Male patients and their female partners of childbearing age must use effective contraception during treatment with ribavirin and for the 6 months post-treatment follow-up period (15 half-lives for ribavirin clearance from the body).

Female and male patients: Whenever pregnancy is a possibility, the use of two forms of contraception, one for each partner, is recommended.

Acute Hypersensitivity: If an acute hypersensitivity reaction (e.g. urticaria, angioedema, bronchoconstriction, anaphylaxis) develops, PEGATRON Combination Therapy should be discontinued immediately and appropriate medical therapy instituted. Transient rashes do not necessitate interruption of treatment.

Hepatic Failure: PEG-INTRON increases the risk of hepatic decompensation and death in patients with cirrhosis. Discontinue treatment with PEG-INTRON in patients with signs of liver decompensation. Monitor hepatic function with serum bilirubin, ALT (alanine transaminase), AST (aspartate aminotransferase), alkaline phosphatase and LDH (lactate dehydrogenase) at 2, 8, and 12 weeks following initiation of PEG-INTRON, then every 6 months while receiving PEG-INTRON. Permanently discontinue PEG-INTRON for evidence of severe (Grade 3) hepatic injury or hepatic decompensation (Child-Pugh score >6 [class B and C]).

Bone Marrow Toxicity: Alfa interferons including PEG-INTRON are known to suppress bone marrow function, sometimes resulting in severe cytopaenia. PEG-INTRON should be discontinued in patients who develop severe decreases in neutrophil or platelet counts (see DOSAGE AND ADMINISTRATION: Table 18). Ribavirin may potentiate the neutropaenia induced by interferon alfa. Very rarely alfa interferons may be associated with aplastic anaemia.

Haemolysis: A decrease in haemoglobin levels to <100 g/L was observed in up to 28% of patients treated with PEGATRON Combination Therapy in a clinical trial. Although ribavirin has no direct cardiovascular effects, anaemia associated with ribavirin may result in deterioration of cardiac function and/or exacerbation of the symptoms of coronary disease. Thus, PEGATRON Combination Therapy should be administered with caution in patients with pre-existing cardiac disease (see CONTRAINDICATIONS). Cardiac status should be assessed before start of therapy and monitored clinically during therapy; if any deterioration occurs, therapy should be stopped (see DOSAGE AND ADMINISTRATION).

Cardiovascular: Patients with a history of congestive heart failure, myocardial infarction and/or previous or current arrhythmic disorders receiving PEGATRON Combination Therapy should be closely monitored. Those patients who have pre-existing cardiac abnormalities should have electrocardiograms taken prior to and during the course of treatment. Cardiac arrhythmias (primarily supraventricular) usually respond to conventional therapy but may require discontinuation of therapy. There are no data in children or adolescents with a history of cardiac disease.

Pyrexia: While pyrexia may be associated with the flu-like syndrome reported commonly during interferon therapy, other causes of persistent pyrexia should be ruled out.

Hydration: Adequate hydration must be maintained in patients undergoing therapy with PEGATRON Combination Therapy since hypotension related to fluid depletion has been seen in some patients treated with alfa interferons. Fluid replacement may be necessary.

Liver Function: Any patient developing significant liver function abnormalities during treatment should be monitored closely. The treatment should be discontinued if signs and symptoms progress. The safety and efficacy of PEGATRON Combination Therapy has not been evaluated in patients with severe hepatic dysfunction, therefore PEGATRON should not be used for these patients.

Metabolic Disturbances: Hypertriglyceridaemia and aggravation of hypertriglyceridaemia, sometimes severe, have been observed. Monitoring of lipid levels is, therefore, recommended.

Use in patients with rare hereditary disorders: Each REBETOL capsule contains 40 mg of lactose. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

Ocular Changes: Ophthalmologic disorders, including retinal haemorrhages, retinal exudate, and retinal artery or vein occlusion, have been reported in rare instances after treatment with alfa interferons (see ADVERSE EFFECTS). All patients should have a baseline eye examination. Any patient complaining of ocular symptoms, including loss of visual acuity or visual field must have a prompt and complete eye examination. Because these ocular events may occur in conjunction with other disease states, periodic visual examinations during PEG-INTRON therapy are recommended in patients with disorders that may be associated with retinopathy, such as diabetes mellitus or hypertension. Discontinuation of PEGATRON Combination Therapy should be considered in patients who develop new or worsening ophthalmologic disorders.

Pulmonary changes: Pulmonary infiltrates, pneumonitis, and pneumonia, occasionally resulting in fatality, have been observed rarely in interferon alfa treated patients. These symptoms have been reported more frequently when shosaikoto, a Chinese herbal medicine, is administered concomitantly with alfa interferon. Any patient developing pyrexia, cough, dyspnoea or other respiratory symptoms must have a chest X-ray taken. If the chest X-ray shows pulmonary infiltrates or there is evidence of pulmonary function impairment, the patient is to be monitored closely. If appropriate, discontinue PEGATRON Combination Therapy.

Renal function: Patients with severe renal dysfunction (including chronic renal failure) or creatinine clearance <50 mL/min must not be treated with PEGATRON Combination Therapy. When PEGATRON Combination Therapy is administered, subjects with impaired renal function should be more carefully monitored with respect to the development of anaemia.

It is recommended that renal function be evaluated in all patients prior to initiation of PEGATRON Combination Therapy. Patients with impairment of renal function should be closely monitored and, should have their dose of PEGATRON Combination Therapy reduced if medically appropriate. If serum creatinine rises to >0.02 g/L (approx 177 mmol/L), PEGATRON Combination Therapy must be discontinued (see DOSAGE AND ADMINISTRATION: Table 18) (also see Special Populations).

Thyroid changes: Infrequently, adult patients treated for chronic hepatitis C with interferon alfa have developed thyroid abnormalities, either hypothyroidism or hyperthyroidism. Approximately 21% of children treated with PEGATRON Combination Therapy developed increase in thyroid stimulating hormone (TSH). Another approximately 2% had a transient decrease below the lower limit of normal. Prior to initiation of PEG-INTRON therapy, TSH levels must be evaluated and any thyroid abnormality detected at that time must be treated with conventional therapy. Determine TSH levels if, during the course of therapy, a patient develops symptoms consistent with possible thyroid dysfunction. In the presence of thyroid dysfunction, PEGATRON Combination Therapy may be continued if TSH levels can be maintained in the normal range by medication. PEGATRON Combination Therapy should be discontinued in patients developing thyroid abnormalities during treatment, if thyroid function cannot be controlled by medication. Children and adolescents should be monitored every 3 months for evidence of thyroid

dysfunction (e.g. TSH).

Dental and periodontal disorders: Dental and periodontal disorders have been reported in patients receiving ribavirin peginterferon combination therapy. In addition, dry mouth could have a damaging effect on teeth and mucous membranes of the mouth during long-term treatment with the combination of REBETOL and peginterferon alfa-2b. Patients should brush their teeth thoroughly twice daily and have regular dental examinations. In addition, some patients may experience vomiting. If this reaction occurs, they should be advised to rinse out their mouth thoroughly afterwards.

Organ transplantation: The safety and efficacy of PEGATRON Combination Therapy for the treatment of hepatitis C in liver and other organ transplant recipients have not been studied. Preliminary data indicates that interferon alfa therapy may be associated with an increased rate of kidney graft rejection. Liver graft rejection has also been reported but a causal association with interferon alfa therapy has not been established.

HCV/HIV coinfection: Patients taking NRTI treatment in association with ribavirin and peg-interferon alfa-2b may be at increased risk of mitochondrial toxicity, lactic acidosis and hepatic decompensation.

Co-infected patients with advanced cirrhosis receiving Highly Active Antiretroviral Therapy (HAART) may be at increased risk of hepatic decompensation and death. Adding treatment with alfa interferons in combination with ribavirin may increase the risk in this patient subset.

