

NEW ZEALAND DATA SHEET PEGATRON Combination Therapy

PEG-INTRON® (Peginterferon alfa-2b) REDIPEN® INJECTOR + REBETOL® (Ribavirin) Capsules

NAME OF DRUG

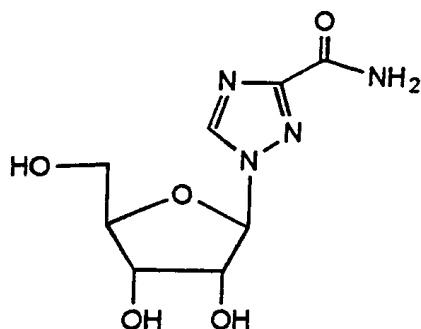
PEGATRON Combination Therapy is the brand name for composite packs containing peginterferon alfa-2b (rbe) for subcutaneous injection (PEG-INTRON) plus ribavirin capsules for oral administration (REBETOL).

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.

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-1H-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 Redipen Injector and REBETOL Capsules.

PEG-INTRON Redipen 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 Redipen Injector.

PEG-INTRON Redipen 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 Redipen 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 Redipen 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 and silicon dioxide.

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 which 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 ¹⁴C 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 ¹⁴C-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 was 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 $AUC_{0-\infty}$ 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 $AUC_{0-\infty}$ 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).

Patients under the age of 18 years: Specific pharmacokinetic evaluations have not been performed on these patients. PEGATRON Combination Therapy is indicated for the treatment of chronic hepatitis C only in patients 18 years of age or older.

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 HIV/HCV: Patients taking 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.

In patients co-infected with HIV/HCV, limited efficacy and safety data (N=25) are available in subjects with CD4 counts less than 200cells/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 REBETON (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 which 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 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 log₁₀ reduction in HCV RNA at Week 12 developed a sustained viral response. No patients who were HCV RNA positive with < 2 log₁₀ reduction in HCV RNA at Week 12 developed a sustained viral response.

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

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

RVR+= HCV RNA negative or a $\geq 2 \log_{10}$ reduction in HCV RNA at Week 12

PPV= positive predictive value

NPV= negative predictive value

In a non-comparative trial, 235 patients with genotype 1 and low viral load ($\leq 2,000,000$ copies/ml; a value of 2,000,000 copies/mL is approximately equivalent to 600.000IU/mL) received PegIntron, 1.5 microgram/kg subcutaneously, once weekly, in combination with weight adjusted ribavirin. The overall sustained response rate after a 24-week treatment duration was 50 %.

In the group of patients who had nondetectable plasma HCV-RNA levels at Week 4 and Week 24 of therapy, there was a high sustained virological response rate (over 90%). This subgroup of patients was identified in an interim analysis and prospectively confirmed.

Limited historical data indicate that treatment for 48 weeks might be associated with a higher sustained response rate (100% 11/11) and with a lower risk of relapse compared to following 24 weeks of treatment.

Retreatment of prior treatment failures (relapse and non-responder patients)

In a non-comparative trial, 2293 patients with moderate to severe fibrosis who failed previous treatment with combination alpha interferon/ribavirin were retreated with peginterferon alfa-2b, 1.5 microgram/kg subcutaneously, once weekly, in combination with weight adjusted ribavirin.

The majority (80%) of the patients were infected with HCV Genotype 1. The previous treatment consisted of nonpegylated alfa interferon (62%), peginterferon alfa-2a (16%) and peginterferon alfa-2b (21%) with ribavirin, at least 6 months prior to retreatment.

These patients were retreated with peginterferon alfa-2b 1.5 μ g/kg subcutaneously, once weekly, in combination with weight-adjusted ribavirin. Patients who were HCV-RNA negative at Treatment Week 12 continued treatment for 48 weeks and were followed for 24 weeks post-treatment. Response to treatment was defined as undetectable HCV- RNA at 24 weeks post treatment (**Table 4**).

