1. NAME OF THE MEDICINAL PRODUCT

PegIntron 80, 100, 120, 150 micrograms, powder and solvent for solution for injection in pre-filled pen.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each pre-filled pen of PegIntron 80, 100, 120, 150 micrograms contains a sufficient amount of peginterferon alfa-2b as measured on a protein basis in a powder for solution for injection, and the corresponding amount of solvent, to provide 80, 100, 120, 150 micrograms in 0.5 ml of peginterferon alfa-2b when reconstituted as recommended.

The active substance is a covalent conjugate of recombinant interferon alfa-2b* with monomethoxy polyethylene glycol. The potency of this product should not be compared to that of another pegylated or non-pegylated protein of the same therapeutic class (see section 5.1).
*produced by rDNA technology in *E.coli* cells harbouring a genetically engineered plasmid hybrid encompassing an interferon alfa-2b gene from human leukocytes.

Excipients with known effect:
Each pre-filled pen contains 40 mg of sucrose per 0.5 ml.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Powder and solvent for solution for injection in pre-filled pen.

White powder.
Clear and colourless solvent.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Tritherapy
PegIntron in combination with ribavirin and boceprevir (tritherapy) is indicated for the treatment of chronic hepatitis C (CHC) genotype 1 infection in adult patients (18 years of age and older) with compensated liver disease who are previously untreated or who have failed previous therapy (see section 5.1).
Please refer to the ribavirin and boceprevir Physician's Insert when PegIntron is to be used in combination with these medicines.
Bitherapy and monotherapy
PegIntron is indicated for the treatment of adult patients (18 years of age and older) with chronic hepatitis C (CHC) who have elevated transaminases without liver decompensation and who are positive for serum hepatitis C virus RNA (HCV-RNA) or anti-HCV, including naïve patients with clinically stable HIV co-infection (see section 4.4).

PegIntron in combination with ribavirin (bitherapy) is indicated for the treatment of chronic hepatitis C (CHC) infection in patients who are previously untreated including patients with clinically stable HIV co-infection and in patients who have failed previous treatment with interferon alpha (pegylated or nonpegylated) and ribavirin combination therapy or interferon alpha monotherapy (see section 5.1).

Interferon monotherapy, including PegIntron, is indicated mainly in case of intolerance or contraindication to ribavirin.

Please refer to the ribavirin Physician's Insert when PegIntron is to be used in combination with ribavirin.

4.2 Posology and method of administration
Treatment should be initiated and monitored only by a physician experienced in the management of patients with hepatitis C.

MSD

Posology
PegIntron should be administered as a once weekly subcutaneous injection. The dose administered depends on whether it is used in combination therapy (bitherapy or tritherapy) or as monotherapy.

PegIntron combination therapy (bitherapy or tritherapy)
Bitherapy (PegIntron with ribavirin): applies to all adult patients.
Tritherapy (PegIntron with ribavirin and boceprevir): applies to adult patients with genotype 1 CHC.

Dose to be administered
PegIntron 1.5 micrograms/kg/week in combination with ribavirin capsules.

The intended dose of 1.5 µg/kg of PegIntron to be used in combination with ribavirin may be delivered in weight categories with the PegIntron strengths according to **Table 1**. Ribavirin capsules are to be administered orally each day in two divided doses with food (morning and evening).

Table 1 - Dosing for Combination Therapy*

Body Weight (kg)	**PegIntron**		**Ribavirin Capsules**	
	PegIntron 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	1200	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
* Refer to the Physician's Insert of boceprevir for details about the dose of boceprevir to be administered in tritherapy.

Duration of treatment – Naïve patients
Tritherapy: Refer to the Physician's Insert for boceprevir.

Bitherapy: Predictability of sustained virological response**-** Patients infected with virus genotype 1 who fail to achieve undetectable HCV-RNA or demonstrate adequate virological response at week 4 or 12 are highly unlikely to become sustained virological responders and should be evaluated for discontinuation (see also section 5.1).

- Genotype 1:
  - Patients who have undetectable HCV-RNA at treatment week 12, treatment should be continued for another nine month period (i.e., a total of 48 weeks).
  - Patients with detectable but ≥ 2 log decrease in HCV-RNA level from baseline at treatment week 12 should be reassessed at treatment week 24 and, if HCV-RNA is undetectable, they should continue with full course of therapy (i.e. a total of 48 weeks). However, if HCV-RNA is still detectable at treatment week 24, discontinuation of therapy should be considered.
  - In the subset of patients with genotype 1 infection and low viral load (< 600,000 IU/ml) who become 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 (see section 5.1).

- Genotypes 2 or 3:
  It is recommended that all patients be treated with bitherapy 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 with bitherapy as for genotype 1.

Duration of treatment - HCV/HIV Co-infection
*Bitherapy:*The recommended duration of treatment for HCV/HIV co-infected patients is 48 weeks with bitherapy, regardless of genotype.

Predictability of response and non-response in HCV/HIV 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 HCV/HIV co-infected patients treated with PegIntron in combination with ribavirin was 99 % (67/68; Study 1) (see section 5.1). A positive predictive value of 50 % (52/104; Study 1) was observed for HCV/HIV co-infected patients receiving combination therapy.

Duration of treatment - Retreatment
Tritherapy: Refer to the Physician's Insert for boceprevir.

Bitherapy: Predictability of sustained virological response: All patients, irrespective of genotype, who have demonstrated serum HCV-RNA below the limits of detection at week 12 should receive 48 weeks of bitherapy. Retreated patients who fail to achieve virological response (i.e. HCV-RNA below the limits of detection) at week 12 are unlikely to become sustained virological responders after 48 weeks of therapy (see also section 5.1).
Retreatment duration greater than 48 weeks in non-responder patients with genotype 1 has not been studied with pegylated interferon alfa-2b and ribavirin combination therapy.

PegIntron monotherapy
Dose to be administered
As monotherapy the PegIntron regimen is 0.5 or 1.0 µg/kg/week. The lowest PegIntron strength available is 80 µg/0.5 ml; therefore for patients prescribed 0.5 µg/kg/week, doses must be adjusted by volume as shown in **Table 2**. For the 1.0 µg/kg dose, similar volume adjustments can be made or alternate strengths can be used as shown in **Table 2**. PegIntron monotherapy was not studied in HCV/HIV co-infected patients.

Table 2- Monotherapy Dosing

	0.5 µg/kg		**1.0 µg/kg**	
Body Weight (kg)	**PegIntron Strength (µg/0.5ml)**	**Administer Once Weekly (ml)**	**PegIntron Strength (µg/0.5ml)**	**Administer Once Weekly (ml)**
30-35	50*	0.15	80*	0.2
36-45	50*	0.2	50	0.4
46-56	50*	0.25	50	0.5
57-72	80*	0.2	80	0.4
73-88	50	0.4	80	0.5
89-106	50	0.5	100	0.5
106-120**	80	0.4	120	0.5

MSD

* Minimum delivery for pen is 0.3 ml. ** For patients > 120 kg, the PegIntron dose should be calculated based on the individual patient weight. This may require combinations of various PegIntron dose strengths and volumes.

Duration of treatment

For patients who exhibit virological response at week 12, treatment should be continued for at least another three-month period (i.e., a total of six months). The decision to extend therapy to one year of treatment should be based on prognostic factors (e.g., genotype, age > 40 years, male gender, bridging fibrosis).

Dose modification for all patients (monotherapy and combination therapy)

If severe adverse reactions or laboratory abnormalities develop during treatment with PegIntron monotherapy or combination therapy, the dosages of PegIntron and/or ribavirin must be modified as appropriate, until the adverse reactions abate. Dose reduction of boceprevir is not recommended. Boceprevir must not be administered in the absence of PegIntron and ribavirin.

