PEG-INTRON* Powder and Solvent for Solution for Injection

Brand of peginterferon alfa-2b

FOR SUBCUTANEOUS ADMINISTRATION

DESCRIPTION: PEG-INTRON Powder for Solution for Injection (hereafter referred to as PEG-INTRON Injection) is available in vials to deliver either 50, 80, 100 and 120 micrograms of peginterferon alfa-2b, which is a conjugation of recombinant interferon alfa-2b with monomethoxy polyethylene glycol. When reconstituted with Solvent as recommended, each vial provides 0.5 ml of PEG-INTRON Injection.

PEG-INTRON 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 injection.

ACTIONS: *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. These responses include inhibition of virus replication in virus-infected cells, suppression of cell proliferation and immunomodulating activities (e.g. 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.

Pharmacodynamics: The pharmacodynamics of peginterferon alfa-2b were assessed in a rising single-dose trial in healthy subjects by examining changes in oral temperature, concentrations of effector proteins such as serum neopterin as well as white cell and neutrophil counts. Subjects treated with peginterferon alfa-2b showed mild dose-related elevations in body temperature and neopterin levels and reductions in white cell and neutrophil counts.

Pharmacokinetics: Peginterferon alfa-2b is a well characterized polyethylene glycol-modified ("pegylated") derivative of interferon alfa-2b and it is predominantly composed of monopegylated species. The plasma half-life of peginterferon alfa-2b is prolonged compared with non-pegylated 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. Mean apparent volume of distribution is 0.99 l/kg. Upon multiple dosing, there is an accumulation of immunoreactive interferons.

Mean (SD) peginterferon alfa-2b elimination half-life is approximately 40 hours (13.3 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 the 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 was 1.1% and 1.5 micrograms/kg was 2 to 3 %.

Special Populations:

Renal function: Renal clearance appears to account for 30 % of total clearance of peginterferon alfa-2b. In a single dose study (1.0 microgram/kg) in patients with impaired renal function, C_{max}, AUC, and half-life increased in relation to the degree of renal impairment (see Contraindication and Precautions).

Following multiple dosing of PEG-INTRON Solution for Injection (1 mcg/kg subcutaneously administered every week for four weeks) the clearance of PEG-INTRON is reduced by a mean of 17% in patients with moderate renal impairment (creatinine clearance 30-49 ml/min) and by a mean of 44% in patients with severe renal impairment (creatinine clearance 10-29 ml/min) compared to subjects with normal renal function. Clearance was similar in patients with severe renal impairment not on dialysis and in patients who were receiving hemodialysis. The dose of PEG-INTRON for monotherapy should be reduced in patients with moderate or severe renal impairment (See DOSAGE AND ADMINISTRATION: DOSE REDUCTION).

Hepatic function: The pharmacokinetics of peginterferon alfa-2b have not been evaluated in patients with severe hepatic dysfunction. Therefore, PEG-INTRON Injection must not be used in these patients.

Elderly patients ≥ 65 years of age: There does not appear to be a significant age-related effect on the pharmacokinetics of PEG-INTRON Injection. However, as in younger patients, renal function must be determined prior to the administration of PEG-INTRON Injection.

Patients under the age of 18 years: Specific pharmacokinetic evaluations in patients under 18 years of age were not performed. PEG-INTRON Injection is indicated for the treatment of chronic hepatitis C only in patients 18 years of age or older.

Methadone Drug Interaction Study: The pharmacokinetics of concomitant administration of methadone and PEG-INTRON Solution for Injection were evaluated in 18 patients with chronic hepatitis C, who were naïve to peginterferon alfa-2b, and were receiving 1.5 mcg/kg/week of PEG-INTRON subcutaneously. All patients were on stable methadone maintenance therapy receiving ≥40 mg/day prior to initiating therapy with PEG-INTRON. Mean methadone AUC was approximately 16% higher after 4 weeks of PEG-INTRON treatment as compared to baseline.

CLINICAL TRIALS: PEG-INTRON Injection:

Hepatitis

I. Chronic Hepatitis C

A. Naïve Patients

The results of a large multi-center randomized, Phase III clinical trial demonstrated efficacy and safety of PEG-INTRON Injection for the treatment of chronic hepatitis C. The objectives of this trial in 1,219 patients were to assess the safety and efficacy of 48 weeks of treatment with 3 doses of PEG-INTRON (0.5, 1.0, 1.5 micrograms/kg administered once weekly subcutaneously) vs Intron A (3 MIU administered subcutaneously three times a week). Eligible patients for these trials had chronic hepatitis C confirmed by a positive HCV-RNA polymerase chain reaction assay (PCR) (>100 copies/ml), a liver biopsy consistent with a histologic diagnosis of chronic hepatitis with no other cause for the chronic hepatitis, as well as abnormal serum ALT.

The primary measures of efficacy in the clinical trial were loss of HCV-RNA (< 100 copies/ml) (virologic) and normalisation of ALT (biochemical) 6 months after completing 1 year of treatment. Using the virologic assessment, all doses of PEG-INTRON in the clinical trial were statistically superior to Intron A (Table 1).