The risk of spontaneous hepatic decompensation was increased in patients with elevated bilirubin, advanced cirrhosis and treatment with didanosine. In Study 1 in HCV/HIV co-infection, 7 patients presented with hepatic decompensation. Cirrhosis was present in 5 out of these 7 patients. All patients were receiving antiretroviral therapy at the onset of hepatic decompensation. Five patients died as a result of the hepatic decompensation.

The use of PEGATRON Combination Therapy in children with HCV/HIV co-infection has not been studied.

Potential to exacerbate immunosuppression: Pancytopenia and bone marrow suppression have been reported in the literature to occur within 3 to 7 weeks after the administration of a peginterferon and ribavirin concomitantly with azathioprine. This myelotoxicity was reversible within 4 to 6 weeks upon withdrawal of HCV antiviral therapy and concomitant azathioprine and did not recur upon reintroduction of either treatment alone (see Concomitant Therapy and Drug Interactions).

Others: Because of reports of exacerbating pre-existing psoriatic disease and sarcoidosis with interferons, PEGATRON Combination Therapy should be used in patients with psoriasis and sarcoidosis only if the potential benefit justifies the potential risk.

Development of different auto-antibodies has been reported during treatment with alfa interferons. Clinical manifestations of autoimmune disease during interferon therapy may occur more frequently in patients predisposed to the development of autoimmune disorders.

Laboratory Tests

Standard haematological tests, blood chemistry (complete blood count and differential, platelet count, electrolytes, serum creatinine, liver function tests, uric acid) and a test of thyroid function should be conducted in all patients prior to initiating therapy. Acceptable baseline values that may be considered as a guideline prior to initiation of PEGATRON Combination Therapy are:

Haemoglobin	≥120 g/L (females), ≥130 g/L (males)
	Children and adolescents: ≥110 g/L (females), ≥120 g/L (males)
Platelets	≥100 $x10^9$/L
Neutrophil Count	≥1.5 $x10^9$/L
TSH Levels	must be within normal limits

These laboratory evaluations should be conducted at Weeks 2, 4 and 8 of therapy, and periodically thereafter as clinically appropriate. HCV-RNA should be measured periodically during treatment (see DOSAGE AND ADMINISTRATION).

For women of childbearing potential, a routine pregnancy test must be performed monthly during treatment and for 6 months thereafter (see PRECAUTIONS). Female partners of male patients must have a routine pregnancy test performed monthly during treatment and for six months thereafter.

Uric acid may increase with ribavirin due to haemolysis; therefore, the potential for development of gout must be carefully monitored in pre-disposed patients.

Use in Children and Adolescents

PEGATRON Combination Therapy can be used in children and adolescents ≥ 27 kg bodyweight (see INDICATIONS). The use of PEGATRON Combination Therapy has not been studied in children under 3 years of age.

Growth and development: During the course of therapy lasting up to 48 weeks in patients ages 3 to 17 years, weight loss and growth inhibition were common (see ADVERSE REACTIONS). Long- term data in a limited number of patients indicates that combination therapy may induce a growth inhibition that results in reduced final adult height in some patients.

Case by case benefit/risk assessment in children:

The expected benefit of treatment should be carefully weighed against the safety findings observed for children and adolescents in the clinical trials.

It is important to consider that the combination therapy induced a growth inhibition, the reversibility of which is uncertain.

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 (such as HIV co-infection), as well as prognostic factors of response (HCV genotype and viral load).

Whenever possible the child should be treated after the pubertal growth spurt, in order to reduce the risk of growth inhibition. There are no data on long term effects on sexual maturation.

The use of PEGATRON Combination Therapy in children with HCV/HIV co-infection has not been studied.

Use in the Elderly

Since renal and hepatic function may be decreased in the elderly, renal and hepatic status should be determined prior to initiation of PEGATRON Combination Therapy (see PRECAUTIONS; CONTRAINDICATIONS).

Carcinogenicity

Ribavirin: Conventional carcinogenicity rodent studies with low exposures compared to human exposure under therapeutic conditions (factor 0.1 in rats and 1 in mice) did not reveal tumorigenicity of ribavirin. In addition, in a 26-week carcinogenicity study using the heterozygous p53 (+/-) mouse model, ribavirin did not produce tumours at the maximally tolerated dose of 300 mg/kg/day (plasma exposure factor approximately 1.2 compared to human exposure).

Peginterferon*:* Peginterferon alfa-2b has not been tested for its carcinogenic potential.

PEGATRON Combination Therapy*:* No carcinogenicity studies have been conducted with peginterferon alfa-2b in combination with ribavirin**.**

Genotoxicity

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

Neither peginterferon alfa-2b, nor its components recombinant interferon alfa-2b and methoxypolyethylene glycol, was positive in assays for gene mutations and chromosomal damage.

Impairment of fertility

Ribavirin: Ribavirin has induced testicular toxicity in mice and rats. In a three to six month gavage study in mice, ribavirin significantly increased the percentage of morphologically abnormal sperm at 15 mg/kg/day (approximately 0.1 times the clinical exposure (AUC) at the maximum recommended dose) and above (see PRECAUTIONS), and reduced spermatid and sperm concentrations at 35 mg/kg/day and above. After cessation of dosing, mice almost completely recovered from testicular toxicity within one to two spermatogenesis cycles i.e. approximately 1.5 to 3 months. In rats, gavage doses of 160 mg/kg/day (approximately 0.4 times the clinical exposure (AUC) at the maximum recommended dose) for nine weeks reduced spermatid counts and lowered epididymal weights, and testicular tubular atrophy occurred after administration of 160 mg/kg/day in the diet for 30 days. Testicular toxicity was not observed in

other rat studies at gavage doses of up to 200 mg/kg/day for 90 days, or at 90 mg/kg/day in the diet for 12 months.

Peginterferon: Reproductive studies with peginterferon alfa-2b have not been performed, however, animal studies have indicated that recombinant interferon alfa-2b may impair fertility. Peginterferon alfa-2b may also cause this effect. A study with recombinant interferon alfa-2b showed menstrual cycle abnormalities in some cynomolgus monkeys.

PEGATRON Combination Therapy: No reproductive studies have been conducted with peginterferon alfa-2b in combination with ribavirin.

Use in Pregnancy (Category X)

Extreme care must be taken to avoid pregnancy in female patients and female partners of male patients taking REBETOL Capsules.

PEGATRON Combination Therapy must not be used during pregnancy. Women of childbearing potential and their male partners should not receive PEGATRON Combination Therapy unless they are using effective contraception during the therapy period (see CONTRAINDICATIONS, PRECAUTIONS). In addition, effective contraception should be used for 6 months (24 weeks) post- therapy, based on a multiple dose ribavirin half-life of 12 days.

The use of two reliable forms of contraception is recommended, one for each partner.

There are no studies in pregnant women. Animal teratology studies have not been conducted with peginterferon alfa-2b in combination with ribavirin, however, studies with ribavirin alone have shown that this is teratogenic in animals (see below). It should be assumed that the teratogenic effects of ribavirin will also be caused by the drug combination.

Ribavirin*:* 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, jaw, limbs, skeleton and gastrointestinal tract were noted.

Based on postmarketing surveillance, there are reports of congenital abnormalities, childhood disorders and miscarriages in female patients directly exposed to ribavirin during pregnancy and those female patients whose male partners were exposed to ribavirin therapy. The relationship of these outcomes to ribavirin exposure is unknown.

Peginterferon alfa-2b: Reproductive studies with peginterferon alfa-2b have not been performed. Results of animal reproduction studies have indicated that recombinant interferon alfa-2b was not teratogenic in rats or rabbits, nor did it adversely affect pregnancy, foetal development or reproductive capacity in the offspring of treated rats. Animal studies have also shown that interferons do not cross the placental barrier. Interferon has been shown to have abortifacient effects in rhesus monkeys (*Macaca mulatta*). Peginterferon alfa-2b is also likely to cause this effect. Abortion was observed in all dose groups (7.5, 15 and 30 million IU/kg intramuscularly from Day 20 to Day 80 of gestation), and was statistically significant versus control in the mid- and high-dose groups.