As adherence might be of importance for outcome of therapy, the dose of PegIntron and ribavirin should be kept as close as possible to the recommended standard dose. Guidelines were developed in clinical trials for dose modification.

Combination Therapy Dose Reduction Guidelines

Table 2a Dose modification guidelines for combination therapy based on laboratory parameters

Laboratory values	**Reduce only ribavirin daily dose (see note 1) if:**	**Reduce only PegIntron dose (see note 2) if:**	**Discontinue combination therapy if:**
Haemoglobin	≥ 8.5 g/dl, and < 10 g/dl	-	< 8.5 g/dl
Haemoglobin in Patients with history of stable cardiac disease	≥ 2 g/dl decrease in haemoglobin during any four week period during treatment (permanent dose reduction)		< 12 g/dl after four weeks of dose reduction
Leukocytes	-	≥ 1.0 x 10^9/l, and < 1.5 x 10^9/l	< 1.0 x 10^9/l
Neutrophils	-	≥ 0.5 x 10^9/l, and < 0.75 x 10^9/l	< 0.5 x 10^9/l
Platelets	-	≥ 25 x 10^9/l, and < 50 x 10^9/l	< 25 x 10^9/l
Bilirubin – direct	-	-	2.5 x ULN*
Bilirubin – indirect	> 5 mg/dl	-	> 4 mg/dl (for > 4 weeks)
Serum Creatinine	-	-	> 2.0 mg/dl
Creatinine Clearance	-	-	Discontinue ribavirin if CrCL < 50ml/min
Alanine Aminotransferase (ALT) or Aspartate Aminotransferase (AST)	-	-	2 x baseline and > 10 x ULN* 2 x baseline and > 10 x ULN*

* Upper limit of normal

Note 1: In adult patients 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. Patients whose dose of ribavirin is reduced to 600 mg daily receive one 200 mg capsule in the morning and two 200 mg capsules in the evening.

Note 2: In adult patients 1st dose reduction of PegIntron is to 1 µg/kg/week. If needed, 2nd dose reduction of PegIntron is to 0.5 µg/kg/week. For patients on PegIntron monotherapy: refer to monotherapy dose reduction guidelines section for dose reduction.

Dose reduction of PegIntron may be accomplished by either reducing the prescribed volume or by utilizing a lower dose strength as shown in **Table 2b**.

Table 2b Two-step dose reduction of PegIntron in combination therapy

First dose reduction to PegIntron 1 µg/kg				**Second dose reduction to PegIntron 0.5 µg/kg**			
Body weight (kg)	**PegIntron strength (µg/0.5 ml)**	**Amount of PegIntron to administer (µg)**	**Volume of PegIntron to administer (ml)**	**Body weight (kg)**	**PegIntron strength (µg/0.5 ml)**	**Amount of PegIntron to administer (µg)**	**Volume of PegIntron to administer (ml)**
< 40	50	35	0.35	< 40	50*	20	0.2
40-50	120*	48	0.2	40-50	50*	25	0.25
51-64	80	56	0.35	51-64	80*	32	0.2
65-75	100	70	0.35	65-75	50	35	0.35
76-85	80	80	0.5	76-85	120*	48	0.2
86-105	120	96	0.4	86-105	50	50	0.5
> 105	150	105	0.35	> 105	80	64	0.4

* Minimum delivery for pen is 0.3 ml.

PegIntron monotherapy dose reduction guidelines

Dose modification guidelines for patients who use PegIntron monotherapy are shown in **Table 3a.**

Table 3a Dose modification guidelines for PegIntron monotherapy based on laboratory parameters

Laboratory values	**Reduce PegIntron to one-half dose if:**	**Discontinue PegIntron if:**
Neutrophils	≥ 0.5 x 10^9/l, and < 0.75 x 10^9/l	< 0.5 x 10^9/l
Platelets	≥ 25 x 10^9/l, and < 50 x 10^9/l	< 25 x 10^9/l

For patients who use 0.5 µg/kg PegIntron monotherapy, dose reduction may be accomplished by reducing the prescribed volume by one-half as shown in **Table 3b**.

Table 3b Reduced PegIntron dose (0.25 µg/kg) for the 0.5 µg/kg monotherapy regimen

Body weight (kg)	**PegIntron strength (µg/0.5 ml)**	**Amount of PegIntron to administer (µg)**	**Volume of PegIntron to administer (ml)**
30-35	50*	8	0.08
36-45	50*	10	0.1
46-56	50*	13	0.13
57-72	80*	16	0.1
73-88	50*	20	0.2
89-106	50*	35	0.25
107-120**	80*	32	0.2

* Minimum delivery for pen is 0.3 ml.

** For patients > 120 kg, the PegIntron dose should be calculated based on the individual patient weight. This may require combinations of various PegIntron dose strengths and volumes.

For patients who use 1.0 µg/kg PegIntron monotherapy, dose reduction may be accomplished by reducing the prescribed volume by one-half or by utilizing a lower dose strength as shown in **Table 3**c.

		Table 3c – Reduced PegIntron dose (0.5 µg/kg) for the 1.0 µg/kg monotherapy regimen				
Body Weight (kg)	**PegIntron strength (µg/0.5 ml)**			**Amount of PegIntron to administer (µg)**	**Volume of PegIntron to administer (ml)**	
30-35	50*			15	0.15	
36-45	50*			20	0.20	
46-56	50*			25	0.25	
57-72	80*			32	0.2	
73-88	50			40	0.4	
89-106	50			50	0.5	
107-120**	80			64	0.4	

* Minimum delivery for pen is 0.3 ml.
** For patients > 120 kg, the PegIntron dose should be calculated based on the individual patient weight. This may require combinations of various PegIntron dose strengths and volumes.

Special populations
Renal impairment
Monotherapy
PegIntron should be used with caution in patients with moderate to severe renal impairment. In patients with moderate renal dysfunction (creatinine clearance 30-50 ml/minute), the starting dose of PegIntron should be reduced by 25 %. Patients with severe renal dysfunction (creatinine clearance 15-29 ml/minute) should have the starting dose of PegIntron reduced by 50 %. Data are not available for the use of PegIntron in patients with creatinine clearance < 15 ml/minute (see section 5.2). Patients with severe renal impairment, including those on hemodialysis, should be closely monitored. If renal function decreases during treatment, PegIntron therapy should be discontinued.

Combination therapy
Patients with creatinine clearance < 50 ml/minute must not be treated with PegIntron in combination with ribavirin (see ribavirin Physician's Insert). When administered in combination therapy**,** patients with impaired renal function should be more carefully monitored with respect to the development of anaemia.

Hepatic impairment
The safety and efficacy of PegIntron therapy has not been evaluated in patients with severe hepatic dysfunction, therefore PegIntron must not be used for these patients.

Elderly (≥ 65 years of age)
There are no apparent age-related effects on the pharmacokinetics of PegIntron. Data from elderly patients treated with a single dose of PegIntron suggest no alteration in PegIntron dose is necessary based on age (see section 5.2).

Method of administration
PegIntron should be administered as a subcutaneous injection. For special handling information see section 6.6. Patients may self-inject PegIntron if their physician determines that it is appropriate and with medical follow-up as necessary.

4.3 Contraindications

- Hypersensitivity to the active substance or to any interferon or to any of the excipients listed in section 6.1;
- A history of severe pre-existing cardiac disease, including unstable or uncontrolled cardiac disease in the previous six months (see section 4.4);
- Severe, debilitating medical conditions;

- Autoimmune hepatitis or a history of autoimmune disease;
- Severe hepatic dysfunction or decompensated cirrhosis of the liver;
- Pre-existing thyroid disease unless it can be controlled with conventional treatment;
- Epilepsy and/or compromised central nervous system (CNS) function;
- HCV/HIV patients with cirrhosis and a Child-Pugh score ≥ 6.
- Combination of PegIntron with telbivudine.