Table 4 Rates of Response to Retreatment in Prior Treatment Failures				
	Interferon alfa-2b/Ribavirin		Peginterferon alfa-2a & -2b/Ribavirin	
	SVR% (n)	99% CI	SVR% (n)	99% CI
Overall	25 (348/1423)	22, 27	17 (149/863)	14, 21
Prior Relapsers	43 (130/300)	36, 51	33 (113/344)	26, 39
Genotype 1/4	34 (74/216)	26, 43	24 (60/251)	17, 31
Genotype 2/3	67 (54/81)	53, 80	57 (52/92)	43, 70
Prior Non-responders*	18 (158/903)	14, 21	6 (30/476)	3, 9
Genotype 1/4	13 (103/790)	10, 16	5 (20/446)	2, 7
Genotype 2/3	49 (53/109)	36, 61	36 (10/28)	-
Genotype				
1	17 (192/1135)	14, 20	11 (78/704)	8, 14
2/3	58 (139/1240)	50, 66	50 (64/127)	39, 62
4	33 (13/40)	13, 52	22 (6/27)	-
METAVIR fibrosis Score				
F2	34 (141/420)	28, 40	22 (50/232)	15, 29
F3	25 (106/429)	19, 30	17 (41/241)	11, 23
F4	18 (101/572)	14, 22	15 (58/390)	10, 20
Baseline Viral Load				
HVL (>600,000 IU/mL)	20 (170/864)	16, 23	12 (69/573)	9, 16
LVL (≤600,000 IU/mL)	32 (178/557)	27, 37	27 (78, 288)	20, 34

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

After one retreatment attempt, the response in patients who relapsed after treatment with peginterferon/ribavirin combination was 33% (113/344) compared with 43% (130/300) 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 6% (30/476) compared with 18% (158/903) in patients who were non-responders to non-pegylated interferon/ribavirin combination.

Approximately 36% of subjects had undetectable plasma HCV-RNA levels at Week 12 of therapy measured using a research-based test (limit of detection 125 IU/mL). In this subgroup, there was a 56% (463/823) 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. For patients with prior failure on therapy with non-pegylated interferon or pegylated interferon and undetectable HCV-RNA at Treatment Week 12, the sustained virological response rates were 59% and 50%, respectively. The response rates by baseline characteristics for these patients are summarized in **Table 5**.

Table 5 Baseline Characteristics of Prior Treatment Failures with undetectable HCV-RNA at treatment Week 12 and their Rates of Response to Retreatment

	%(n) ^a	SVR %(n)
HCV Genotype		
G1	28 (507/1846)	48 (245/507)
G2/3	77 (281/367)	70 (196/281)
G4	43 (29/67)	62 (18/29)
Fibrosis		
F2	42 (271/653)	64 (174/271)
F3	36 (242/672)	59 (142/242)
F4	32 (309/966)	48 (147/309)
Baseline Viral Load		
HVL (>600,000 IU/ml)	30 (432/1441)	51 (220/432)
LVL (≤600,000 IU/ml)	46 (389/853)	62 (241/389)
Prior Response		
Relapsers	63 (404/645)	56 (226/404)
Non-responder	23 (318/1385)	54 (173/318)
Prior Therapy		
peginterferon alfa-2b/ ribavirin	31 (150/488)	51 (76/150)
peginterferon alfa-2a/ ribavirin	33 (122/375)	50 (61/122)
interferon alpha/ribavirin	39 (549/1423)	59 (326/549)

^a %/Number of subjects who had undetectable HCV-RNA at Treatment Week 12 out of the entire study population

In patients with > 2 log₁₀ viral reduction but detectable virus at Week 12, the estimated sustained virological response rate is approximately 12 %.

HCV/HIV co-infected patients

Two trials have been conducted in patients coinfecting with HIV and HCV. The response to treatment in both of these trials is presented in **Table 6**. Study 1 (RIBAVIC; P01017) was a randomized, multicentre study which enrolled 412 previously untreated adult patients with chronic hepatitis C who were co-infected with HIV. Patients were randomized 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 randomized, single center study that enrolled 95 previously untreated adult patients with chronic hepatitis C who were coinfecting with HIV. Patients were randomized 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.