Use in Lactation

It is not known whether either component of PEGATRON Combination Therapy is excreted in human milk. Because of the potential for adverse reactions in breast-feeding infants, breast-feeding should be discontinued prior to initiation of treatment (see CONTRAINDICATIONS).

Driving and Operating Machinery

Patients who develop fatigue, somnolence or confusion during treatment with PEGATRON Combination Therapy should be cautioned to avoid driving or operating machinery.

Concomitant Therapy and Drug Interactions

No pharmacokinetic interactions were noted between PEG-INTRON Injection and REBETOL Capsules in a multiple-dose pharmacokinetic study.

Pharmacokinetic interactions between PEGATRON Combination Therapy and methadone have not been studied.

Patients co-infected with the Human Immunodeficiency Virus (HIV) and are receiving Highly Active Anti-Retroviral Therapy (HAART) may be at increased risk of developing lactic acidosis. Caution should be used when adding treatment with PEGATRON Combination Therapy to HAART.

Rebetol (Ribavirin): Clinically, no pharmacokinetic or pharmacodynamic interactions have been noted between ribavirin and other compounds, e.g., theophylline or didanosine, although the clinical literature in this area is limited. Ribavirin is not a substrate for any cytochrome P450 enzymes, nor does it inhibit or induce these enzymes.

Ribavirin, by having an inhibitory effect on inosine monophosphate dehydrogenase, may interfere with azathioprine metabolism possibly leading to an accumulation of 6-methylthioinosine monophosphate (6-MTIMP), which has been associated with myelotoxicity in patients treated with azathioprine. The use of pegylated alfa interferons and ribavirin concomitantly with azathioprine should be avoided. In individual cases where the benefit of administering ribavirin concomitantly with azathioprine warrants the potential risk, it is recommended that close hematologic monitoring be done during concomitant azathioprine use to identify signs of myelotoxicity, at which time treatment with these medicines should be stopped.

Antacid effect: Although co-administration of ribavirin 600 mg with an antacid (Mylanta®) containing magnesium, aluminium hydroxides and simethicone decreased bioavailability of ribavirin by 14%, it is possible that the decreased bioavailability in the study was due to delayed transit of ribavirin or modified gastrointestinal pH. This interaction was not considered to be clinically relevant.

Nucleoside analogues: Ribavirin was shown *in vitro* to inhibit phosphorylation of zidovudine and stavudine. The clinical significance of these findings is unknown. However, these *in vitro* findings raise the possibility that concurrent use of REBETOL 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 PEGATRON Combination Therapy

concurrently with either of these two agents. If HIV-RNA levels increase, the use of PEGATRON Combination Therapy concomitantly with reverse transcriptase inhibitors must be reviewed.

Exacerbation of anaemia due to ribavirin has been reported when zidovudine is part of the regimen used to treat HIV, although the exact mechanism remains to be elucidated. The concomitant use of ribavirin with zidovudine is not recommended due to an increased risk of anaemia (see Special Populations).

Consideration should be given to replacing zidovudine in a combination anti-retroviral treatment (ART) regimen if this is already established. This would be particularly important in patients with a known history of zidovudine-induced anaemia.

Use of nucleoside analogues, alone or in combination with other nucleosides, has resulted in lactic acidosis. Pharmacologically, ribavirin increases phosphorylated metabolites of purine nucleosides *in vitro*. This activity could potentiate the risk of lactic acidosis induced by purine nucleoside analogues (e.g. didanosine or abacavir). Coadministration of ribavirin and nucleoside analogues should be undertaken with caution and only if the potential benefit outweighs the potential risks.

Conflicting findings are reported in literature on co-administration between abacavir and ribavirin.

Some data suggest that HCV/HIV co-infected patients receiving abacavir-containing ART may be at risk of a lower response rate to pegylated interferon/ribavirin therapy. Caution should be exercised when both medicines are co-administered.

Didanosine: Exposure to didanosine or its active metabolite (dideoxyadenosine 5”-triphosphate) is increased when didanosine is co-administered with ribavirin, which could cause or worsen clinical toxicities. Co-administration of didanosine and ribavirin is not recommended. There have been reports of mitochondrial toxicity, in particular fatal hepatic failure, as well as peripheral neuropathy, pancreatitis (some of which were fatal), and symptomatic hyperlactactaemia/lactic acidosis.

Based on the half-life of ribavirin (mean 298 hours), there is a theoretical potential for interactions for up to 2 months after cessation of PEGATRON Combination Therapy.

There is no evidence that ribavirin interacts with non-nucleoside reverse transcriptase inhibitors or protease inhibitors.

PEG-INTRON (Peginterferon alfa-2b): Results of a pharmacokinetic interaction study with a single dose of PEG-INTRON demonstrated no effect on the activity of cytochrome P450 (CYP) 1A2, CYP2C8/9, CYP2D6, and hepatic CYP3A4 or N-acetyl transferase. The literature, however, reports up to a 50% reduction in clearance of CYP1A2 substrates (e.g. theophylline) when administered with other forms of interferon alfa and therefore caution should be exercised when PEG-INTRON Injection is used with medications metabolised by CYP1A2.

Caution should be used when administering interferon alfa-2b with medications metabolised by CYP2C8/9 and CYP2D6, especially those with narrow therapeutic indices.

Methadone: In patients with chronic hepatitis C that were on stable methadone maintenance therapy and naïve to peginterferon alfa-2b, addition of 1.5 microgram/kg/week of PEG-INTRON

subcutaneously for 4 weeks increased R-methadone AUC by approximately 15% (95% Cl for AUC ratio estimate 103 – 128%). The clinical significance of this finding is unknown; however, patients should be monitored for signs and symptoms of increased sedative effect, as well as respiratory depression. Especially in patients on a high dose of methadone, the risk for QTc prolongation should be considered.

ADVERSE REACTIONS

The safety of PEGATRON Combination Therapy was evaluated from data from a large randomized Phase III clinical study (see CLINICAL TRIALS) in which patients were treated for one year with one of two different dosage regimens. The control group in this study received interferon alfa-2b (3 MIU three times a week) + ribavirin (1,000/1,200 mg/day) for one year. Adverse events reported by ≥10% of patients in this study are shown in Table 12.

Table 12: Most common (≥ 10%) treatment-related adverse events reported in the Phase III study

Body system	**% of Subjects**		
	P 1.5/R PEG-INTRON 1.5 µg/kg + Rebetol 800 mg *(n=511)*	**P 0.5/R** PEG-INTRON 1.5 → 0.5 µg/kg + Rebetol 1000/1200 mg *(n=511)*	**I/R (=Rebetron)** Intron A 3 MIU TIW + Rebetol 1000/1200 mg *(n=511)*
Application site			
Injection site inflammation	25	27	17
Injection site reaction	58	59	36
Autonomic Nervous System			
Mouth dry	11	8	8
Sweating increased	11	9	7
Body as a whole			
Asthenia	18	15	17
Fatigue	64	61	59
Fever	45	43	32
Flu-like symptoms	24	27	23
Headache	62	57	57
Rigors	48	44	40
Weight decrease	28	16	19
Central and Peripheral Nervous System			
Dizziness	20	18	16
Gastrointestinal			
Abdominal pain	10	9	9
Anorexia	32	29	26
Diarrhoea	19	15	13

Body system	% of Subjects		
	P 1.5/R PEG-INTRON 1.5 µg/kg + Rebetol 800 mg *(n=511)*	**P 0.5/R** PEG-INTRON 1.5 → 0.5 µg/kg + Rebetol 1000/1200 mg *(n=511)*	**I/R (=Rebetron)** Intron A 3 MIU TIW + Rebetol 1000/1200 mg *(n=511)*
Nausea	43	35	31
Vomiting	12	13	10
Musculoskeletal			
Arthralgia	32	31	26
Musculoskeletal pain	13	13	11
Myalgia	55	47	49
Psychiatric			
Anxiety	14	14	14
Concentration impaired	17	16	21
Depression	30	29	32
Emotional lability	11	11	10
Insomnia	39	39	41
Irritability	35	34	34
Respiratory system			
Coughing	14	11	11
Dyspnoea	25	23	22
Skin and appendages			
Alopecia	36	29	32
Pruritus	27	25	27
Rash			
Skin dry	22	20	21
	23	17	21

Undesirable effects reported between 5% and 10% in the high dose PEGATRON treatment group (P1.5/R) were chest pain, right upper quadrant (RUQ) pain, paraesthesia, hypothyroidism, dyspepsia, stomatitis, thrombocytopaenia, agitation, nervousness, menstrual disorder, viral infection, nonproductive cough, pharyngitis, rhinitis, taste perversion, blurred vision, and leukopaenia.