Table 1 *Proportion of Patients with Sustained Loss of HCV*
 # (%) of Patients

	A	*B*	*C*	*D*	*p Values***
*Response **	*PEG-INTRON 0.5 micrograms/kg*	*PEG-INTRON 1.0 micrograms/kg*	*PEG-INTRON 1.5 micrograms/kg*	*Intron A 3 MIU*	*A vs D B vs D C vs D*
Sustained Response 6 Months Post Treatment	*57 (18%)*	*73 (25%)*	*71 (23%)*	*37(12%)*	*0.042 <0.001 <0.001*

**Serum HCV-RNA is measured by quantitative polymerase chain reaction with a lower limit of detection of 100 copies/ml (National Genetics Institute, Culver City, CA)*
***Chi-square Test*

The Quality of Life was less affected by the 0.5 microgram/kg dose of PEG-INTRON Injection than by either the 1.0 microgram/kg dose once weekly or the 3 million IU of Intron A three times a week.

PEG-INTRON Injection with ribavirin: A single pivotal randomized clinical trial (C/I98-580) has been conducted with PEG-INTRON Injection in combination with ribavirin. In this trial, two combination regimens were compared with the combination of interferon alfa-2b + ribavirin. Eligible patients for this trial had chronic hepatitis C confirmed by a positive HCV-RNA polymerase chain reaction (PCR) assay (> 100 copies/ml), a liver biopsy consistent with a histological diagnosis of chronic hepatitis with no other cause for the chronic hepatitis, and abnormal serum ALT.

In this trial, 1,530 naïve patients were treated for one year with one of the following combination regimens:

- PEG-INTRON Injection (1.5 micrograms/kg/week) + PEG-INTRON Capsules (800 mg/day), (n = 511).
- PEG-INTRON Injection (1.5 micrograms/kg/week for one month followed by 0.5 microgram/kg/week for 11 months) + PEG-INTRON Capsules (1,000/1,200 mg/day), (n = 514).
- Interferon alfa-2b (3 MIU TIW) + ribavirin (1,000/1,200 mg/day) (n = 505).

PEG-INTRON Injection with ribavirin was significantly more effective than the combination of interferon alfa 2b and ribavirin particularly in patients infected with Genotype 1 (**Table 2**). Sustained response was assessed by the response rate six months after the cessation of treatment.

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 capsules (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 1). Response rates in patients who received >13.2 mg/kg ribavirin were even higher.

The benefit of the combination regimen of PEG-INTRON Injection with ribavirin was 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 the combination of PEG-INTRON Injection with 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 peginterferon alfa-2b and ribavirin had a higher sustained response 6 months after 1 year of treatment than those who took < 80 % of their treatment (72 % vs. 46 %).

In a non-comparative trial, 235 patients with genotype 1 and low viral load (≤ 2,000,000 copies/ml) received PEG-INTRON, 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 %. Forty-one percent of subjects (97/235) had nondetectable plasma HCV-RNA levels at Week 4 and Week 24 of therapy. In this subgroup, there was a 92 % (89/97) sustained virological response rate. The high sustained response rate in this subgroup of patients was identified in an interim analysis (n=49) and prospectively confirmed (n=48).

Limited historical data indicate that treatment for 48 weeks might be associated with a higher sustained response rate (11/11) and with a lower risk of relapse (0/11 as compared to 7/96 following 24 weeks of treatment).

Table 2 Sustained response rates with combination treatment by ribavirin dose [mg/kg])

HCV Genotype	**Ribavirin dose (mg/kg)**	**P 1.5/R**	**P 0.5/R**	**I/R**
All Genotypes	**All**	**54 %**	**47 %**	**47 %**
	≤ 10.6	50 %	41 %	27 %
	> 10.6	61 %	48 %	47 %
Genotype 1	**All**	**42 %**	**34 %**	**33 %**
	≤ 10.6	38 %	25 %	20 %
	> 10.6	48 %	34 %	34 %
Genotype 1 ≤ 2 million copies/ml	All	73 %	51 %	45 %
	≤ 10.6	74 %	25 %	33 %
	> 10.6	71 %	52 %	45 %
Genotype 1 > 2 million copies/ml	All	30 %	27 %	29 %
	≤ 10.6	27 %	25 %	17 %
	> 10.6	37 %	27 %	29 %
Genotype 2/3	**All**	**82 %**	**80 %**	**79 %**
	≤ 10.6	79 %	73 %	50 %
	> 10.6	88 %	80 %	80 %

P 1.5/R: PEG-INTRON Injection in combination with ribavirin (PEG-INTRON 1.5 micrograms/kg + ribavirin 800 mg)

P 0.5/R: PEG-INTRON Injection in combination with ribavirin (PEG-INTRON 1.5 to 0.5 microgram/kg + ribavirin 1,000/1,200 mg)

I/R: Interferon alfa-2b 3 MIU + ribavirin 1,000/1,200 mg

A large randomized 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 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 posttreatment (see **Table 3**).

Table 3 Virologic Response at End of Treatment, Sustained Virologic Response and Relapse Rate*

Treatment Group	% (number) of Patients		
	PEG-INTRON 1.5 µg/kg/ ribavirin	PEG-INTRON 1 µg/kg/ ribavirin	peginterferon alfa-2a 180 µg/ ribavirin
End of Treatment Response	53 (542/1,019)	49 (500/1,016)	64 (667/1,035)
Relapse	24 (123/523)	20 (95/475)	32 (193/612)
Sustained Virologic Response	40 (406/1,019)	38 (386/1016)	41 (423/1,035)

* HCV-RNA PCR assay, with a lower limit of quantitation of 27 IU/ml

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 a higher sustained virologic response rate compared to PEG-INTRON 1 µg/kg dose. 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%. 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. In patients with undetectable HCV-RNA at treatment week 12 who received PEG-INTRON (1.5 µg/kg)/ribavirin, the sustained virologic response rate was 81% (328/407).