Combination therapy
Also see Physician's Insert for ribavirin and boceprevir if PegIntron is to be administered in combination therapy in patients with chronic hepatitis C.

4.4 Special warnings and precautions for use

Psychiatric and Central Nervous System (CNS):
Severe CNS effects, particularly depression, suicidal ideation and attempted suicide have been observed in some patients during PegIntron therapy, and even after treatment discontinuation mainly during the 6-month follow-up period. Other CNS effects including aggressive behaviour (sometimes directed against others such as homicidal ideation) bipolar disorders, mania, confusion and alterations of mental status have been observed with alpha interferons. Patients should be closely monitored for any signs or symptoms of psychiatric disorders. If such symptoms appear, the potential seriousness of these undesirable effects must be borne in mind by the prescribing physician and the need for adequate therapeutic management should be considered. If psychiatric symptoms persist or worsen, or suicidal or homicidal ideation is identified, it is recommended that treatment with PegIntron be discontinued, and the patient followed, with psychiatric intervention as appropriate.

Patients with existence of, or history of severe psychiatric conditions
If treatment with peginterferon alfa-2b is judged necessary in patients with existence or history of severe psychiatric conditions, this should only be initiated after having ensured appropriate individualised diagnostic and therapeutic management of the psychiatric condition.

Patients with substance use/abuse
HCV infected patients having a co-occurring substance use disorder (alcohol, cannabis, etc) are at an increased risk of developing psychiatric disorders or exacerbation of already existing psychiatric disorders when treated with alpha interferon. If treatment with alpha interferon is judged necessary in these patients, the presence of psychiatric co-morbidities and the potential for other substance use should be carefully assessed and adequately managed before initiating therapy. If necessary, an inter-disciplinary approach including a mental health care provider or addiction specialist should be considered to evaluate, treat and follow the patient. Patients should be closely monitored during therapy and even after treatment discontinuation. Early intervention for re-emergence or development of psychiatric disorders and substance use is recommended.

More significant obtundation and coma, including cases of encephalopathy, have been observed in some patients, usually elderly, treated at higher doses for oncology indications. 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 interferon alpha.

All patients in the selected chronic hepatitis C studies had a liver biopsy before inclusion, but in certain cases (i.e. patients with genotype 2 and 3), treatment may be possible without histological confirmation. Current treatment guidelines should be consulted as to whether a liver biopsy is needed prior to commencing treatment.

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 PegIntron, discontinue treatment and institute appropriate medical therapy immediately. Transient rashes do not necessitate interruption of treatment.

Cardiovascular system

As with interferon alfa-2b, patients with a history of congestive heart failure, myocardial infarction and/or previous or current arrhythmic disorders, receiving PegIntron therapy 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 PegIntron therapy.

Hepatic Failure
PegIntron increases the risk of hepatic decompensation and death in patients with cirrhosis. As with all interferons, discontinue treatment with PegIntron in patients who develop prolongation of coagulation markers which might indicate liver decompensation. Liver enzymes and hepatic function should be closely monitored in cirrhotic patients.

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

Hydration
Adequate hydration must be maintained in patients undergoing PegIntron therapy 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 pyrexia, 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, and, if appropriate, discontinue interferon alpha. Prompt discontinuation of interferon alpha administration and treatment with corticosteroids appear to be associated with resolution of pulmonary adverse events.

Autoimmune disease
The development of auto-antibodies and autoimmune disorders has been reported during treatment with alpha interferons. Patients predisposed to the development of autoimmune disorders may be at increased risk. Patients with signs or symptoms compatible with autoimmune disorders should be evaluated carefully, and the benefit-risk of continued interferon therapy should be reassessed (see also section 4.4 Thyroid changes and 4.8).
Cases of Vogt-Koyanagi-Harada (VKH) syndrome have been reported in patients with chronic hepatitis C treated with interferon. This syndrome is a granulomatous inflammatory disorder affecting the eyes, auditory system, meninges, and skin. If VKH syndrome is suspected, antiviral treatment should be withdrawn and corticosteroid therapy discussed (see section 4.8).

Ocular changes
Ophthalmologic disorders, including retinal haemorrhages, serous retinal detachment , and retinal artery or vein occlusion have been reported in rare instances after treatment with alpha interferons (see section 4.8). 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. Periodic visual examinations are recommended during PegIntron therapy, particularly in patients with disorders that may be associated with retinopathy, such as diabetes mellitus or hypertension. Discontinuation of PegIntron 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. Prior to initiation of PegIntron therapy, TSH levels must be evaluated and any thyroid abnormality detected at that time must be treated with conventional therapy. Determine TSH levels if, during the course of therapy, a patient develops symptoms consistent with possible thyroid dysfunction. In the presence of thyroid dysfunction, PegIntron treatment may be continued if TSH levels can be maintained in the normal range by medication.

Metabolic disturbances

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

HCV/HIV Co-infection

Mitochondrial toxicity and lactic acidosis

Patients co-infected with HIV and receiving Highly Active Anti-Retroviral Therapy (HAART) may be at increased risk of developing lactic acidosis. Caution should be used when adding PegIntron and ribavirin to HAART therapy (see ribavirin Physician's Insert).

Hepatic decompensation in HCV/HIV co-infected patients with advanced cirrhosis

Co-infected patients with advanced cirrhosis receiving HAART may be at increased risk of hepatic decompensation and death. Adding treatment with alfa interferons alone or in combination with ribavirin may increase the risk in this patient subset. Other baseline factors in co-infected patients that may be associated with a higher risk of hepatic decompensation include treatment with didanosine and elevated bilirubin serum concentration.

Co-infected patients receiving both antiretroviral (ARV) and anti-hepatitis treatment should be closely monitored, assessing their Child-Pugh score during treatment. Patients progressing to hepatic decompensation should have their anti-hepatitis treatment immediately discontinued and the ARV treatment reassessed.

Haematological abnormalities in HCV/HIV co-infected patients

HCV/HIV co-infected patients receiving peginterferon alfa-2b/ribavirin treatment and HAART may be at increased risk to develop haematological abnormalities (as neutropenia, thrombocytopenia and anaemia) compared to HCV mono-infected patients. Although, the majority of them could be managed by dose reduction, close monitoring of haematological parameters should be undertaken in this population of patients (see section 4.2 and below “Laboratory tests” and section 4.8).

Patients treated with PegIntron and ribavirin combination therapy and zidovudine are at increased risk of developing anaemia and therefore the concomitant use of this combination with zidovudine is not recommended (see section 4.5).

Patients with low CD4 counts

In patients co-infected with HCV/HIV, limited efficacy and safety data (N = 25) are available in subjects with CD4 counts less than 200 cells/µl. Caution is therefore warranted in the treatment of patients with low CD4 counts.

Please refer to the respective Physician's Inserts 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 PegIntron and ribavirin.

Dental and periodontal disorders

Dental and periodontal disorders, which may lead to loss of teeth, have been reported in patients receiving PegIntron and ribavirin 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 PegIntron and ribavirin. 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 transplant recipients

The safety and efficacy of PegIntron 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 has also been reported.

Other

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

Laboratory tests

Standard haematologic 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 PegIntron therapy are:

- Platelets: ≥ 100,000/mm^3
- Neutrophil count: ≥ 1,500/mm^3
- TSH level: must be within normal limits

Laboratory evaluations are to be conducted at weeks 2 and 4 of therapy, and periodically thereafter as clinically appropriate. HCV-RNA should be measured periodically during treatment (see section 4.2).