Undesirable effects reported between 2% and 5% in the P1.5/R treatment group were injection site pain, flushing, impotence, lacrimal gland disorder, erythema, malaise, hypertension, syncope, confusion, hyperaesthesia, hypoaesthesia, hypertonia, decreased libido, tremor, vertigo, hyperthyroidism, constipation, flatulence, gingival bleeding, glossitis, loose stools, stomatitis, ulcerative stomatitis, hearing/vestibular disorders (including tinnitus and hearing impairment/loss), palpitation, tachycardia, hepatomegaly, hyperuricaemia, hypocalcaemia, thirst, bruise, aggressive behaviour, apathy, somnolence, herpes simplex, fungal infection, amenorrhoea, menorrhagia, bronchitis, epistaxis, nasal congestion, respiratory disorder, rhinorrhoea, sinusitis, eczema, abnormal hair texture, photosensitivity reaction, psoriasis, erythematous rash, maculopapular rash, frequent micturition, conjunctivitis, abnormal vision, migraine, hypotension, prostatitis, otitis media and lymphadenopathy.

Haemoglobin levels dropped below 100 g/L in up to 14% of patients treated with PEGATRON Combination Therapy. Most cases of anaemia, neutropaenia and thrombocytopaenia were mild (WHO grades 1 or 2). There were some cases of more severe neutropaenia in patients of the P1.5/R treatment group (WHO grade 3: 92 of 511 [18%]; and WHO grade 4: 22 of 511 [4%]).

Dosage modification due to adverse events was more common in patients receiving the PEGATRON regimens (P1.5/R: 42%; P0.5/R: 36%) compared to REBETRON (I/R: 34%). The most common reasons for dose modification were anaemia and neutropaenia, both of which were dose-related. Dose modification for neutropaenia was higher in the P1.5/R treatment group (18%) compared with the P0.5/R (10%) and the I/R (8%) groups. Both anaemia and neutropaenia were successfully managed by dose modification, thus discontinuations due to anaemia (0.6-0.8%) and neutropaenia (0.4-1%) were rare. Discontinuation rates in the three treatment groups were similar: 14% for P1.5/R, 13% for P0.5/R and 13% for I/R.

In the clinical study, approximately 1.2% of patients treated with PEGATRON Combination Therapy reported life-threatening psychiatric events during treatment. These events included suicidal ideation, aggressive behaviour, sometimes directed towards others, suicide and attempted suicide and psychosis including hallucinations.

An increase in uric acid and indirect bilirubin values associated with haemolysis was observed in some patients treated with PEGATRON Combination Therapy, but values returned to baseline levels by four weeks after the end of therapy. Among those patients with elevated uric acid levels, very few patients treated with PEGATRON Combination Therapy developed clinical gout, none of which required treatment modification or discontinuation from the clinical studies.

HCV/HIV co-infected patients

The risk of spontaneous hepatic decompensation was increased in patients with elevated bilirubin, advanced cirrhosis and treatment with didanosine. In Study 1 in HCV/HIV co-infection, 7 patients presented with hepatic decompensation. Cirrhosis was present in 5 out of these 7 patients. All patients were receiving antiretroviral therapy at the onset of hepatic decompensation. Five patients died as a result of the hepatic decompensation.

Treatment with peginterferon alfa-2b in combination with ribavirin was associated with decreases in absolute CD4+ cell counts within the first 4 weeks without a reduction in CD4+ cell percentage. The nadir for CD4+ cell reduction was reached around 36 weeks of therapy. The decrease in CD4+ cell counts was reversible upon dose reduction or cessation of therapy. The use of peginterferon alfa-2b in combination with ribavirin had no observable negative impact on the control of HIV viraemia during therapy or follow-up. The two trials conducted in HCV/HIV co-infection were limited to patients with CD4+ cell count above 200/mL (also see PRECAUTIONS - HCV/HIV Co-Infection).

Table 13: Safety overview in clinical trials of HCV/HIV co-infected patients treated with peginterferon alfa-2b in combination with ribavirin

	Study 1		Study 2	
	Peginterferon alfa-2b/ribavirin n=194	Interferon alfa-2b/ribavirin n=189	Peginterferon alfa-2b/ribavirin n=52	Interferon alfa-2b/ribavirin n=43
Treatment Discontinuation				
All Reasons	76 (39%)	73 (39%)	21 (40%)	27 (63%)
Any Adverse Event	33 (17%)	29 (15%)	9 (17%)	5 (12%)
Dose Modification				
Any Adverse Event	54 (28%)	23 (12%)	25 (48%)	23 (53%)
Anaemia	19 (10%)	8 (4%)	4 (8%)	7 (16%)
Neutropaenia	14 (7%)	5 (3%)	7 (13%)	3 (7%)
Thrombocytopaenia	9 (5%)	1 (<1%)	2 (4%)	2 (5%)

For HCV/HIV co-infected patients receiving peginterferon alfa-2b in combination with ribavirin, other undesirable effects which have been reported in the larger study (Study 1): neutropaenia (26%), lipodystrophy acquired (13%), CD4+ lymphocytes decreased (8%), appetite decreased (8%), gamma-glutamyltransferase increased (9%), back pain (5%), rhinitis (5%), blood amylase increased (6%), blood lactic acid increased (5%), cytolytic hepatitis (6%), paraesthesia (5%), lipase increased (6%).

Laboratory values for HCV/HIV co-infected patients

Although haematological toxicities of neutropaenia, thrombocytopaenia and anaemia occurred more frequently in HCV/HIV co-infected patients, the majority could be managed by dose modification and rarely required premature discontinuation of treatment. In the larger study (Study 1), decrease in absolute neutrophil count levels below 500 cells/mm^3 was observed in 4% (8/194) of patients and decrease in platelets below 50,000/mm^3 was observed in 4% (8/194) of patients receiving peginterferon alfa-2b in combination with ribavirin. Anaemia (haemoglobin <9.4 g/dL) was reported in 11% (22/194) of patients treated with peginterferon alfa-2b in combination with ribavirin.

Please refer to the respective product information of the antiretroviral medicinal products that are to be taken concurrently with HCV therapy for awareness and management of toxicities specific for each product and the potential for overlapping toxicities with PEGATRON Combination Therapy.

Postmarketing Experience

Following the marketing of PEGATRON Combination Therapy, rhabdomyolysis, myositis, renal insufficiency and renal failure have been reported rarely.

Rarely reported events with interferon alfa-2b include seizures, pancreatitis, hypertriglyceridaemia arrhythmia, diabetes and peripheral neuropathy.

Other ophthalmologic disorders that have been reported rarely with alfa interferons include retinopathies (including macular oedema), retinal haemorrhages, retinal artery or vein occlusion, retinal exudates, loss of visual acuity or visual field, optic neuritis, papilloedema and serious retinal detachment (see PRECAUTIONS).