HCV/HIV Co-infected patients

Two trials have been conducted in patients coinfected with HIV and HCV. The response to treatment in both of these trials is presented in Table 4. 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 PEG-INTRON (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 coinfected with HIV. Patients were randomized to receive either PEG-INTRON (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 4 Sustained virological response based on genotype after PEG-INTRON in combination with Ribavirin in HIV/HCV Co-infected patients

	Study 1[1]			**Study 2**[2]		
	peginterferon alfa-2b (1.5 µg	Interferon alfa-2b (3 MIU TIW) +	p value[a]	peginterferon alfa-2b (100 or 150[c]	Interferon alfa-2b (3 MIU TIW) +	p value[b]

	/kg/week) + ribavirin (800 mg)	ribavirin (800 mg)		µg/week) + ribavirin (800-1200 mg)[d]	ribavirin (800-1200 mg)[d]	
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.

B. PEG-INTRON/ribavirin retreatment of prior treatment failures clinical trial

In a non-comparative trial, 2,293 patients with moderate to severe fibrosis who failed previous treatment with combination alpha interferon/ribavirin were retreated with PEG-INTRON, 1.5 microgram/kg subcutaneously, once weekly, in combination with weight adjusted ribavirin. All patients were treated for 48 weeks and followed for 24 weeks posttreatment. Response to treatment was defined as undetectable HCV-RNA at 24 weeks posttreatment (**Table 5***)*.

Table 5 Rates of Response to Retreatment in Prior Treatment Failures		
	PEG-INTRON 1.5 mcg/kg QW ribavirin 800-1400 mg QD	99% Confidence Interval %
Overall response [1,2]	21.7% (497/2293)	19.5, 23.9
Genotype 1	14.6% (270/1846)	12.5, 16.7
Genotype 2	58.7% (44/75)	44.0, 73.3
Genotype 3	54.5% (159/292)	46.9,62.0
Genotype 4	28.4% (19/67)	14.2, 42.5

[1]Plasma HCV-RNA is measured with a research-based quantitative polymerase chain reaction assay by a

central laboratory.

[2]Nine subjects had missing/other genotypes.

Approximately 36% of subjects had undetectable plasma HCV-RNA levels at Week 12 of therapy. 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 the subset of subjects with undetectable HCV-RNA at Treatment Week 12, SVR rates by baseline characteristics are summarized in **Table 6**.

Table 6 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	27.5 (507/1846)	48.3 (245/507)
G2/3	76.6 (281/367)	69.8 (196/281)
G4	43.3 (29/67)	62.1 (18/29)
Fibrosis		
F2	41.5 (271/653)	64.2 (174/271)
F3	36.0 (242/672)	58.7 (142/242)
F4	32.0 (309/966)	47.6 (147/309)
Baseline Viral Load		
HVL (>600,000 IU/ml)	30.0 (432/1441)	50.9 (220/432)
LVL (≤600,000 IU/ml)	45.6 (389/853)	62.0 (241/389)
Prior Response		
Relapsers	62.6 (404/645)	55.9 (226/404)
Nonresponder	23.0 (318/1385)	54.4 (173/318)
Prior Therapy		
PEG-INTRON/ribavirin	30.7 (150/488)	50.7 (76/150)
peginterferon alfa-2a/ribavirin	32.5 (122/375)	50.0 (61/122)
interferon alpha/ribavirin	38.6 (549/1423)	59.4 (326/549)

a:%/Number of subjects who were negative at week 12 out of the entire study population

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 AND USAGE:

Hepatitis

PEG-INTRON Injection is indicated for the treatment of chronic hepatitis C.

The optimal treatment for chronic hepatitis C is considered to be the administration of the combination of PEG-INTRON with ribavirin. ***When PEG-INTRON Injection is to be used in combination with ribavirin, please refer also to the ribavirin product information.***

This combination of PEG-INTRON with ribavirin is indicated for the treatment of naïve, relapse and nonresponder patients with chronic hepatitis C who have normal or elevated transaminases without liver decompensation, including those with histologic evidence of cirrhosis (Child-Pugh class A), and who are positive for HCV-RNA. This combination is also indicated for the treatment of patients with chronic hepatitis C who are co-infected with clinically stable HIV.

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

DOSAGE AND ADMINISTRATION

Chronic Hepatitis C:

PEG-INTRON INJECTION MONOTHERAPY:

PEG-INTRON Injection monotherapy is administered subcutaneously at a dose of 1.0 microgram/kg once weekly for at least 6 months. The dose should be selected based on the anticipated efficacy and safety. Treatment with PEG-INTRON should be initiated and monitored only by a physician experienced in the treatment of patients with hepatitis C. In patients showing loss of HCV-RNA at 6 months, treatment is continued for an additional 6 months, (i.e.1 year of treatment). For patients who exhibit virological response at week 12, treatment should be continued for another nine month period (i.e., a total of one year).

When self-administration is recommended, the patient should be advised to vary the injection site each time the injection is administered.

In patients who fail to show loss of HCV-RNA at 6 months, treatment with PEG-INTRON should be discontinued.

PEG-INTRON monotherapy was not studied in HCV/HIV co-infected patients.

PEG-INTRON INJECTION AND RIBAVIRIN COMBINATION THERAPY:

PEG-INTRON Injection 1.5 micrograms/kg/week subcutaneously in combination with ribavirin capsules.

The dose of ribavirin to be used in combination with PEG-INTRON Injection is based on patient body weight (**Table 7**). Ribavirin capsules are to be administered orally each day in two divided doses with food (morning and evening).