Long term maintenance monotherapy
It has been demonstrated in a clinical study that peginterferon alfa-2b at low-dose (0.5 µg/kg/week) is not effective in long term maintenance monotherapy (for a mean duration of 2.5 years) for the prevention of disease progression in non responders with compensated cirrhosis. No statistically significant effect on the time to development of the first clinical event (liver decompensation, hepatocellular carcinoma, death and/or liver transplantation) was observed as compared to the absence of treatment. PegIntron should therefore not be used as long term maintenance monotherapy.

Important information about some of the ingredients of PegIntron
Patients with rare hereditary problems of fructose intolerance, glucose galactose malabsorption or sucrase-isomaltase insufficiency should not take this medicine.
This medicinal product contains less than 1 mmol sodium (23 mg) per 0.7 ml, i.e., essentially "sodium-free".

4.5 Interaction with other medicinal products and other forms of interaction

Telbivudine
A clinical trial investigating the combination of telbivudine, 600 mg daily, with pegylated interferon alfa-2a, 180 micrograms once weekly by subcutaneous administration, indicates that this combination is associated with an increased risk of developing peripheral neuropathy. The mechanism behind these events is not known (see telbivudine SmPC). Moreover, the safety and efficacy of telbivudine in combination with interferons for the treatment of chronic hepatitis B has not been demonstrated. Therefore, the combination of PegIntron with telbivudine is contraindicated (see section 4.3).

Methadone
In patients with chronic hepatitis C that were on stable methadone maintenance therapy and naïve to peginterferon alfa-2b, addition of 1.5 microgram/kg/week of PegIntron subcutaneously for 4 weeks increased R-methadone AUC by approximately 15 % (95 % CI for AUC ratio estimate 103 – 128 %).
The clinical significance of this finding is unknown; however, patients should be monitored for signs and symptoms of increased sedative effect, as well as respiratory depression. Especially in patients on a high dose of methadone, the risk for QTc prolongation should be considered.

Effect of Peginterferon alfa-2b on Co-administered Medicines

The potential interaction of peginterferon alfa-2b (PegIntron) on substrates of metabolic enzymes was evaluated in 3 multiple-dose clinical pharmacology studies. In these studies, the effects of multiple-dose regimens of peginterferon alfa-2b (PegIntron) were investigated in Hepatitis C subjects (1.5 mcg/week) or healthy subjects (1 mcg/week or 3 mcg/week) (**Table 4**). A clinically significant pharmacokinetic interaction was not observed between peginterferon alfa-2b (PegIntron) and tolbutamide, midazolam or dapsone; therefore, no dosing adjustment is necessary when peginterferon alfa-2b (PegIntron) is administered with medicines metabolized by CYP2C9, CYP3A4 and N-acetyltransferase. Concomitant administration of peginterferon alfa-2b (PegIntron) with caffeine or desipramine modestly increased the exposure of caffeine and desipramine. When patients are administered PegIntron with medications metabolized by CYP1A2 or CYP2D6, the extent of the decrease in cytochrome P 450 activity is unlikely to have a clinical impact, except with medicines which have a narrow therapeutic margin (**Table 5**).

MSD

Table 4 Effect of Peginterferon alfa-2b on Co-administered Medicines

Co-administered Medicine	Dose of peginterferon alfa-2b	Study Population	Geometric Mean Ratio (Ratio with/without peginterferon alfa-2b)	
			AUC (90% CI)	C_{max} (90% CI)
Caffeine (CYP1A2 substrate)	1.5 mcg/kg/week (4 weeks)	Chronic Hepatitis C Subjects (N=22)	1.39 (1.27, 1.51)	1.02 (0.95, 1.09)
	1 mcg/kg/week (4 weeks)	Healthy Subjects (N=24)	1.18 (1.07, 1.31)	1.12 (1.05, 1.19)
	3 mcg/kg/week (2 weeks)	Healthy Subjects (N=13)	1.36 (1.25, 1.49)	1.16 (1.10, 1.24)
Tolbutamide (CYP2C9 substrate)	1.5 mcg/kg/week (4 weeks)	Chronic Hepatitis C Subjects (N=22)	1.1# (0.94, 1.28)	NA
	1 mcg/kg/week (4 weeks)	Healthy Subjects (N=24)	0.90# (0.81, 1.00)	NA
	3 mcg/kg/week (2 weeks)	Healthy Subjects (N=13)	0.95 (0.89, 1.01)	0.99 (0.92, 1.07)
Dextromethorphan hydrobromide (CYP2D6 and CYP3A substrate)	1.5 mcg/kg/week (4 weeks)	Chronic Hepatitis C Subjects (N=22)	0.96## (0.73, 1.26)	NA
	1 mcg/kg/week (4 weeks)	Healthy Subjects (N=24)	2.03# (1.55, 2.67)	NA
Desipramine (CYP2D6 substrate)	3 mcg/kg/week (2 weeks)	Healthy Subjects (N=13)	1.30 (1.18, 1.43)	1.08 (1.00, 1.16)
Midazolam (CYP3A4 substrate)	1.5 mcg/kg/week (4 weeks)	Chronic Hepatitis C Subjects (N=24)	1.07 (0.91, 1.25)	1.12 (0.94, 1.33)
	1 mcg/kg/week (4 weeks)	Healthy Subjects (N=24)	1.07 (0.99, 1.16)	1.33 (1.15, 1.53)
	3 mcg/kg/week (2 weeks)	Healthy Subjects (N=13)	1.18 (1.06, 1.32)	1.24 (1.07, 1.43)
Dapsone (N-acetyltransferase substrate)	1.5 mcg/kg/week (4 weeks)	Chronic Hepatitis C Subjects (N=24)	1.05 (1.02, 1.08)	1.03 (1.00, 1.06)

Calculated from urine data collected over an interval of 48-hours
Calculated from urine data collected over an interval of 24-hours

Table 5 Precautions for co-administration (PegIntron should be administered with care when co-administered with the following medicines)

Medicines	Signs, Symptoms, and Treatment	Mechanism and Risk Factors
Theophylline	Co-administration of theophylline with the product (PegIntron) may increase the blood concentrations of theophylline. Careful co-administration of theophylline with the product (PegIntron) is recommended. Package inserts of theophylline should be referred to when co-administering with the product (PegIntron)	Metabolism of theophylline is suppressed by inhibitory action of the product (PegIntron) on CYP1A2.
Thioridazine	Co-administration of thioridazine with the product (PegIntron) may increase the blood concentrations of thioridazine. Careful co-administration of thioridazine with the product (PegIntron) is recommended. Package inserts of	Metabolism of thioridazine is suppressed by inhibitory action of the product (PegIntron) on CYP2D6.

	thioridazine should be referred to when co-administering with the product (PegIntron)	
Theophylline, Antipyrine, Warfarin	Elevation of blood concentrations of these medicines has been reported when administered in combination with other interferon preparations and therefore care should be taken.	Metabolism of other medicines in the liver may be suppressed.
Zidovudine	When administered in combination with other interferon preparations, suppressive effect on bone marrow function may be strengthened and aggravation of blood cell reduction such as white blood cells decreased may occur.	Mechanism of action is unknown, but it is considered that both medicines have bone marrow depressive effects.
Immuno-suppressive therapy	When administered in combination with other interferon preparations, effect of immunosuppressive therapy may be weakened in transplant (kidney, bone marrow, etc.) patients.	It is considered that graft rejection reactions may be induced.

No pharmacokinetic interactions were noted between PegIntron and ribavirin in a multiple-dose pharmacokinetic study.

HCV/HIV Co-infection

Nucleoside analogues

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 Physician's Insert).