Cardiovascular (CVS) adverse events, particularly arrhythmia, appeared to be correlated mostly with pre-existing CVS disease and prior therapy with cardiotoxic agents. Cardiomyopathy that may be reversible upon discontinuation of interferon alfa, has been reported rarely in patients without prior evidence of cardiac disease.

Very rarely cardiac ischaemia, ulcerative and ischaemic colitis, pulmonary fibrosis, myocardial infarction, cerebrovascular ischemia, cerebrovascular haemorrhage, encephalopathy (see PRECAUTIONS), sarcoidosis or exacerbation of sarcoidosis, erythema multiforme, Stevens Johnson syndrome, toxic epidermal necrolysis, injection site necrosis and hepatitis B reactivation in HCV/HBV co-infected patients have been reported. Also, very rarely ribavirin in combination with interferon alfa-2b, including PEG-INTRON, may be associated with aplastic anaemia or pure red cell aplasia.

A wide variety of autoimmune and immune-mediated disorders have been reported with alfa interferons including idiopathic thrombocytopaenic purpura, thrombotic thrombocytopaenic purpura, rheumatoid arthritis, SLE, vasculitis and Vogt-Koyanagi-Harada syndrome.

Cases of acute hypersensitivity reactions, including anaphylaxis, urticaria, angioedema have been reported.

Other adverse events reported with PEG-INTRON alone or in combination with ribavirin include: pericarditis, chest pain, congestive heart failure, asthenic conditions (including asthenia, malaise and fatigue), abdominal pain, hypothyroidism, hyperthyroidism, hypertriglyceridemia, anxiety, emotional lability, irritability, dyspnea, cough, pruritus, rash, dry skin, migraine headache, homicidal ideation, peripheral neuropathy, facial palsy, paraesthesia, dehydration, hypertension, hypotension, palpitations, fungal infection, bacterial infection including sepsis, diabetes mellitus, diabetic ketoacidosis.

Table 14: Undesirable effects reported (1% - ≥ 10% incidence) in adult patients taking REBETOL capsules with pegylated interferon alfa-2b or interferon alfa-2b injection.
Very common (≥ 1/10) - Common (≥1/100 and <1/10) (CIOMS III)

Body system	≥10%	5% - <10%	1% - <5%
Infections and infestations	Viral infection, pharyngitis	Rhinitis	Bronchitis, herpes simplex, bacterial infections (including sepsis),fungal infection, upper respiratory tract infection, influenza, otitis media, urinary tract infection, sinusitis, rhinitis
Neoplasms benign, malignant and unspecified (including cysts and polyps)			Neoplasm unspecified
Blood and lymphatic system disorders	Anaemia, neutropaenia	Leukopaenia	Haemolytic anaemia, lymphopaenia, lymphadenopathy, thrombocytopaenia
Endocrine disorders		Hypothyroidism	Hyperthyroidism
Metabolism and nutrition disorders	Anorexia, weight decreased		Hyperglycaemia, hyperuricaemia, hypocalcaemia, dehydration, increased appetite
Psychiatric disorders	Depression, insomnia, emotional lability, anxiety	Agitation, nervousness	Aggression, apathy, anger, abnormal dreams, mood altered, psychosis, sleep disorder, suicidal ideation, decreased libido, confusion, crying
Nervous system disorders	Headache, dizziness, concentration impaired	Paraesthaesia, dysgeusia	Amnesia, memory impairment, migraine, flushing, hyperaesthesia, somnolence, hypoaesthesia, tremor, migraine, hypertonia, ataxia, sleep disorder, disturbance in attention, syncope, taste loss
Eye disorders		Blurred vision	Visual disturbance, conjunctivitis, eye irritation, abnormal vision, photophobia, eye pain, lacrimal disorder, dry eye
Ear and labyrinth disorders			Vertigo, hearing impaired/loss, tinnitus, ear pain
Cardiac disorders		Tachycardia	Palpitation
Vascular disorders			Flushing, hypotension, hypertension
Respiratory, thoracic and mediastinal disorders	Cough, Dyspnoea	Nonproductive cough	Nasal congestion, dysphonia, respiratory disorder, respiratory tract congestion, sinus congestion, rhinorrhoea, increased upper airway secretion, pharyngolaryngeal pain, epistaxis

Body system	≥10%	5% - <10%	1% - <5%
Gastro-intestinal disorders	Dry mouth, nausea, diarrhoea, abdominal pain, vomiting	Constipation, dyspepsia, right upper quadrant pain	Flatulence, gingival bleeding, glossitis, cheilitis, abdominal distension, gastroesophageal reflux disease, loose stools, stomatitis, ulcerative stomatitis, mouth ulceration, gingivitis, colitis, haemorrhoids
Hepatobiliary disorders			Hepatomegaly, jaundice
Skin and subcutaneous tissue disorders	Alopecia, pruritus, dry skin, rash	Hyperhidrosis	Eczema, abnormal hair texture, photosensitivity reaction, erythema, erythematous rash, night sweats, maculopapular rash, acne, dermatitis, psoriasis, aggravated psoriasis, skin disorder, bruise
Musculoskeletal and connective tissue disorders	Myalgia, arthralgia, musculoskeletal pain	Back pain	Arthritis, muscle spasms, pain in extremity
Renal and urinary disorders			Micturition frequency, polyuria, urine abnormality
Reproductive system and breast disorders		Female: menorrhagia, menstrual disorder	Female: amenorrhoea, dysmenorrhoea, breast pain, ovarian disorder, vaginal disorder. Male: impotence, prostatitis, erectile dysfunction
General disorders and administration site conditions	Injection site inflammation, injection site reaction, fatigue, pyrexia, influenza like illness, rigours, flu-like symptoms, pain, asthenia, irritability	Chest pain, feeling abnormal	Injection site pain, chest discomfort, peripheral oedema, malaise, thirst
Investigations	Weight decrease	Anaemia	Cardiac murmur

Less common clinical trial adverse drug reactions (<1%)

Adverse drug reactions that occurred at rates less than 1% included the following events listed by system organ class:

Infections and infestations: Injection site infection, lower respiratory tract infection

Immune disorders: Drug hypersensitivity, sarcoidosis, and rheumatoid arthritis (new or aggravated)

Metabolism and Nutritional disorders: Diabetes mellitus, hypertriglyceridaemia

Psychiatric disorders: Panic attack, hallucination, panic reaction, abnormal behavior

Nervous system disorders: Neuropathy, peripheral neuropathy, seizure (convulsion), neuralgia

Eye disorders: retinal exudates, papilloedema, retinal haemorrhage, retinopathy

Cardiac disorders: Myocardial infarction, cardiomyopathy

Vascular disorders: Vasculitis

Gastro-intestinal disorders: Pancreatitis, oral pain and ischaemic colitis, tooth disorder, tooth fracture

Hepatobiliary disorders: hyperbilirubinemia

Skin and subcutaneous tissue disorders: Cutaneous sarcoidosis, seborrhoea, nail disorder, pigmentation disorder, urticaria

Musculoskeletal and connective tissue disorders: Bone pain, muscle weakness

Renal and urinary disorders: Renal failure

General disorders and administration site conditions: Face oedema, injection site necrosis

Children and adolescents

In a clinical trial with 107 children and adolescent patients (3 to 17 years of age) treated with PEGATRON Combination Therapy, dose modifications were required in 25% of patients, most commonly for anaemia, neutropaenia and weight loss. In general, the adverse reactions profile in children and adolescents was similar to that observed in adults, although there is a paediatric-specific concern regarding growth inhibition. During treatment for up to 48 weeks with PEGATRON Combination Therapy, growth inhibition is observed, the reversibility of which is uncertain (see PRECAUTIONS). Weight loss and growth inhibition were very common during the treatment (at the end of treatment, mean decrease from baseline in height and weight percentile of 15 percentiles and 8 percentiles) and growth velocity was inhibited (< 3rd percentile in 70% of the patients).