Table 7 Ribavirin dose based on body weight		
Patient weight (kg)	**Daily ribavirin dose**	**Number of 200 mg capsules**
< 65	800 mg	4[a]
65 – 80	1,000 mg	5[b]
81-105	1,200 mg	6[c]
>105	1,400 mg	7[d]

a: 2 morning, 2 evening

b: 2 morning, 3 evening

c: 3 morning, 3 evening

d: 3 morning, 4 evening

As an alternative to exact calculation of dose, a simplified PEG-INTRON Powder for Solution for Injection dosage was developed based on experience in clinical trials (see **Table 8)**. This table coordinates the PEG-INTRON simplified dose by weight-based groups and relates that dose to the most appropriate vial presentation. The corresponding ribavirin capsule dose is also integrated.

PEG-INTRON Powder for Solution for Injection is administered subcutaneously once weekly. Ribavirin capsules are to be administered orally each day in two divided doses with food (morning and evening).

Table 8- Dosing for Combination Therapy

Weight (kg)	**PEG-INTRON**		**Ribavirin Capsules**	
	Vial/Strength (µg/0.5 ml)	**Administer once weekly (ml)**	**Total Daily Dose (mg)**	**Number of Capsules (200 mg)**
<40	50	0.5	800	4[a]
40-50	80	0.4	800	4[a]
51-64	80	0.5	800	4[a]
65-75	100	0.5	1,000	5[b]
76-80	120	0.5	1,000	5[b]
81-85	120	0.5	1,200	6[c]
86-105	150	0.5	1,200	6[c]
>105	150	0.5	1,400	7[d]

a: 2 morning, 2 evening

b: 2 morning, 3 evening

c: 3 morning, 3 evening

d: 3 morning, 4 evening

Duration of treatment- Naïve Patients

Predictability of sustained virological response:

Consideration should be given to discontinuing PEG-INTRON combination therapy after 12 to 24 weeks of therapy if the patient has failed to demonstrate an early virologic response defined as undetectable HCV-RNA or at least a 2 $\log_{10}$ reduction from baseline in viral titer by 12 weeks of therapy.

Patients infected with virus genotype 1 who fail to achieve virological response at Week 12 are highly unlikely to become sustained virological responders.

- **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) 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, except for HCV/HIV co-infected patients who 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.

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 PEG-INTRON/Ribavirin was 99% (67/68; Study 1) (see section on clinical trials in HIV/HCV co-infected patients). A positive predictive value of 50% (52/104; Study 1) was observed for HIV/HCV co-infected patients receiving combination therapy.

Duration of treatment- Retreatment of Prior Treatment Failures (Relapse and Nonresponder 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 also section on clinical trials in prior treatment failures).

Dose modification:

If severe adverse reactions or laboratory abnormalities develop during treatment with PEG-INTRON Injection or PEG-INTRON Injection with ribavirin, modify the dosages of each product if appropriate, until the adverse reactions abate. Dose reduction of PEG-INTRON Injection/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. For patients on PEG-INTRON Injection monotherapy: refer to Table 10a for dose modification guidelines. The following guidelines were developed in clinical trials for dose modification based on laboratory values (see Dosage modification guidelines, **Table 9a** for PEG-INTRON Injection and **Table 9b** for PEG-INTRON Injection with ribavirin).

Table 9a Dose modification guidelines for PEG-INTRON Injection

Laboratory values	**Reduce PEG-INTRON Injection to one-half dose if:**	**Discontinue PEG-INTRON Injection if:**
Neutrophils	$< 0.75 \times 10^9$/l	$< 0.5 \times 10^9$/l
Platelets	$< 50 \times 10^9$/l	$< 25 \times 10^9$/l

Table 9b Dose modification guidelines for PEG-INTRON Combination Therapy

Laboratory values	**Adjust only ribavirin dose (See Note 1) if:**	**Adjust only PEG-INTRON Injection dose (see Note 2) if:**	**Discontinue PEG-INTRON Combination Therapy if:**
Haemoglobin	< 10 g/dl	-	< 8.5 g/dl
Haemoglobin in: Patients with history of stable cardiac disease	≥ 2 g/dl decrease in hemoglobin during any four week period during treatment (permanent dose reduction)		< 12 g/dl after four weeks of dose reduction
White blood cells	-	$< 1.5 \times 10^9$/l	$< 1.0 \times 10^9$/l
Neutrophils	-	$< 0.75 \times 10^9$/l	$< 0.5 \times 10^9$/l
Platelets	-	$< 50 \times 10^9$/l	$< 25 \times 10^9$/l
Bilirubin – direct	-	-	2.5 x ULN*
Bilirubin – indirect	> 5 mg/dl	-	> 4 mg/dl (for > 4 weeks)
Creatinine	-	-	> 2.0 mg/dl
ALT/AST	-	-	2 x baseline and > 10 x ULN*

* Upper limit of normal

Note 1: 1st 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.

Note 2: 1st dose reduction of PEG-INTRON Injection is to 1 μg/kg/week. If needed, 2nd dose reduction of PEG-INTRON Injection is to 0.5 μg/kg/week.

Simplified dosing schedule reduction: Dose reduction in patients using the simplified dosing schedule may be achieved by use of a different vial presentation (lower dose strength) or by administering a lesser volume.