Exacerbation of anaemia due to ribavirin has been reported when zidovudine is part of the regimen used to treat HIV, although the exact mechanism remains to be elucidated. The concomitant use of ribavirin with zidovudine is not recommended due to an increased risk of anaemia (see section 4.4). Consideration should be given to replacing zidovudine in a combination anti-retroviral treatment (ART) regimen if this is already established. This would be particularly important in patients with a known history of zidovudine-induced anaemia.

4.6 Fertility, pregnancy and lactation

Women of childbearing potential/contraception in males and females

PegIntron is recommended for use in fertile women only when they are using effective contraception during the treatment.

Combination therapy with ribavirin

Extreme care must be taken to avoid pregnancy in female patients or in partners of male patients taking PegIntron in combination with ribavirin. Females of childbearing potential must use an effective contraceptive during treatment and for 4 months after treatment has been concluded. Male patients or their female partners must use an effective contraceptive during treatment and for 7 months after treatment has been concluded (see ribavirin Physician's Insert).

Pregnancy

There are no adequate data from the use of interferon alfa-2b in pregnant women. Studies in animals have shown reproductive toxicity (see section 5.3). Interferon alfa-2b has been shown to be abortifacient in primates. PegIntron is likely to also cause this effect.

The potential risk in humans is unknown. PegIntron is to be used during pregnancy only if the potential benefit justifies the potential risk to the foetus.

Combination therapy with ribavirin
Ribavirin causes serious birth defects when administered during pregnancy, therefore ribavirin therapy is contraindicated in women who are pregnant.

Breast-feeding
It is not known whether the components of this medicinal product are excreted in human milk. Because of the potential for adverse reactions in breast-fed infants, breast-feeding should be discontinued prior to initiation of treatment.

Fertility
There are no data available regarding potential effects of PegIntron treatment on male or female fertility.

4.7 Effects on ability to drive and use machines

Patients who develop fatigue, somnolence or confusion during treatment with PegIntron are cautioned to avoid driving or operating machines. In addition patients who develop Visual disturbances, vision blurred, photophobia should be cautioned to avoid driving or operating machines.

4.8 Undesirable effects

Tritherapy
Refer to the Physician's Insert for boceprevir.

Bitherapy and monotherapy
Summary of the safety profile
The most common treatment-related adverse reactions reported during clinical trials with PegIntron in combination with ribavirin, seen in more than half of the study subjects, were fatigue, headache, and injection site reaction. Additional adverse reactions reported in more than 25 % of subjects included nausea, chills, insomnia, anaemia, pyrexia, myalgia, asthenia, pain, alopecia, anorexia, weight decreased, depression, rash and irritability. The most frequently reported adverse reactions were mostly mild to moderate in severity and were manageable without the need for modification of doses or discontinuation of therapy. Fatigue, alopecia, pruritus, nausea, anorexia, weight decrease, irritability and insomnia occur at a notably lower rate in patients treated with PegIntron monotherapy compared to those treated with combination therapy (see **Table 6**).

Tabulated summary of adverse reactions
The following treatment-related adverse reactions were reported in clinical trials or through post-marketing surveillance in patients treated with peginterferon alfa-2b, including PegIntron monotherapy or PegIntron/ribavirin . These reactions are listed in **table 6** by system organ class and frequency (very common (≥ 1/10), common (≥ 1/100 to < 1/10), uncommon (≥ 1/1,000 to < 1/100), rare (≥ 1/10,000 to < 1/1,000), very rare (< 1/10,000) or not known (cannot be estimated from the available data).
Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

Table 6 Adverse reactions reported in clinical trials or through post-marketing surveillance in patients treated with interferon alfa-2b, including PegIntron monotherapy or PegIntron + ribavirin.

Infections and infestations	
Very common:	Viral infection*, pharyngitis*
Common:	Bacterial infection (including sepsis), fungal infection, influenza, upper respiratory tract infection, bronchitis, herpes simplex, sinusitis, otitis media, rhinitis

Uncommon:	Injection site infection, lower respiratory tract infection
Blood and lymphatic system disorders	
Very common:	Anaemia, neutropenia
Common:	Heamolytic anemia , leukopaenia, thrombocytopaenia, lymphadenopathy
Very rare:	Aplastic anaemia
Not known:	Aplasia pure red cell
Immune system disorders	
Uncommon:	Drug hypersensitivity
Rare:	Sarcoidosis
Not known:	Acute hypersensitivity reactions including angioedema, anaphylaxis and anaphylactic reactions including anaphylactic shock, idiopathic thrombocytopenic purpura, thrombotic thrombocytopenic purpura, systemic lupus erythematosus
Endocrine disorders	
Common:	Hypothyroidism, hyperthyroidism
Metabolism and nutrition disorders	
Very common:	Anorexia
Common:	Hypocalcemia, hyperuricemia, dehydration, increased appetite
Uncommon:	Diabetes mellitus, hypertriglyceridaemia
Rare:	Diabetic ketoacidosis
Psychiatric disorders	
Very common:	Depression, anxiety*, emotional lability*, concentration impaired, insomnia
Common:	Aggression, agitation, anger, mood altered, abnormal behaviour, nervousness, sleep disorder, libido decreased, apathy, abnormal dreams, crying
Uncommon:	Suicide, suicide attempted , suicidal ideation, psychosis, hallucination, panic attack
Rare:	Bipolar disorders
Not known:	Homicidal ideation, mania,
Nervous system disorders	
Very common:	Headache, dizziness
Common:	Amnesia, memory impairment, syncope, migraine, ataxia, confusion, neuralgia, paraesthesia, hypoaesthesia, hyperaesthesia, hypertonia, somnolence, disturbance in attention, tremor, dysgeusia

Uncommon:	Neuropathy, peripheral neuropathy
Rare:	Convulsion
Very rare:	Cerebrovascular haemorrhage, cerebrovascular ischaemia, encephalopathy
Not known:	Facial palsy, mononeuropathies
Eye disorders	
Common:	Visual disturbance, vision blurred, photophobia, conjunctivitis, eye irritation, lacrimal disorder, eye pain, dry eye
Uncommon:	Retinal exudates
Rare:	Loss of visual acuity or visual fields, retinal haemorrhage, retinopathy, retinal artery obstruction, retinal vein occlusion, optic neuritis, papilloedema, macular oedema cotton wool spots
Not known:	Serous retinal detachment
Ear and labyrinth disorders	
Common:	Hearing impairment/loss, tinnitus, vertigo
Uncommon:	Ear pain
Cardiac disorders	
Common:	Palpitation, tachycardia
Uncommon:	Myocardial infarction
Rare:	Congestive heart failure, cardiomyopathy, arrhythmia, pericarditis
Very rare:	Cardiac ischaemia
Not known:	Pericardial effusion
Vascular disorders	
Common:	Hypotension, hypertension, flushing
Rare:	Vasculitis
Respiratory, thoracic and mediastinal disorders	
Very common:	Dyspnoea*, cough*
Common:	Dysphonia, epistaxis, respiratory disorder, respiratory tract congestion, sinus congestion, nasal congestion, rhinorrhea, nonproductive cough increased upper airway secretion, pharyngolaryngeal pain
Very rare:	Interstitial lung disease,
Not Known:	pulmonary fibrosis, pulmonary arterial hypertension#
Gastrointestinal disorders	
Very common:	Vomiting*, nausea, abdominal pain, diarrhoea, dry mouth*
Common:	Dyspepsia, gastroesophageal reflux disease, stomatitis, mouth ulceration, glossodynia, gingival bleeding, constipation, flatulence, hemorrhoids, cheilitis, abdominal