At the end of 24 weeks post-treatment follow up, mean decrease from baseline in weight and height percentiles were still of 3 percentiles and 7 percentiles, respectively, and 20% of the children continued to have inhibited growth (growth velocity < 3rd percentile).

In this study, the most prevalent adverse reactions in all subjects were pyrexia (80%), headache (62%), neutropenia (33%), fatigue (30%), anorexia (29%) and injection-site erythema (29%). Only 1 subject discontinued therapy as the result of an adverse reaction (thrombocytopenia). The majority of adverse reactions reported in the study were mild or moderate in severity. Severe adverse reactions were reported in 7% (8/107) of all subjects and included injection site pain (1%), pain in extremity (1%), headache (1%), neutropenia (1%), and pyrexia (4%). Important treatment-emergent adverse reactions that occurred in this patient population were nervousness (8%), aggression (3%), anger (2%), depression/depressed mood (4%) and hypothyroidism (3%) and 5 subjects received levothyroxine treatment for hypothyroidism/elevated TSH.

The following treatment-related adverse reactions were reported in the study in children and adolescent patients treated with PEGATRON Combination Therapy. These reactions are listed in Table 15 by system organ class and frequency (very common (≥ 1/10), common (≥ 1/100 to < 1/10), uncommon (≥ 1/1,000 to < 1/100).

Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

Table 15: Adverse reactions very commonly, commonly and uncommonly reported in the clinical trial in children and adolescent patients treated with PEGATRON Combination Therapy.

Infections and infestations	
Common:	Fungal infection, influenza, oral herpes, otitis media, pharyngitis streptococcal, nasopharyngitis, sinusitis
Uncommon:	Pneumonia, ascariasis, enterobiasis, herpes zoster, cellulitis, urinary tract infection, gastroenteritis
Blood and lymphatic system disorders	
Very common:	Anaemia, leukopaenia, neutropenia
Common:	Thrombocytopenia, lymphadenopathy
Endocrine disorders	
Common:	Hypothyroidism
Metabolism and nutrition disorders	
Very common:	Anorexia, decreased appetite
Psychiatric disorders	
Common:	Depression, aggression, affect lability, anger, agitation, anxiety, mood altered, restlessness, nervousness, insomnia
Uncommon:	Abnormal behaviour, depressed mood, emotional disorder, fear, nightmare
Nervous system disorders	
Very common:	Headache, dizziness
Common:	Dysgeusia, syncope, disturbance in attention, somnolence, poor quality sleep
Uncommon:	Neuralgia, lethargy, paraesthesia, hypoaesthesia, psychomotor hyperactivity, tremor
Eye disorders	
Common:	Eye pain
Uncommon:	Conjunctival haemorrhage, eye pruritus, keratitis, vision blurred, photophobia
Ear and labyrinth disorders	
Common:	Vertigo

Cardiac disorders		
	Common:	Palpitations, tachycardia
Vascular disorders		
	Common:	Flushing
	Uncommon:	Hypotension, pallor
Respiratory, thoracic and mediastinal disorders		
	Common:	Cough, epistaxis, pharyngolaryngeal pain
	Uncommon:	Wheezing, nasal discomfort, rhinorrhoea
Gastrointestinal disorders		
	Very common:	Abdominal pain, abdominal pain upper, vomiting, nausea
	Common:	Diarrhoea, aphthous stomatitis, cheilosis, mouth ulceration, stomach discomfort, oral pain
	Uncommon:	Dyspepsia, gingivitis
Hepatobiliary disorders		
	Uncommon:	Hepatomegaly
Skin and subcutaneous tissue disorders		
	Very common:	Alopecia, dry skin
	Common:	Pruritus, rash, rash erythematous, eczema, acne, erythema
	Uncommon:	Photosensitivity reaction, rash maculo-papular, skin exfoliation, pigmentation disorder, dermatitis atopic, skin discolouration
Musculoskeletal and connective tissue disorders		
	Very common:	Myalgia, arthralgia
	Common:	Musculoskeletal pain, pain in extremity, back pain
	Uncommon:	Muscle contracture, muscle twitching
Renal and urinary disorders		
	Uncommon:	Proteinuria
Reproductive system and breast disorders		
	Uncommon:	Female: Dysmenorrhoea
General disorders and administration site conditions		
	Very common:	Injection site erythema, fatigue, pyrexia, rigors, influenza-like illness, asthenia, pain, malaise, irritability
	Common:	Injection site reaction, injection site pruritus, injection site rash, injection site dryness, injection site pain, feeling cold
	Uncommon:	Chest pain, chest discomfort, facial pain
Investigations		
	Very common:	Body height decreased, weight decreased
	Common:	Blood thyroid stimulating hormone increased, thyroglobulin increased

	Uncommon:	Anti-thyroid antibody positive
Injury and poisoning		
	Uncommon:	Contusion

Most of the changes in laboratory values in the PEGATRON clinical trial were mild or moderate. Decreases in haemoglobin, white blood cells, platelets, neutrophils and increase in bilirubin may require dose reduction or permanent discontinuation from therapy (see DOSAGE and ADMINISTRATION). While changes in laboratory values were observed in some patients treated with PEGATRON Combination Therapy in the clinical trial, values returned to baseline levels within a few weeks after the end of therapy.

DOSAGE AND ADMINISTRATION

PEGATRON Combination Therapy should be initiated only by a physician experienced in the treatment of patients with hepatitis C.

Under no circumstances should REBETOL Capsules be opened, crushed, or broken. REBETOL should be taken with food.

Adults

Recommended Dose

The recommended dose for PEGATRON Combination Therapy is:

- PEG-INTRON Injection administered subcutaneously at a dose of 1.5 μg/kg once weekly, in combination with
- REBETOL Capsules administered orally each day in two divided doses (morning and night). The REBETOL dose to be used in combination with PEG-INTRON is based on patients' body weight.

Table 16: Recommended Starting Dose for REBETOL

Patient Body Weight	Daily dose of REBETOL Capsules	Number of REBETOL Capsules
< 65 kg	800 mg	2 x 200 mg capsules am 2 x 200 mg capsules pm
65 kg to 80 kg	1000 mg	2 x 200 mg capsules am 3 x 200 mg capsules pm
81 kg to 105 kg	1200 mg	3 x 200 mg capsules am 3 x 200 mg capsules pm
>105 kg	1400 mg	3 x 200 mg capsules am 4 x 200 mg capsules pm

Duration of Treatment

Naïve Patients

Predictability of sustained virological response: Patients infected with virus genotype 1 who fail to achieve virological response at Week 4 or 12 are highly unlikely to become sustained virological responders and should be evaluated for discontinuation (see CLINICAL TRIALS Section).

Genotype 1:

- For patients who have undetectable HCV-RNA or demonstrate adequate virological response at week 12, treatment should continue for another nine month period (i.e. a total of 48 weeks).
- Patients with detectable but ≥ 2 $\log_{10}$ decrease in HCV-RNA level from baseline at treatment week 12 should be reassessed at treatment week 24 and if HCV-RNA is undetectable, they should continue with full course of therapy (i.e a total of 48 weeks). However, if HCV-RNA is still detectable at treatment week 24, discontinuation of therapy should be considered.
- In the subset of patients with genotype 1 infection and low viral load (<2,000,000 copies/mL, approximately 600,000 IU/mL) who became HCV-RNA negative at treatment week 4 and remain HCV-RNA negative at week 24, the treatment could either be stopped after this 24-week treatment course or pursued for an additional 24 weeks (i.e. overall 48 week treatment duration). However, an overall 24 weeks treatment duration may be associated with a higher risk of relapse than a 48 weeks treatment duration.

Genotypes 2 or 3: It is recommended that all patients be treated for 24 weeks.

- The decision to extend therapy to one year in patients with negative HCV-RNA after 24 weeks of treatment should be based on other prognostic factors (e.g. genotype or bridging fibrosis, cirrhosis).