Special populations

Use in renal impairment:

Hepatitis

Monotherapy: In patients with Chronic Hepatitis C with moderate renal dysfunction (creatinine clearance 30-50 ml/min), the starting dose of PEG-INTRON should be reduced by 25%. Patients with severe renal dysfunction (creatinine clearance 10-29 ml/min), including those on hemodialysis, should have the starting dose of PEG-INTRON reduced by 50%. If renal function decreases during treatment, PEG-INTRON therapy should be discontinued.

Combination therapy: Patients with creatinine clearance < 50 ml/min must not be treated with PEG-INTRON Injection in combination with ribavirin (see CONTRAINDICATIONS)**.** When PEG-INTRON is administered in combination with REBETOL, subjects with impaired renal function and/or those over the age of 50 should be more carefully monitored with respect to the development of anemia.

It is recommended that renal function be evaluated in all patients prior to initiation of PEG-INTRON Injection. Patients with moderate renal impairment should be closely monitored and, should have their dose of PEG-INTRON Injection reduced if medically appropriate. If serum creatinine rises to > 2 mg/dl (see **Table 9b**), PEG-INTRON Injection must be discontinued (see PRECAUTIONS).

All Patients:

Use in hepatic impairment: The safety and efficacy of PEG-INTRON has not been evaluated in patients with severe hepatic dysfunction. Therefore, PEG-INTRON Injection must not be used in these patients.

Use in the elderly (≥ 65 years of age): There does not appear to be a significant age-related effect on the pharmacokinetics of peginterferon alpha-2b. However, as in younger patients, renal function must be determined prior to the administration of PEG-INTRON Injection.

Use in patients under the age of 18 years: Safety and effectiveness of PEG-INTRON Injection in these patients have not been evaluated. PEG-INTRON Injection is not recommended for use in children and adolescents under the age of 18 (see **Indications and Usage**).

Information for health professionals and patients:

- **Preparation and Administration**:

PEG-INTRON Injection is supplied as a powder of peginterferon alfa-2b at strengths of 50, 80, 100 and 120 micrograms for single use

Before reconstitution, PEG-INTRON Powder for Injection may appear either as a white, tablet-shaped solid that is whole or in pieces, or as a white powder.

Each vial must be reconstituted with 0.7 ml of diluent (sterile water for injection) and up to 0.5 ml of solution will be administered.

To reconstitute the PEG-INTRON Powder for Injection: Use a sterilized syringe and injection needle, inject 0.7 ml of solvent **SLOWLY**, into the vial of PEG-INTRON Powder for Injection aiming the stream of liquid at the glass wall of the vial. It is best not to aim the stream directly at the white solid or powder, or to inject the liquid quickly, as this causes a greater amount of bubbles. The solution may appear cloudy or bubbly for a few minutes. Swirl the vial gently to complete dissolution of powder. **Do not shake** , but gently turn the vial upside down. The contents should now be completely dissolved. Once the solution has settled and all bubbles have risen to the top of the solution, you should have a clear solution with a small ring of tiny bubbles around the top. The appropriate dose can now be withdrawn with a sterilized injection syringe and injected.

A small volume is lost during preparation of PEG-INTRON Powder when the dose is measured and injected. Thus, each unit contains an excess amount of diluent and PEG-INTRON Powder to ensure delivery of the labeled dose in 0.5 ml of PEG-INTRON Injection. **The labeled strength will be contained in 0.5 ml of the reconstituted solution.** The reconstituted solution for each of the available strengths will have a concentration of 50 mcg/0.5 ml, 80 mcg/0.5 ml, 100 mcg/0.5 ml, or 120 mcg/0.5 ml.

As for all parenteral medicinal products, inspect visually the reconstituted solution prior to administration. Do not use if discoloration is present. Discard any unused solution. PEG-INTRON Injection must not be mixed with other injectable products.

- **Stability of the reconstituted solution**:

The chemical and physical in-use stability for the reconstituted solution has been demonstrated for 24 hours at 2º - 8º 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 would normally not be longer than 24 hours at 2º - 8º C.

- **Measuring the dose of PEG-INTRON from the reconstituted powder for injection:**

Turn the vial and the syringe upside down in one hand. Be sure the tip of needle is in the PEG-INTRON reconstituted solution. Your other hand will be free to move the plunger. Pull back on the plunger slowly to draw just more than the dose prescribed by your doctor into the syringe.

Hold the syringe with the needle in the vial pointing up, remove the syringe from the long needle leaving the needle in the vial and without touching the tip of the syringe. Take the short needle and place it firmly on to the tip of the syringe. Remove the needle guard from the syringe needle and check for air bubbles in the syringe. If you see any bubbles, pull the plunger slightly back; tap the syringe gently, with the needle pointing upwards, until the bubbles disappear. Push up the plunger slowly back to the correct dose. Replace the needle guard and place the syringe with the needle on a flat surface.

Be sure the solution is at room temperature up to 25°C. If the solution is cold, warm the syringe between your palms. Inspect visually the reconstituted solution prior to administration: do not use if discolouration or particulate matter is present. You are now ready to inject the dose.

- **Injecting the solution**

Select the injection site. The best sites for injection are tissues with a layer of fat between skin and muscle: thigh, outer surface of the upper arm (you may need the assistance of another person to use this site), abdomen (except the navel or waistline). If you are exceptionally thin, use only the thigh or outer surface of the arm for injection.

Change your injection site each time.