	distension, gingivitis, glossitis, tooth disorder
Uncommon:	Pancreatitis, oral pain
Rare:	Colitis ischaemic
Very rare:	Colitis ulcerative
Not known:	Tongue pigmentation
Hepatobiliary disorders	
Common:	Hyperbilirubinemia, hepatomegaly
Skin and subcutaneous tissue disorders	
Very common:	Alopecia, pruritus*, dry skin*, rash*
Common:	Psoriasis, photosensitivity reaction, rash maculo-papular, dermatitis, erythematous rash, eczema, night sweats, hyperhidrosis, acne, furuncle, erythema, urticaria, abnormal hair texture, nail disorder
Rare:	Cutaneous sarcoidosis
Very rare:	Stevens-Johnson syndrome, toxic epidermal necrolysis, erythema multiforme
Musculoskeletal and connective tissue disorders	
Very common:	Myalgia, arthralgia, musculoskeletal pain
Common:	Arthritis, back pain, muscle spasms, pain in extremity
Uncommon:	Bone pain, muscle weakness
Rare:	Rhabdomyolysis, myositis, rheumatoid arthritis
Renal and urinary disorders	
Common:	Micturition frequency, polyuria, urine abnormality
Rare:	Renal failure, renal insufficiency
Reproductive system and breast disorders	
Common:	Amenorrhoea, impotence, breast pain, menorrhagia, menstrual disorder, ovarian disorder, vaginal disorder, sexual dysfunction, prostatitis, erectile dysfunction
General disorders and administration site conditions	
Very common:	Injection site reaction*, Injection site inflammation, fatigue, asthenia, irritability, chills, pyrexia, influenza like illness, pain
Common:	Chest pain, chest discomfort, injection site pain, malaise, face oedema, oedema peripheral, feeling abnormal thirst
Rare:	Injection site necrosis
Investigations	
Very common:	Weight decreased

*These adverse reactions were common (≥1/100 to < 1/10) in clinical trials in patients treated with PegIntron monotherapy.
#Class label for interferon products, see below Pulmonary arterial hypertension.

Description of selected adverse reactions

Most cases of neutropaenia and thrombocytopaenia were mild (WHO grades 1 or 2). There were some cases of more severe neutropenia in patients treated with the recommended doses of PegIntron in combination with ribavirin (WHO grade 3: 39 of 186 [21 %]; and WHO grade 4: 13 of 186 [7 %]).

In a clinical trial, approximately 1.2 % of patients treated with PegIntron or interferon alfa-2b in combination with ribavirin reported life-threatening psychiatric events during treatment. These events included suicidal ideation and attempted suicide (see section 4.4).

Cardiovascular (CVS) adverse events, particularly arrhythmia, appeared to be correlated mostly with pre-existing CVS disease and prior therapy with cardiotoxic agents (see section 4.4). Cardiomyopathy, that may be reversible upon discontinuation of interferon alpha, has been reported rarely in patients without prior evidence of cardiac disease.

Cases of pulmonary arterial hypertension (PAH) have been reported with interferon alfa products, notably in patients with risk factors for PAH (such as portal hypertension, HIV-infection, cirrhosis). Events were reported at various time points typically several months after starting treatment with interferon alfa.

Ophthalmological disorders that have been reported rarely with alpha 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 section 4.4).

A wide variety of autoimmune and immune-mediated disorders have been reported with alpha interferons including thyroid disorders, systemic lupus erythematosus, rheumatoid arthritis (new or aggravated), idiopathic and thrombotic thrombocytopenic purpura, vasculitis, neuropathies including mononeuropathies and Vogt-Koyanagi-Harada syndrome (see also section 4.4).

HCV/HIV co-infected patients

Summary of the safety profile

For HCV/HIV co-infected patients receiving PegIntron in combination with ribavirin, other undesirable effects (that were not reported in mono-infected patients) which have been reported in the larger studies with a frequency > 5 % were: oral candidiasis (14 %), lipodystrophy acquired (13 %), CD4 lymphocytes decreased (8 %), appetite decreased (8 %), gamma-glutamyltransferase increased (9 %), back pain (5 %), blood amylase increased (6 %), blood lactic acid increased (5 %), cytolytic hepatitis (6 %), lipase increased (6 %) and pain in limb (6 %).

Description of selected adverse reactions

Mitochondrial toxicity

Mitochondrial toxicity and lactic acidosis have been reported in HIV-positive patients receiving NRTI regimen and associated ribavirin for co-HCV infection (see section 4.4).

Laboratory values for HCV/HIV co-infected patients

Although haematological toxicities of neutropenia, thrombocytopenia and anaemia occurred more frequently in HCV/HIV co-infected patients, the majority could be managed by dose modification and rarely required premature discontinuation of treatment (see section 4.4). Haematological abnormalities were more frequently reported in patients receiving PegIntron in combination with ribavirin when compared to patients receiving interferon alfa-2b in combination with ribavirin. In Study 1 (see section 5.1), 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 PegIntron in combination with ribavirin. Anaemia (hemoglobin < 9.4g/dl) was reported in 12% (23/194) of patients treated with PegIntron in combination with ribavirin.

CD4 lymphocytes decrease

Treatment with PegIntron 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 PegIntron in combination with ribavirin had no observable negative impact on the control of HIV viraemia during therapy or follow-up. Limited safety data (N= 25) are available in co-infected patients with CD4+ cell counts < 200/µl (see section 4.4).

Please refer to the respective Physician's Insert 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 PegIntron in combination with ribavirin.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product.

Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form:

http://forms.gov.il/globaldata/getsequence/getsequence.aspx?formType=AdversEffectMedic@moh.gov.il

4.9 Overdose

Doses up to 10.5 times the intended dose have been reported. The maximum daily dose reported is 1,200 µg for one day. In general, the adverse events seen in overdose cases involving PegIntron are consistent with the known safety profile for PegIntron; however, the severity of the events may be increased. Standard methods to increase elimination of the medicinal product, e.g., dialysis, have not been shown to be useful. No specific antidote for PegIntron 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 centre (PCC).

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Immunostimulants, Interferons, ATC code: L03AB10.

Recombinant interferon alfa-2b is covalently conjugated with monomethoxy polyethylene glycol at an average degree of substitution of 1 mole of polymer/mole of protein. The average molecular mass is approximately 31,300 daltons of which the protein moiety constitutes approximately 19,300.

Mechanism of action
In vitro and *in vivo* studies suggest that the biological activity of PegIntron 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.

Pharmacodynamic effects
PegIntron pharmacodynamics 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 and 2'5'-oligoadenylate synthetase (2'5'-OAS), as well as white cell and neutrophil counts. Subjects treated with PegIntron showed mild dose-related elevations in body temperature. Following single doses of PegIntron between 0.25 and 2.0 micrograms/kg/week, serum neopterin concentration was increased in a dose-related

manner. Neutrophil and white cell count reductions at the end of week 4 correlated with the dose of PegIntron.

Clinical efficacy and safety
Tritherapy with PegIntron, ribavirin and boceprevir
Refer to the Physician's Insert for boceprevir.

Monotherapy with PegIntron and bitherapy with PegIntron and ribavirin:
Naïve patients
Two pivotal trials have been conducted, one (C/I97-010) with PegIntron monotherapy; the other (C/I98-580) with PegIntron in combination with ribavirin. Eligible patients for these trials had chronic hepatitis C confirmed by a positive HCV-RNA polymerase chain reaction (PCR) assay (> 30 IU/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 the PegIntron monotherapy trial, a total of 916 naïve chronic hepatitis C patients were treated with PegIntron (0.5, 1.0 or 1.5 micrograms/kg/week) for one year with a follow-up period of six months. In addition, 303 patients received interferon alfa-2b (3 million International Units [MIU] three times a week) as a comparator. This study showed that PegIntron was superior to interferon alfa-2b (**Table 7**).