	Study 1 ¹			Study 2 ²		
	Peginterferon alfa-2b (1.5 µg/kg/week) + ribavirin (800 mg)	Interferon alfa-2b (3 MIU TIW) + ribavirin (800 mg)	p value ^a	Peginterferon alfa-2b (100 or 150c µg/week) + ribavirin (800-1200 mg) ^d	Interferon alfa-2b (3 MIU TIW) + ribavirin (800-1200 mg) ^d	p value ^b
All	27% (56/205)	20% (41/205)	0.047	44% (23/52)	21% (9/43)	0.017
Genotype 1, 4	17% (21/125)	6% (8/129)	0.006	38% (12/32)	7% (2/27)	0.007
Genotype 2, 3	44% (35/80)	43% (33/76)	0.88	53% (10/19)	47% (7/15)	0.730

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%). Both the Metavir score and Ishak grade decreased among subjects treated with peginterferon alfa-2b in combination with ribavirin. This decline was significant among responders (-0.3 for Metavir and -1.2 for Ishak) and stable (-0.1 for Metavir and -0.2 for Ishak) among non-responders. In terms of activity, about one-third of sustained responders showed improvement and none showed worsening. There was little change in fibrosis with approximately the same proportion showing improvement as showed worsening and the majority showing no change. Steatosis was significantly improved in patients infected with HCV Genotype 3.

Long-Term efficacy data

A large long-term follow-up study enrolled 567 patients after treatment in a prior study with pegylated interferon 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 and only 4 out of 366 sustained responders relapsed during the study. The Kaplan-Meier estimate for continued sustained response over 5 years for all patients is 99% (95% CI: 97-100%). SVR after treatment of chronic HCV with pegylated interferon alfa-2b (with or without ribavirin) results in long-term clearance of the virus providing resolution of the hepatic infection and clinical 'cure' from chronic HCV. However, this does not preclude the occurrence of hepatic events in patients with cirrhosis (including hepatocarcinoma).

INDICATIONS

PEGATRON Combination Therapy is indicated for the treatment of naïve, relapse and non-responder patients with chronic hepatitis C (see *Clinical Trials*). Patients must be 18 years of age or older and have compensated liver disease. PEGATRON Combination Therapy is also indicated for the treatment of patients with chronic hepatitis C who are co-infected with clinically stable HIV.

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)
- creatinine clearance <50 mL/min
- decompensated cirrhosis of the liver
- 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

PRECAUTIONS

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.

Bone Marrow Toxicity: Alfa interferons including PEG-INTRON are known to suppress bone marrow function, sometimes resulting in severe cytopenias. PEG-INTRON should be discontinued in patients who develop severe decreases in neutrophil or platelet counts (see DOSAGE AND ADMINISTRATION: **Table 9**). Ribavirin may potentiate the neutropenia 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 14% 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.

Fever: While fever may be associated with the flu-like syndrome reported commonly during interferon therapy, other causes of persistent fever 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: As with treatment with any interferon, discontinue treatment with PEGATRON Combination Therapy in patients who develop prolongation of coagulation markers which might indicate liver decompensation. 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, cotton-wool spots, and retinal artery or vein obstruction, 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 fever, 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.

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, suicide, suicidal ideation and attempted suicide, have been observed in some patients during PEGATRON Combination Therapy. 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. 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 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.

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.

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 >0.02g/L (approx 177 mmol/L), PEGATRON Combination Therapy must be discontinued (see DOSAGE AND ADMINISTRATION: **Table 9**).

Thyroid changes: Infrequently, patients treated for chronic hepatitis C with interferon alfa have developed thyroid abnormalities, either hypothyroidism or hyperthyroidism. Determine thyroid stimulating hormone (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.

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.

HIV/HCV co-infection: 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 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.