Cleanse and disinfect the skin where the injection is to be made. Wait for the area to dry. Remove the needle guard. With one hand, pinch a fold of loose skin. With your other hand, hold the syringe as you would a pencil. Insert the needle into the pinched skin at an angle of approximately 45°. After the needle is in, remove the hand used to pinch the skin and use it to hold the syringe barrel. Pull back the plunger very slightly with one hand. If blood comes into the syringe, the needle has entered a blood vessel. Do not inject into this site; withdraw the needle and repeat the procedure. Inject the solution by pushing the plunger all the way down gently.

Pull the needle straight out of the skin. Press the injection site with a small bandage or sterile gauze if necessary for several seconds. Do not massage the injection site. If there is bleeding, cover with an adhesive bandage.

The vial, ampoule and injection materials, are intended for single use and must be discarded. Dispose of the syringe and needles safely in a closed container.

INCOMPATIBILITIES: PEG-INTRON Injection should only be reconstituted with the solvent provided and must not be mixed with other medicinal products (see also **Preparation and Administration**).

DRUG INTERACTIONS:

Hepatitis

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

Results from a multiple-dose probe study assessing P450 substrates in chronic hepatitis C patients receiving once weekly PEG-INTRON (1.5 mcg/kg) for 4 weeks demonstrated no change in activity of CYP1A2, CYP3A4, or N-acetyltransferase. There was an increase in activity of CYP2C8/9 and CYP2D6. Caution should be used when administering PEG-INTRON with medications metabolized by CYP2C8/9 and CYP2D6, especially those with narrow therapeutic indices.

HIV/HCV Co-infection

Nucleoside analogs: Ribavirin has been shown *in vitro* to inhibit phosphorylation of zidovudine and stavudine. The clinical significance of these finding is unknown. However, these *in vitro* findings raise the possibility that concurrent use of ribavirin 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 ribavirin concurrently with either of these two agents. If HIV RNA levels increase, the use of ribavirin concomitantly with reverse transcriptase inhibitors must be reviewed (see ribavirin product information).

Use of nucleoside analogs, 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 analogs (e.g. didanosine or abacavir). Co-administration of ribavirin and didanosine is not recommended. Reports of mitochondrial toxicity, in particular lactic acidosis and pancreatitis, of which some fatal, have been reported (see ribavirin product information).

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 PEG-INTRON and ribavirin to HAART .

ADVERSE EFFECTS:

Use in Hepatitis Patients:

PEG-INTRON Injection monotherapy:

Most undesirable effects were mild or moderate in severity and not treatment limiting. The majority of patients reported headache and myalgia.

Very commonly reported effects (≥ 10% of patients) were pain/inflammation at injection site, fatigue, rigors, fever, depression, arthralgia, nausea, alopecia, musculoskeletal pain, irritability, influenza-like symptoms, insomnia, diarrhea, abdominal pain, asthenia, pharyngitis, weight decrease, anorexia, anxiety, impaired concentration, dizziness, and injection site reaction.

Commonly reported effects (≥ 2 % of patients) were pruritus, dry skin, malaise, increased sweating, right upper quadrant pain, neutropenia, leukopenia, anemia, rash, vomiting, dry mouth, emotional lability, nervousness, dyspnea, viral infection, somnolence, thyroid disorders, chest pain, dyspepsia, flushing, paresthesia, coughing, agitation, sinusitis, hypertonia, hyperesthesia, blurred vision, confusion, flatulence, decreased libido, erythema, eye pain, apathy, hypoesthesia, loose stool, conjunctivitis, nasal congestion, constipation, vertigo, menorrhagia, menstrual disorder.

In patients treated with PEG-INTRON in clinical trials, severe psychiatric events were uncommon; life-threatening psychiatric events occurred infrequently. These events included suicide, attempted suicide, suicidal ideation, aggressive behavior, sometimes directed towards others, and psychosis including hallucinations.

Granulocytopenia (< 0.75 x 10^9/l) occurred in 4% and 7%, and thrombocytopenia (< 70 x 10^9/l) in 1% and 3%, respectively, in patients receiving 0.5 or 1.0 micrograms/kg of PEG-INTRON Injection.

PEG-INTRON Injection in combination with ribavirin:

In addition to the adverse effects reported with PEG-INTRON Injection Monotherapy, the following adverse effects have been reported with PEG-INTRON Injection in combination with ribavirin:

Adverse effects reported between 5% and 10%: tachycardia, rhinitis and taste perversion.

Adverse effects reported between 2% and 5%: hypotension, syncope, hypertension, lacrimal gland disorder, tremor, gingival bleeding, glossitis, stomatitis, ulcerative stomatitis, hearing impairment/loss, tinnitus, palpitation, thirst, aggressive behavior, fungal infection, prostatitis, otitis media, bronchitis, respiratory disorder, rhinorrhea, eczema, abnormal hair texture, photosensitivity reaction, and lymphadenopathy.

HIV/HCV Co-infected patients

Treatment with PEG-INTRON 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 PEG-INTRON 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/µl.

Table 10 summarises the safety of PEG-INTRON in combination with ribavirin for HIV/HCV co-infected patients.

Table 10 Safety overview in clinical trials of HIV/HCV co-infected patients treated with PEG-INTRON in combination with ribavirin

	Study 1		Study 2	
	PEG-INTRON / ribavirin n=194	Interferon alfa-2b/ ribavirin n=189	PEG-INTRON / 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 PEG-INTRON 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/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 PEG-INTRON in combination with ribavirin. Anaemia (hemoglobin < 9.4g/dl) was reported in 12% (23/194) of patients treated with PEG-INTRON 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 PEG-INTRON in combination with ribavirin.