In the PegIntron combination trial, 1,530 naïve patients were treated for one year with one of the following combination regimens:
- PegIntron (1.5 micrograms/kg/week) + ribavirin (800 mg/day), (n = 511).
- PegIntron (1.5 micrograms/kg/week for one month followed by 0.5 microgram/kg/week for 11 months) + ribavirin (1,000/1,200 mg/day), (n = 514).
- Interferon alfa-2b (3 MIU three times a week) + ribavirin (1,000/1,200 mg/day) (n = 505).

In this trial, the combination of PegIntron (1.5 micrograms/kg/week) and ribavirin was significantly more effective than the combination of interferon alfa-2b and ribavirin (**Table 7**), particularly in patients infected with Genotype 1 (**Table 8**). Sustained response was assessed by the response rate six months after the cessation of treatment.

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 combination with PegIntron or interferon alfa-2b. In those patients that received > 10.6 mg/kg ribavirin (800 mg dose in typical 75 kg patient), regardless of genotype or viral load, response rates were significantly higher than in those patients that received ≤ 10.6 mg/kg ribavirin (**Table 8**), while response rates in patients that received > 13.2 mg/kg ribavirin were even higher.

Table 7 Sustained virological response (% patients HCV negative)

	PegIntron monotherapy				**PegIntron + ribavirin**		
Treatment regimen	P 1.5	P 1.0	P 0.5	I	P 1.5/R	P 0.5/R	I/R
Number of patients	304	297	315	303	511	514	505
Response at end of treatment	49 %	41 %	33 %	24 %	65 %	56 %	54 %
Sustained response	23 %*	25 %	18 %	12 %	54 %**	47 %	47 %

P 1.5 PegIntron 1.5 micrograms/kg
P 1.0 PegIntron 1.0 microgram/kg
P 0.5 PegIntron 0.5 microgram/kg
I Interferon alfa-2b 3 MIU
P 1.5/R PegIntron (1.5 micrograms/kg) + ribavirin (800 mg)
P 0.5/R PegIntron (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)
* $p < 0.001$ P 1.5 vs. I
** $p = 0.0143$ P 1.5/R vs. I/R

Table 8	Sustained response rates with PegIntron + ribavirin (by ribavirin dose, genotype and viral load)			
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 ≤ 600,000 IU/ml	All	73 %	51 %	45 %
	≤ 10.6	74 %	25 %	33 %
	> 10.6	71 %	52 %	45 %
Genotype 1 > 600,000 IU/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 PegIntron (1.5 micrograms/kg) + ribavirin (800 mg)
P 0.5/R PegIntron (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)

In the PegIntron monotherapy study, the Quality of Life was generally less affected by 0.5 microgram/kg of PegIntron than by either 1.0 microgram/kg of PegIntron once weekly or 3 MIU of interferon alfa-2b three times a week.

In a separate trial, 224 patients with genotype 2 or 3 received PegIntron, 1.5 microgram/kg subcutaneously, once weekly, in combination with ribavirin 800 mg –1,400 mg p.o. for 6 months (based on body weight, only three patients weighing > 105 kg, received the 1,400 mg dose) (**Table 9**). Twenty-four % had bridging fibrosis or cirrhosis.

Table 9	Virologic response at end of treatment, Sustained Virologic Response and relapse by HCV Genotype and viral load*		
	PegIntron 1.5 μg/kg once weekly plus Ribavirin 800-1,400 mg/day		
	End of Treatment Response	Sustained Virologic Response	Relapse
All Subjects	94 % (211/224)	81 % (182/224)	12 % (27/224)
HCV 2	100 % (42/42)	93 % (39/42)	7 % (3/42)
≤ 600,000 IU/ml	100 % (20/20)	95 % (19/20)	5 % (1/20)
> 600,000 IU/ml	100 % (22/22)	91 % (20/22)	9 % (2/22)
HCV 3	93 % (169/182)	79 % (143/182)	14 % (24/166)
≤ 600,000 IU/ml	93 % (92/99)	86 % (85/99)	8 % (7/91)
> 600,000 IU/ml	93 % (77/83)	70 % (58/83)	23 % (17/75)

* Any subject with an undetectable HCV-RNA level at the Follow-Up Week 12 visit and missing data at the Follow-Up Week 24 visit was considered a sustained responder. Any subject with missing data in and after the Follow-Up Week 12 window was considered to be a non-responder at Week 24 of follow-up.

The 6 month treatment duration in this trial was better tolerated than one year of treatment in the pivotal combination trial; for discontinuation 5 % vs. 14 %, for dose modification 18 % vs. 49 %.

In a non-comparative trial, 235 patients with genotype 1 and low viral load (< 600,000 IU/ml) received PegIntron, 1.5 micrograms/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).

A large randomized trial compared the safety and efficacy of treatment for 48 weeks with two PegIntron/ribavirin regimens [PegIntron 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 measured by Sustained Virologic Response (SVR) which is defined as undetectable HCV-RNA at 24 weeks post-treatment (see **Table 10**).

Table 10 Virologic response at treatment week 12, end of treatment response, relapse rate* and Sustained Virologic Response (SVR)

Treatment group	% (number) of patients		
	PegIntron 1.5 µg/kg + ribavirin	PegIntron 1 µg/kg + ribavirin	peginterferon alfa-2a 180 µg + ribavirin
Undetectable HCV-RNA at treatment week 12	40 (407/1,019)	36 (366/1,016)	45 (466/1,035)
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)
SVR	40 (406/1,019)	38 (386/1,016)	41 (423/1,035)
SVR in patients With undetectable HCV-RNA at treatment week 12	81 (328/407)	83 (303/366)	74 (344/466)

* (HCV-RNA PCR assay, with a lower limit of quantitation of 27 IU/ml)
Lack of early virologic response by Treatment week 12 (detectable HCV-RNA with a < 2 $\log_{10}$ reduction from baseline) was a criterion for discontinuation of treatment.

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

Predictability of sustained virological response – Naïve patients
Virological response by week 12 is defined as at least 2-log viral load decrease or undetectable levels of HCV-RNA.Virological response by week 4 is defined as at least 1-log viral load decrease or undetectable levels of HCV-RNA. These time points (treatment week 4 and treatment week 12) have been shown to be predictive for sustained response (**Table 11**).

Table 11 Predictive value of in-treatment Virologic Response while on PegIntron 1.5 µg/kg/ribavirin 800-1,400 mg combination therapy						
	Negative			**Positive**		
	No response at treatment week	No sustained response	Negative predictive value	Response at treatment week	Sustained response	Positive predictive value
Genotype 1*						
By week 4** **(n=950)**						
HCV-RNA negative	834	539	**65%** (539/834)	116	107	**92%** (107/116)
HCV-RNA negative or ≥ 1 log decrease in viral load	220	210	**95%** (210/220)	730	392	**54%** (392/730)
By week 12** **(n=915*)***						
HCV-RNA negative	508	433	**85%** (433/508)	407	328	**81%** (328/407)
HCV-RNA negative or ≥ 2 log decrease in viral load	206	205	**N/A†**	709	402	**57%** (402/709)
Genotype 2, 3**						
By week 12 **(n= 215)**						
HCV-RNA negative or ≥ 2 log decrease in viral load	2	1	**50%** (1/2)	213	177	**83%** (177/213)

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

The negative predictive value for sustained response in patients treated with PegIntron in monotherapy was 98 %.