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)
- Platelets $\geq 100 \times 10^9/L$
- Neutrophil Count $\geq 1.5 \times 10^9/L$
- 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.

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

Safety and effectiveness in paediatric patients have not been established. Therefore, use in children under the age of 18 is not recommended (see INDICATIONS).

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 and Mutagenicity

Ribavirin: Adequate studies to assess the carcinogenic potential of ribavirin in animals have not been conducted. Ribavirin is a nucleoside analogue that has produced positive findings in multiple *in vitro* and animal *in vivo* genotoxicity assays. Potential carcinogenicity cannot be ruled out. Further studies to assess the carcinogenic potential of ribavirin in animals are ongoing.

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).

Peginterferon: Peginterferon alfa-2b has not been tested for its carcinogenic potential. Neither peginterferon alfa-2b, nor its components recombinant interferon alfa-2b and methoxypolyethylene glycol, were positive in assays for gene mutations and chromosomal damage.

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

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.

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.

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.

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 hyperlactactemia/ 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 CYP 1A2 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 CYP 1A2.

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

ADVERSE REACTIONS

The safety of PEGATRON Combination Therapy was evaluated from data from a large randomised 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 $\geq 10\%$ of patients in this study are shown in **Table 7**

Body system	% of Subjects		
	<i>P 1.5/R</i> <i>PEG-INTRON</i> <i>1.5 μg/kg</i> <i>+ Rebetol 800 mg</i> <i>(n=511)</i>	<i>P 0.5/R</i> <i>PEG-INTRON</i> <i>1.5 \rightarrow0.5 μg/kg +</i> <i>Rebetol 1000/1200 mg</i> <i>(n=514)</i>	<i>I/R (=Rebetron)</i> <i>Intron A 3 MIU TIW</i> <i>+ Rebetol</i> <i>1000/1200 mg</i> <i>(n=505)</i>
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
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

Body system	% of Subjects		
	<i>P 1.5/R</i> PEG-INTRON 1.5 $\mu\text{g}/\text{kg}$ + Rebetol 800 mg (n=511)	<i>P 0.5/R</i> PEG-INTRON 1.5 \rightarrow 0.5 $\mu\text{g}/\text{kg}$ + Rebetol 1000/1200 mg (n=514)	<i>I/R (=Rebetron)</i> Intron A 3 MIU TIW + Rebetol 1000/1200 mg (n=505)
Respiratory system			
Coughing	14	11	11
Dyspnoea	25	23	22
Skin and appendages			
Alopecia	36	29	32
Pruritus	27	25	27
Rash	22	20	21
Skin dry	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, thrombocytopenia, agitation, nervousness, menstrual disorder, viral infection, nonproductive cough, pharyngitis, rhinitis, taste perversion, blurred vision, and leucopenia.

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, neutropenia and thrombocytopenia were mild (WHO grades 1 or 2). There were some cases of more severe neutropenia 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 neutropenia, both of which were dose-related. Dose modification for neutropenia 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 neutropenia were successfully managed by dose modification, thus discontinuations due to anaemia (0.6-0.8%) and neutropenia (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.

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 obstruction, cotton wool spots, loss of visual acuity or visual field, optic neuritis and papilloedema (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, myocardial infarction, cerebrovascular ischemia, cerebrovascular haemorrhage, encephalopathy (see PRECAUTIONS), sarcoidosis or exacerbation of sarcoidosis, erythema multiforme, Stevens Johnson syndrome, toxic epidermal necrolysis, and injection site necrosis 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 alpha interferons including idiopathic thrombocytopenic purpura and thrombotic thrombocytopenic purpura, rheumatoid arthritis, SLE, vasculitis, 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: chest pain, 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, diabetic ketoacidosis.

HIV/HCV co-infected patients

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 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 viremia during therapy or follow-up. Limited safety data (N= 25) are available in co-infected patients with CD4+ cell counts <200/ μ l.

Table 8 summarizes the safety of peginterferon alfa-2b in combination with ribavirin for HIV/HCV co-infected patients.