All patients/Post-marketing:

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

Very rarely, alfa interferons, including PEG-INTRON, used alone or in combination with ribavirin may be associated with aplastic anemia or pure red cell aplasia**.**

Other reported adverse effects that may occur in association with PEG-INTRON Injection Monotherapy or PEG-INTRON Injection in combination with ribavirin:
Ophthalmological disorders that have been reported rarely with alpha interferons include retinopathies (including macular edema), retinal hemorrhages, retinal artery or vein obstruction, cotton wool spots, loss of visual acuity or visual field, optic neuritis, and papilledema (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.

Following the marketing of PEG-INTRON Injection, rhabdomyolysis, myositis, renal insufficiency and renal failure have been reported rarely. Cardiac ischemia, myocardial infarction, cerebrovascular ischaemia, cerebrovascular hemorrhage, encephalopathy (see PRECAUTIONS) ulcerative and ischemic colitis, sarcoidosis or exacerbation of sarcoidosis, erythema multiforme, Stevens Johnson syndrome, toxic epidermal necrolysis, and injection site necrosis also have been reported very rarely. Diabetes, diabetic ketoacidosis and hypertriglyeridemia have also been reported.

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, systemic lupus erythematosus, vasculitis, Vogt-Koyanagi-Harada syndrome.

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

Asthenic conditions (including asthenia, malaise and fatigue), dehydration, facial palsy, migraine headache, homicidal ideation, bacterial infection including sepsis, hypothyroidism, hyperthyroidism, and psoriasis have been reported.

CONTRAINDICATIONS:

- Hypersensitivity to the active substance or to any interferon or to any of the excipients;
- Pregnant women. PEG-INTRON Injection in combination with ribavirin must not be initiated until a report of a negative pregnancy test has been obtained immediately prior to initiation of therapy;

- Men whose female partners are pregnant must not be treated with PEG-INTRON Injection when used in combination with ribavirin.
- Autoimmune hepatitis or a history of autoimmune disease
- Decompensated liver disease.
- When used in combination with ribavirin, patients with creatinine clearance < 50 ml/min.

PRECAUTIONS: **Psychiatric and Central Nervous System (CNS)**: *Patients with existence of or history of severe psychiatric conditions*: If treatment with PEG-INTRON Combination Therapy is judged necessary in adult patients with existence or history of severe psychiatric conditions, this should only be initiated after having ensured appropriate individualized diagnostic and therapeutic management of the psychiatric condition.

If severe neuropsychiatric effects, particularly depression, are observed, PEG-INTRON Combination Therapy should be discontinued. Severe central nervous system (CNS) effects particularly depression, homicidal ideation, have been observed in patients treated with PEG-INTRON and suicidal ideation, suicide or attempted suicide have been observed in some hepatitis patients during PEG-INTRON Combination Therapy. Other CNS effects including aggressive behavior, sometimes directed towards others, psychosis including hallucinations, confusion and alterations of mental status have been observed. These adverse effects have occurred in adult patients treated with recommended doses as well as in patients treated with higher doses of alfa interferon. More significant obtundation and coma, including cases of encephalopathy, have been observed in some patients, usually elderly, treated at higher doses of interferon alfa. 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 alfa interferon.

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. If such symptoms appear, the potential seriousness of these undesirable effects must be borne in mind by the prescribing physician. If psychiatric symptoms persist or worsen, or suicidal ideation or aggressive behavior towards others is identified, it is recommended that PEG-INTRON Combination Therapy be discontinued, and the patient followed with psychiatric intervention as appropriate.

Cardiovascular system: As with interferon alpha, patients with a history of congestive heart failure, myocardial infarction and/or previous or current arrhythmic disorders receiving therapy with PEG-INTRON Injection require close monitoring. It is recommended that patients who have pre-existing cardiac abnormalities 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 PEG-INTRON Injection

Acute hypersensitivity: Acute hypersensitivity reactions, (e.g. urticaria, angioedema, bronchoconstriction, anaphylaxis), have been observed rarely during interferon alfa-2b therapy. If such a reaction develops during

treatment with PEG-INTRON Injection, discontinue treatment and institute appropriate medical therapy immediately. Transient rashes do not necessitate interruption of treatment.

Liver function: As with treatment with any interferon, discontinue treatment with PEG-INTRON Injection in patients who develop prolongation of coagulation markers which might indicate liver decompensation. .

Liver/kidney graft rejection: The safety and efficacy of PEG-INTRON Injection alone or in combination with ribavirin for the treatment of hepatitis C in liver or other organ transplant recipients have not been studied. Preliminary data indicates that interferon alpha therapy may be associated with an increased rate of kidney graft rejection. Liver graft rejection also has been reported but a causal association with interferon alpha therapy has not been established.

Fever: While fever may be associated with the flu-like syndrome reported commonly during any interferon therapy, other causes of persistent fever must be ruled out.

Hydration: Adequate hydration must be maintained in patients undergoing therapy with PEG-INTRON Injection since hypotension related to fluid depletion has been seen in some patients treated with alpha interferons. Fluid replacement may be necessary.

Pulmonary changes: Pulmonary infiltrates, pneumonitis, and pneumonia, occasionally resulting in fatality, have been observed rarely in interferon alpha treated patients. Any patient developing fever, cough, dyspnea 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 PEG-INTRON Injection. Prompt discontinuation of therapy and treatment with corticosteroids appear to be associated with resolution of pulmonary adverse events.

Autoimmune disease: The development of autoantibodies has been reported during treatment with alpha interferons. Clinical manifestations of autoimmune disease during interferon therapy may occur more frequently in patients predisposed to the development of autoimmune disorders.