Genotype 4: Limited study data (n=66) showed that 48 weeks treatment with peginterferon alfa-2b (1.5 µg/kg/week) plus ribavirin (800-1200 mg/day) was effective in treating patients with HCV genotype 4.

HCV/HIV Co-infection

The recommended duration of dosing for HCV/HIV co-infected patients is 48 weeks, regardless of genotype.

An early virologic response is defined as at least a two log decrease or absence of detectable HCV- RNA at week 12. Patients who fail to achieve this early response are unlikely to become sustained virologic responders. In clinical trials, among patients who failed to achieve this early virologic response at week 12, none became sustained virologic responders after a full course of combination therapy (negative predictive value[a] was 100%).

[a]; negative predictive value: likelihood of not having a sustained viral response among patients who do not have an early viral response

Adults with HCV/HBV Co-infection

The safety and efficacy of PEG-INTRON alone or in combination with boceprevir or ribavirin for the treatment of chronic hepatitis C genotype 1 infection in patients co-infected with hepatitis B Virus (HBV) and HCV have not been studied.

Retreatment of Prior Treatment Failures (Relapse and Non-responder Patients)

Re-treatment experience is limited to one attempt only.

Predictability of sustained virological response: All relapse and non-responder patients, irrespective of genotype, who have demonstrated undetectable serum HCV-RNA at Week 12 should receive 48 weeks of therapy. Retreated patients who fail to achieve virological response at Week 12 are highly unlikely to become sustained virological responders (see also section in CLINICAL TRIALS on prior treatment failures).

Children and Adolescents

The ability of younger children to swallow the REBETOL capsule should be carefully assessed prior to prescribing.

Recommended Dose

Dosing for children and adolescent patients is determined by body surface area for PEG-INTRON and by body weight for REBETOL. The recommended dose of PEG-INTRON is 60 µg/m^2/wk subcutaneously in combination with 15 mg/kg/day of REBETOL orally in two divided doses with food (morning and evening). Patients who reach their 18th birthday while receiving PEGATRON Combination Therapy should remain on the paediatric dosing regimen. It is recommended that children and adolescent patients receiving PEGATRON Combination Therapy be discontinued from treatment if their week 12 HCV-RNA dropped < 2 log_{10} compared to pre-treatment or if they have detectable HCV-RNA at treatment week 24.

Table 17: REBETOL dose based on body weight when used in combination with peginterferon alfa-2b in children and adolescents

Patient weight (kg)	Daily REBETOL dose	Number of 200 mg capsules
≥27 - 35	400 mg	2 capsules [a]
36 - 49	600 mg	3 capsules [b]
50 - 65	800 mg	4 capsules [c]
> 65	Refer to adult dosing table (Table 14)	

[a] 1 morning, 1 evening
[b] 1 morning, 2 evening
[c] 2 morning, 2 evening

Duration of Treatment

- Genotype 1: The recommended treatment duration is 48 weeks.
- Genotype 2 or 3: The recommended treatment duration is 24 weeks.
- Genotype 4: Only 5 children and adolescents with Genotype 4 were treated in the PEGATRON Combination Therapy clinical trial. The recommended duration of treatment is 48 weeks.

Dosage Modification

If severe adverse reactions or laboratory abnormalities develop during PEGATRON Combination Therapy, the dosages should be modified or therapy temporarily discontinued until the adverse reactions abate. Guidelines were developed in clinical trials for dose modification of PEGATRON Combination Therapy (see Table 18, Dosage modification guidelines). If persistent or recurrent intolerance develops following adequate dosage adjustment, or if the disease progresses rapidly, treatment with PEGATRON should be discontinued.

Table 18: Adult and Children and Adolescent patients - Dose modification guidelines for PEGATRON Combination Therapy based on laboratory parameters

Laboratory values	**Reduce REBETOL daily dose (see Note 1) if:**	**Reduce only PEG-INTRON dose (see Note 2) if:**	**Discontinue Combination Therapy if:**
Haemoglobin in patients without cardiac disease	85 to <100 g/L	-	<85 g/L
Haemoglobin in patients with history of cardiac* disease. Adult: Child: Not Applicable	≥ 20 g/L decrease in haemoglobin during any 4 wk period during treatment (permanent dose reduction)		<85 g/L or <120 g/L after 4 wks of dose reduction
Leukocytes	-	1.0 to <1.5 x 10^9/L	<1.0 x 10^9/L
Neutrophils	-	0.5 to <0.75 x 10^9/L	<0.5 x 10^9/L
Platelets	-	Adult: 25 to <50 x 10^9/L Child: <70 x 10^9/L	Adult: <25 x 10^9/L Child : <50 x 10^9/L
Bilirubin – direct	-	-	2.5 x ULN**
Bilirubin - indirect	>0.05 g/L	-	Adult: >0.04 g/L Child: > 0.04 g/L for >4 weeks
Serum Creatinine	-	-	> 0.02 g/L
Creatinine Clearance	-	-	Discontinue REBETOL if CrCl < 50mL/min
Alanine aminotransferase (ALT) or Aspartate aminotransferase (AST)	-	-	2 x baseline and >10 x ULN** or 2 x baseline and >10 x ULN**

[*] These guidelines are for patients with stable cardiac disease. See PRECAUTIONS.
[**] Upper limit of normal
Note 1: In adult patients first dose reduction of ribavirin is by 200 mg/day (except in patients receiving the 1,400 mg, dose reduction should be by 400 mg/day). If needed, 2nd dose reduction of ribavirin is by an additional 200 mg/day. Patients whose dose of ribavirin is reduced to 600 mg daily receive one 200 mg capsule in the morning and two 200 mg capsules in the evening.
In children and adolescent patients 1st dose reduction of REBETOL is to 12 mg/kg/day. 2nd dose reduction of REBETOL is to 8 mg/kg/day. For patients weighing 27-35 kg, only a 1st dose reduction to 8 mg/kg/day is possible using the 200 mg REBETOL capsule.
Note 2: In adult patients first dose reduction of PEG-INTRON is to 1μg/kg/week. If needed, 2nd dose reduction of PEG- INTRON is to 0.5 μg/kg/week. For patients on PEG-INTRON monotherapy: refer to monotherapy dose reduction guidelines section for dose reduction.
In children and adolescent patients 1st dose reduction of PEG-INTRON is to 40 μg/m^2/week, 2nd dose reduction of PEG- INTRON is to 20 μg/m^2/week.

Dose reduction of PEG-INTRON/ribavirin combination therapy is accomplished in a two step process from the original starting dose of 1.5 μg/kg/week, to 1 μg/kg/week, then to 0.5 μg/kg/week if needed by reducing the prescribed volume or by utilizing a lower dose strength as shown in Table 19.

Table 19: Two-Step Dose Reduction of PEG-INTRON in Combination Therapy

First Dose Reduction to PEG-INTRON 1μg/kg				**Second Dose Reduction to PEG-INTRON 0.5 μg/kg**			
Body Weight kg	Peg-Intron strength to use	Amount of Peg-Intron (μg) to administer	Volume (mL) of Peg-Intron to administer	Body weight kg	Peg-Intron strength to use	Amount of Peg-Intron (μg) to administer	Volume (mL) of Peg-Intron to administer
< 40	50 μg per 0.5 mL	35	0.35	< 40	50 μg per 0.5 mL	20	0.2
40-50	120 μg per 0.5 mL	48	0.2	40-50	50 μg per 0.5 mL	25	0.25
51-64	80 μg per 0.5 mL	56	0.35	51-64	80 μg per 0.5 mL	32	0.2
65-75	100 μg per 0.5 mL	70	0.35	65-75	50 μg per 0.5 mL	35	0.35
76-85	80 μg per 0.5 mL	80	0.5	76-85	120 μg per 0.5 mL	48	0.2
86-105	120 μg per 0.5 mL	96	0.4	86-105	50 μg per 0.5 mL	50	0.5
> 105	150 μg per 0.5 mL	105	0.35	> 105	80 μg per 0.5 mL	64	0.4

Concomitant Therapy

Paracetamol has been used successfully to alleviate the symptoms of fever and headache which can occur with interferon alfa-2b therapy. The recommended paracetamol adult dosage is 500 mg to 1 g given 30 minutes before administration of PEG-INTRON. The maximum dosage of paracetamol to be given is 1 g four times daily.