Table 8 Safety overview in clinical trials of HIV/HCV 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%)
Anemia	19 (10%)	8 (4%)	4 (8%)	7 (16%)
Neutropenia	14 (7%)	5 (3%)	7 (13%)	3 (7%)
Thrombocytopenia	9 (5%)	1 (<1%)	2 (4%)	2 (5%)

For HIV/HCV co-infected patients receiving peginterferon alfa-2b in combination with ribavirin, other undesirable effects which have been reported in the larger study (Study 1): neutropenia (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 HIV/HCV co-infected patients

Although hematological toxicities of neutropenia, thrombocytopenia and anemia occurred more frequently in HIV/HCV 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/mm³ was observed in 4% (8/194) of patients and decrease in platelets below 50,000/mm³ was observed in 4% (8/194) of patients receiving peginterferon alfa-2b in combination with ribavirin. Anaemia (hemoglobin < 9.4g/dl) was reported in 12% (23/194) 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.

DOSAGE AND ADMINISTRATION

Recommended Dose:

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

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). REBETOL Capsules should be administered with food. The REBETOL dose to be used in combination with PEG-INTRON is based on patients body weight.

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 85 kg	1000 mg	2 x 200 mg capsules am 3 x 200 mg capsules pm
86-105kg	1200 mg	3 x 200 mg capsules am 3 x 200 mg capsules pm
>105kg	1,400mg	3 x 200 mg capsules am 4 x 200 mg capsules pm (not marketed)

Duration of Treatment-Naïve patients:

Predictability of sustained virological response: Patients infected with virus genotype 1 who fail to achieve virological response at Week 12 are highly unlikely to become sustained virological responders (see description of early viral response in the Clinical Trials Section).

- **Genotype 1:** For patients who exhibit virological response at week 12, treatment should be continued for another nine month period (i.e., a total of 48 weeks). 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 weeks 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 six months of treatment should be based on other prognostic factors (e.g. bridging fibrosis, cirrhosis). HIV/HCV co-infected patients should receive 48 weeks of treatment.
- **Genotype 4:** In general, patients infected with genotype 4 are considered harder to treat and limited study data (n=66) indicate they are compatible with a duration of treatment as for genotype 1.

Duration of treatment – Retreatment of prior treatment failures (relapse and non-responder patients):

Predictability of sustained virological response: All relapse and nonresponder 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 CLINICAL TRIALS).

HIV/HCV Co-infection

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

Predictability of response and non-response in HIV/HCV co-infection: Early virological response by Week 12, defined as a 2 log viral load decrease or undetectable levels of HCV RNA, has been shown to be predictive for sustained response. The negative predictive value for sustained response in HIV/HCV co-infected patients treated with peginterferon alfa-2b/ribavirin was 99% (67/68; Study 1) (see CLINICAL TRIALS). A positive predictive value of 50% (52/104; Study 1) was observed for HIV/HCV co-infected patients receiving combination therapy.

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 9**, 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.

Laboratory values	Reduce only ribavirin dose to 600 mg/day* if:	Reduce only PEG-INTRON to one-half dose if:	Discontinue PEGATRON Combination Therapy if:
Haemoglobin	<100 g/L	-	<85 g/L
Haemoglobin in: Patients with history of stable cardiac disease	≥20 g/L decrease in haemoglobin during any 4-week period during treatment (permanent dose reduction)		<120 g/L after 4 weeks of dose reduction
White blood cells	-	<1.5 x 10 ⁹ /L	<1.0 x 10 ⁹ /L
Neutrophils	-	<0.75 x 10 ⁹ /L	<0.5 x 10 ⁹ /L
Platelets	-	<50 x 10 ⁹ /L	<25 x 10 ⁹ /L
Bilirubin – direct	-	-	2.5 x ULN**
Bilirubin - indirect	>0.05 g/L	-	>0.04 g/L (for >4 weeks)
Creatinine	-	-	> 0.02 g/L
ALT/AST	-	-	2 x baseline and >10 x ULN**

- Patients whose dose of ribavirin is reduced to 600 mg daily should receive one 200 mg capsule in the morning and two 200 mg capsules in the evening.