Ocular changes: Ophthalmologic disorders, including retinal hemorrhages, cotton wool spots, and retinal artery or vein obstruction have been reported in rare instances after treatment with alpha 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 PEG-INTRON Injection should be considered in patients who develop new or worsening ophthalmological disorders.

Thyroid changes: Infrequently, patients treated for chronic hepatitis C with interferon alpha 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, PEG-INTRON Injection may be continued if TSH levels can be maintained in the normal range by medication.

Dental and periodontal disorders: Dental and periodontal disorders have been reported in hepatitis 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 peg-interferon 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.

Metabolic disturbances: Hypertriglyceridemia and aggravation of hypertriglyceridemia, sometimes severe, have been observed. Monitoring of lipid levels is, therefore, recommended.

HCV/HIV Co-infection: In patients co-infected with HIV/HCV, limited efficacy and safety data (N = 25) are available in subjects with CD4 counts less than 200 cells/ul. 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 PEG-INTRON and ribavirin.

Other: Due to reports of interferon alpha exacerbating pre-existing psoriatic disease and sarcoidosis, use of PEG-INTRON Injection in patients with psoriasis or sarcoidosis is recommended only if the potential benefit justifies the potential risk.

Laboratory tests: In all patients, standard hematologic tests, blood chemistry and a test of thyroid function must be conducted in all patients prior to initiating therapy. Acceptable baseline values that may be considered as a guideline prior to initiation of PEG-INTRON Injection are:

- Platelets $\geq 100{,}000/mm^3$
- Neutrophil count $\geq 1{,}500/mm^3$
- TSH level must be within normal limits

In Hepatitis patients:

Laboratory evaluations are to be conducted at weeks 2 and 4 of therapy, and periodically thereafter as clinically appropriate.

Effects on ability to drive and use machines: Patients who develop fatigue, somnolence or confusion during treatment with PEG-INTRON Injection are cautioned to avoid driving or operating machinery.

USAGE DURING PREGNANCY AND LACTATION

MONOTHERAPY for Hepatitis:

Interferon alfa-2b has been shown to be abortifacient in primates. PEG-INTRON is likely to also cause this effect. Because there are no data on the use of PEG-INTRON Injection in pregnant women, PEG-INTRON Injection is not recommended for use during pregnancy.

PEG-INTRON Injection is recommended for use in fertile women only when they are using effective contraception during the treatment period.

It is not known whether the components of this medicinal product are excreted in human milk. Therefore, a decision must be made whether to discontinue the treatment or discontinue nursing, taking into account the importance of the medicinal product to the mother.

COMBINATION THERAPY for Hepatitis:

PEG-INTRON Injection with ribavirin must not be used during pregnancy.

Significant teratogenic and/or embryocidal potential have 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. Malformations of the skull, palate, eye, jaw, limbs, skeleton and gastrointestinal tract were noted. The incidence and severity of teratogenic effects increased with escalation of the ribavirin dose. Survival of fetuses and offspring was reduced.

Female patients: Ribavirin capsules must not be used by women who are pregnant (see **C**ONTRAINDICATIONS). . Extreme care must be taken to avoid pregnancy in female patients. Therapy with ribavirin 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 their partners must each use an effective contraceptive during treatment and for six months after treatment has been concluded; routine monthly pregnancy tests must be performed during this time. If pregnancy does occur during treatment or within six months from stopping treatment, the patient must be advised of the significant teratogenic risk of ribavirin to the fetus.

Male patients and their female partners: Extreme care must be taken to avoid pregnancy in partners of male patients taking ribavirin. Ribavirin accumulates intracellularly and is cleared from the body very slowly. In animal studies, ribavirin produced changes in sperm at doses below the clinical dose. It is unknown whether the ribavirin that is contained in sperm will exert its known teratogenic effects upon fertilisation of the ova. Male patients and their female partners of childbearing age must, therefore, be counseled to each use an effective

contraceptive during treatment with ribavirin and for six months after treatment has been concluded. PEG-INTRON Injection in combination with ribavirin is recommended for use in fertile women only when they are using effective contraception during the treatment period.

Lactation: It is not known whether pegylated interferon alfa -2b in combination with ribavirin is excreted in human milk. Because of the potential for adverse reactions in nursing infants, nursing must be discontinued prior to initiation of treatment.

OVERDOSAGE INFORMATION:

Doses up to 10.5 times the intended dose have been reported in hepatitis patients. The maximum daily dose reported is 1200 mcg/day for one day. In general, the adverse events seen in overdose cases involving PEG-INTRON are consistent with the known safety profile for PEG-INTRON; however, the severity of the events may be increased. No specific antidote for PEG-INTRON is available; therefore, symptomatic treatment and close observation of the patient are recommended in cases of overdose. If available, prescribers are advised to consult with a poison control center (PCC).

HOW SUPPLIED:

PEG-INTRON is available in vials of 50, 80, 100 and 120 micrograms of peginterferon alpha-2b powder and solvent for solution for injection.

The powder is contained in a 2 ml vial, Type I flint glass, with a grey butyl rubber stopper in an aluminum flip-off seal with a polypropylene bonnet. The solvent is presented in a 2 ml ampoule, Type I flint glass.

PEG-INTRON is supplied as 1 vial of powder for solution for injection, 1 ampoule of solvent for parenteral use, 1 injection syringe, 2 injection needles and 1 cleaning swab.

STORAGE: Store at 2° to 8° C.

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