Directions for use, handling and disposal of PEG-INTRON CLEARCLICK Injector

The dose should be administered subcutaneously on the same day of each week. The patient may self-administer the dose at the discretion of the physician. When self-administration is recommended, the patient should be advised to vary the injection site each time the injection is administered.

***Please refer to enclosed package insert for detailed instructions on the use of the PEG- INTRON CLEARCLICK Injector*.**

Some important points to note are:

In each CLEARCLICK Injector there is a two-chamber cartridge containing powder of peginterferon alfa-2b (at strength of 50 μg or 80 μg or 100 μg or 120 μg or 150 μg) and sterile Water for Injections in separate compartments for single use. The powder is reconstituted with the sterile water just before use. A small volume is lost during preparation of PEG-INTRON for injection when dose is measured and injected. Therefore, each pen contains an excess amount of solvent and PEG- INTRON powder to ensure delivery of the labelled dose in 0.5 mL of PEG-INTRON, solution for Injection.

1. Each PEG-INTRON CLEARCLICK Injector has five dosage settings and is capable of delivering one of the five different doses:

Table 20

Strength	**Actual Dose** (μg) **for each Dosage Settings** (mL)				
	0.2 mL	**0.25 mL**	**0.35 mL**	**0.4 mL**	**0.5 mL**
50 μg	20 μg	25 μg	35 μg	40 μg	50 μg
80 μg	32 μg	40 μg	56 μg	64 μg	80 μg
100 μg	40 μg	50 μg	70 μg	80 μg	100 μg
120 μg	48 μg	60 μg	84 μg	96 μg	120 μg
150 μg	60 μg	75 μg	105 μg	120 μg	150 μg

2. PEG-INTRON should be administered subcutaneously after reconstituting the powder as instructed attaching the injection needle provided in the packaging and setting the prescribed dose. **A complete and illustrated set of instructions is provided in the enclosed package insert.**
3. Remove the PEG-INTRON CLEARCLICK Injector from the refrigerator before administration to allow the solvent to reach room temperature (not more than 25°C).
4. Only use the needle supplied with the PEG-INTRON CLEARCLICK Injector. The use of other needles may result in the wrong dose being delivered and/or cause the pen to not operate properly.
5. As for all parenteral medicinal products, inspect visually the reconstituted solution prior to administration. Do not use if discoloration is present.

6. The reconstituted PEG-INTRON solution contains no antimicrobial agent and is for use in a single patient on one occasion only. Discard any unused solution. PEG-INTRON Injection must not be mixed with other medicinal injectable products.
7. Once the prescribed dose is administered, discard the PEG-INTRON CLEARCLICK Injector with any unused solution safely in a sharps container. The PEG-INTRON CLEARCLICK Injector is for use in a single patient on one occasion only and MUST NOT BE SHARED.

The chemical and physical in-use stability for the reconstituted solution has been demonstrated for 24 hours at 2°C to 8°C. From a microbiological point of view, the reconstituted product is to be used immediately. If storage is necessary, hold at 2°C to 8°C for not more than 24 hours.

OVERDOSAGE

There is limited experience with overdosage of the combination of PEG-INTRON and REBETOL. In the clinical studies, a few patients accidentally received a dose greater than that prescribed. There were no serious reactions attributed to these overdosages. Ribavirin concentration is essentially unchanged by haemodialysis.

In clinical trials with REBETRON (interferon alfa-2b plus ribavirin), the maximum overdose reported was a total dose of 10 g of ribavirin capsules (50 x 200 mg capsules) and 39 million IU of interferon alfa-2b (13 subcutaneous injections of 3 million IU each), taken in one day by a patient in an attempt at suicide. The patient was observed for two days in the emergency room, during which time no adverse event from the overdose was noted.

PRESENTATION

PEGATRON Combination Therapy composite packs contain PEG-INTRON CLEARCLICK Injector and REBETOL Capsules:

1. PEG-INTRON CLEARCLICK Injector is a single use disposable injection pen and is available in 5 strengths: 50, 80, 100, 120 and 150 µg of peginterferon alfa-2b and solvent (sterile Water for Injections). Each strength of the PEG-INTRON CLEARCLICK Injector has a different colour- coded dosing button (at the end of the pen):

Table 21

Strength (microgram)	Colour of 'Dosing Button'
50 µg	Red
80 µg	Dark Green
100 µg	Light Blue
120 µg	Pink
150 µg	Rust

One injection needle and two cleansing swabs are provided for use with each PEG-INTRON CLEARCLICK Injector.

2. REBETOL 200 mg capsules are white, opaque capsules imprinted in blue ink with

"200 mg" and a stripe on the body, and the S-P logo and a stripe on the cap. The capsules are packaged in blisters.

PEGATRON is available in the following package presentations, providing sufficient quantities of PEG-INTRON CLEARCLICK Injector and REBETOL Capsules for four weeks of PEGATRON Combination Therapy:

Table 22

PEG-INTRON CLEARCLICK Injector *(Single Use Injection Pen)*	***REBETOL 200 mg Capsules***
4 x **50 µg** CLEARCLICK Injector	84 capsules [600 mg/d for 4 wks] *****
4 x **50 µg** CLEARCLICK Injector	112 capsules [800 mg/d for 4 wks]
4 x **80 µg** CLEARCLICK Injector	84 capsules [600 mg/d for 4 wks]
4 x **80 µg** CLEARCLICK Injector	140 capsules [1000 mg/d for 4 wks]
4 x **80 µg** CLEARCLICK Injector	168 capsules [1200 mg/d for 4 wks] *****
4 x **100 µg** CLEARCLICK Injector	84 capsules [600 mg/d for 4 wks] *****
4 x **100 µg** CLEARCLICK Injector	112 capsules [800 mg/d for 4 wks]
4 x **120 µg** CLEARCLICK Injector	84 capsules [600 mg/d for 4 wks] *****
4 x **120 µg** CLEARCLICK Injector	140 capsules [1000 mg/d for 4 wks]
4 x **150 µg** CLEARCLICK Injector	84 capsules [600 mg/d for 4 wks] *****
4 x **150 µg** CLEARCLICK Injector	140 capsules [1000 mg/d for 4 wks]
4 x **150 µg** CLEARCLICK Injector	168 capsules [1200 mg/d for 4 wks]
4 x **150 µg** CLEARCLICK Injector	196 capsules [1400 mg/d for 4 wks]

* Not currently marketed

STORAGE

PEGATRON Combination Therapy packs are to be stored at 2°C to 8°C. (Refrigerate. Do not freeze.)

After dispensing, the REBETOL Capsules may be removed from the PEGATRON Combination Therapy carton and stored below 25°C.

PEG-INTRON CLEARCLICK Injector should be stored at 2°C to 8°C. (Refrigerate. Do not freeze.) The reconstituted solution should be used immediately or stored at 2°C to 8°C (Refrigerate. Do not freeze.) and used within 24 hours.

SPONSOR

Merck Sharp & Dohme (Australia) Pty Limited
Level 1, Building A, 26 Talavera Road,
Macquarie Park, NSW 2113
Australia

POISON SCHEDULE OF THE DRUG

Schedule 4
Prescription Only Medicine

This Product Information was approved by the Therapeutic Goods Administration on: 27 May 2003

DATE OF MOST RECENT SAFETY-RELATED CHANGE: 10 May 2017