** Upper limit of normal

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 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 Redipen 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 Redipen Injector.

Some important points to note are:

In each Redipen Injector there is a two-chamber cartridge containing powder of peginterferon alfa-2b (at strength of 50µg or 80µg or 100µg or 120µg or 150µg) and sterile water for injection 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 0.5mL of PEG-INTRON, solution for Injection.

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

Table 10

Strength	Actual Dose (μg) for each Dosage Settings (mL)				
	0.3 mL	0.35 mL	0.4 mL	0.45 mL	0.5 mL
50 μg	30 μg	35 μg	40 μg	45 μg	50 μg
80 μg	48 μg	56 μg	64 μg	72 μg	80 μg
100 μg	60 μg	70 μg	80 μg	90 μg	100 μg
120 μg	72 μg	84 μg	96 μg	108 μg	120 μg
150 μg	90 μg	105 μg	120 μg	135 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 Redipen 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 Redipen 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 Redipen Injector with any unused solution safely in a sharps container. The PEG-INTRON Redipen 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 not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and should normally not be longer than 24 hours at 2°C to 8°C.

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 Redipen Injector and REBETOL Capsules:

- PEG-INTRON Redipen Injector is a single use disposable injection pen and is available in the following strength:
 - 50, 80, 100, 120 and 150 µg of peginterferon alfa-2b and solvent (sterile Water for Injections). Also, one injection needle and two cleansing swabs are provided for use with each PEG-INTRON Redipen Injector.
- REBETOL 200 mg capsules are white, opaque capsules imprinted in blue ink with “200mg” 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 Redipen Injector and REBETOL Capsules for four weeks of PEGATRON Combination Therapy:

Table 11

Patient Group based on Body Weight:	PEG-INTRON Redipen Injector (Single Use Injection Pen)	REBETOL 200 mg Capsules
<65 kg:	4 x 100 µg Redipen Injector	112 capsules [800 mg/d for 4 wks]
65 to 80 kg:	4 x 120 µg Redipen Injector	140 capsules [1000 mg/d for 4 wks]
>80 and ≤85 kg:	4 x 150 µg Redipen Injector	140 capsules [1000 mg/d for 4 wks]
86-105 kg:	4 x 150 µg Redipen Injector	168 capsules [1200 mg/d for 4 wks]
>105 kg	4 x 150 µg Redipen Injector	196 capsules * [1400 mg/d for 4 wks]
For Patient requiring REBETOL dose reduction (600 mg/day) only		
<65 kg:	4 x 100 µg Redipen Injector	84 capsules [600 mg/d for 4 wks]
65 to 80 kg:	4 x 120 µg Redipen Injector	84 capsules
>80 kg:	4 x 150 µg Redipen Injector	84 capsules
For patient requiring PEG-INTRON dose reduction (0.75 µg/kg/week) only		
<65 kg:	4 x 50 µg Redipen Injector	112 capsules [800 mg/d for 4 wks]
65 to 85 kg:	4 x 80 µg Redipen Injector	140 capsules [1000 mg/d for 4 wks]
>85 kg:	4 x 80 µg Redipen Injector	168 capsules [1200 mg/d for 4 wks]

<i>For Patient requiring PEG-INTRON (0.75 µg/kg/week) and REBETOL (600 mg/day) dose reductions</i>		
<65 kg:	4 x 50 µg Redipen Injector	84 capsules [600 mg/d for 4 wks]
≥65 kg:	4 x 80 µg Redipen Injector	84 capsules

- not 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 Redipen 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 (NZ) Ltd
P O Box 99 851
Newmarket
Auckland 1149

Tel: 0800 500 673

MEDICINES CLASSIFICATION

Prescription Only Medicine

DATE OF PREPARATION

20 January 2011