HCV/HIV Co-infected patients

Two trials have been conducted in patients co-infected with HIV and HCV. The response to treatment in both of these trials is presented in **Table 12.** 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 PegIntron (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 centre study that enrolled 95 previously untreated adult patients with chronic hepatitis C who were coinfected with HIV. Patients were randomized to receive either PegIntron (100 or 150 µg /week based on weight) plus ribavirin (800-1,200 mg/day based on weight) or interferon alfa-2b (3 MIU TIW) plus ribavirin (800-1,200 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.

MSD

Table 12	Sustained virological response based on genotype after PegIntron in combination with Ribavirin in HCV/HIV Co-infected patients					
	Study 1[1]			Study 2 [2]		
	PegIntron (1.5 µg/kg/ week) + ribavirin (800 mg)	Interferon alfa-2b (3 MIU TIW) + ribavirin (800 mg)	p value[a]	PegIntron (100 or 150[c] µg/week) + ribavirin (800-1,200 mg)[d]	Interferon alfa-2b (3 MIU TIW) + ribavirin (800-1,200 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 PegIntron and subjects ≥ 75 kg received 150 µg/week PegIntron.
d: ribavirin dosing was 800 mg for patients < 60 kg, 1,000 mg for patients 60-75 kg, and 1,200 mg for patients > 75 kg.

1Carrat F, Bani-Sadr F, Pol S et al. JAMA 2004; 292(23): 2839-2848.
2 Laguno M, Murillas J, Blanco J.L 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 PegIntron 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 no improvement in terms of fibrosis observed in this study. Steatosis was significantly improved in patients infected with HCV Genotype 3.

PegIntron/ribavirin retreatment of prior treatment failures
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 PegIntron, 1.5 micrograms/kg subcutaneously, once weekly, in combination with weight adjusted ribavirin. Failure to prior therapy was defined as relapse or non-response (HCV-RNA positive at the end of a minimum of 12 weeks of treatment). Patients who were HCV-RNA negative at treatment week 12 continued treatment for 48 weeks and were followed for 24 weeks post-treatment. Response week 12 was defined as undetectable HCVRNA after 12 weeks of treatment. Sustained Virologic Response (SVR) is defined as undetectable HCV-RNA at 24 weeks post-treatment (**Table 13**).

Table 13	Rates of response to retreatment in prior treatment failures				
	Patients with undetectable HCV–RNA at treatment week 12 and SVR upon retreatement				
	interferon alpha/ribavirin		peginterferon alpha/ribavirin		Overall population*
	Response week 12 % (n/N)	SVR % (n/N) 99% CI	Response week 12 % (n/N)	SVR % (n/N) 99% CI	SVR % (n/N) 99 % CI
Overall	38.6 (549/1,423)	59.4 (326/549) 54.0,64.8	31.5 (272/863)	50.4 (137/272) 42.6, 58.2	21.7 (497/2,293) 19.5, 23.9
Prior Response					
Relapse	67.7 (203/300)	59.6 (121/203) 50.7, 68.5	58.1 (200/344)	52.5 (105/200) 43.4, 61.6	37.7 (243/645) 32.8, 42.6
Genotype 1/4	59.7 (129/216)	51.2 (66/129) 39.8, 62.5	48.6 (122/251)	44.3 (54/122) 32.7, 55.8	28.6 (134/468) 23.3, 34.0

Genotype 2/3	88.9 (72/81)	73.6 (53/72) (60.2, 87.0)	83.7 (77/92)	64.9 (50/77) 50.9, 78.9	61.3 (106/173) 51.7, 70.8
NR	28.6 (258/903)	57.0 (147/258) 49.0, 64.9	12.4 (59/476)	44.1 (26/59) 27.4, 60.7	13.6 (188/1,385) 11.2, 15.9
Genotype 1/4	23.0 (182/790)	51.6 (94/182) 42.1, 61.2	9.9 (44/446)	38.6 (17/44) 19.7, 57.5	9.9 (123/1,242) 7.7, 12.1
Genotype 2/3	67.9 (74/109)	70.3 (52/74) 56.6, 84.0	53.6 (15/28)	60.0 (9/15) 27.4, 92.6	46.0 (63/137) 35.0, 57.0
Genotype					
1	30.2 (343/1,135)	51.3 (176/343) 44.4, 58.3	23.0 (162/704)	42.6 (69/162) 32.6, 52.6	14.6 (270/1,846) 12.5, 16.7
2/3	77.1 (185/240)	73.0 (135/185) 64.6, 81.4	75.6 (96/127)	63.5 (61/96) 50.9, 76.2	55.3 (203/367) 48.6, 62.0
4	42.5 (17/40)	70.6 (12/17) 42.1, 99.1	44.4 (12/27)	50.0 (6/12) 12.8, 87.2	28.4 (19/67) 14.2, 42.5
METAVIR Fibrosis score					
F2	46.0 (193/420)	66.8 (129/193) 58.1, 75.6	33.6 (78/232)	57.7 (45/78) 43.3, 72.1	29.2 (191/653) 24.7, 33.8
F3	38.0 (163/429)	62.6 (102/163) 52.8, 72.3	32.4 (78/241)	51.3 (40/78) 36.7, 65.9	21.9 (147/672) 17.8, 26.0
F4	33.6 (192/572)	49.5 (95/192) 40.2, 58.8	29.7 (116/390)	44.8 (52/116) 32.9, 56.7	16.5 (159/966) 13.4, 19.5
Baseline Viral Load					
HVL (>600,000 IU/ml)	32.4 (280/864)	56.1 (157/280) 48.4, 63.7	26.5 (152/573)	41.4 (63/152) 31.2, 51.7	16.6 (239/1,441) 14.1, 19.1
LVL (≤600,000 IU/ml)	48.3 (269/557)	62.8 (169/269) 55.2, 70.4	41.0 (118/288)	61.0 (72/118) 49.5, 72.6	30.2 (256/848) 26.1, 34.2

NR: Non-responder defined as serum/plasma HCV-RNA positive at the end of a minimum of 12 weeks of treatment.
Plasma HCV-RNA is measured with a research-based quantitative polymerase chain reaction assay by a central Laboratory
*Intent to treat population includes 7 patients for whom at least 12 weeks of prior therapy could not be confirmed.

Overall, approximately 36 % (821/2,286) of patients 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. For patients with prior failure on therapy with nonpegylated interferon or pegylated interferon and negative at week 12, the sustained response rates were 59 % and 50 %, respectively. Among 480 patients with > 2 log viral reduction but detectable virus at week 12, altogether 188 patients continued therapy. In those patients the SVR was 12 %.

Non-responders to prior therapy with pegylated interferon alpha/ribavirin were less likely to achieve a week 12 response to retreatment than non-responders to nonpegylated interferon alpha/ribavirin (12.4 % vs. 28.6 %). However, if a week 12 response was achieved, there was little difference in SVR regardless of prior treatment or prior response.

Long-term efficacy data

A large long-term follow-up study enrolled 567 patients after treatment in a prior study with PegIntron (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 3 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: 98-100 %). SVR after treatment of chronic HCV with PegIntron (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).

5.2 Pharmacokinetic properties

PegIntron is a well characterized polyethylene glycol-modified ("pegylated") derivative of interferon alfa-2b and is predominantly composed of monopegylated species. The plasma half-life of PegIntron is prolonged compared with nonpegylated interferon alfa-2b. PegIntron has a potential to depegylate to free interferon alfa-2b. The biologic activity of the 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.

PegIntron 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 biologic activity as measured by a bioassay.

Mean (SD) PegIntron 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 PegIntron apparent clearance.

Renal impairment
Renal clearance appears to account for 30 % of total clearance of PegIntron. 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.

Following multiple dosing of Pegintron (1.0 microgram/kg subcutaneously administered every week for four weeks) the clearance of Pegintron is reduced by a mean of 17 % in patients with moderate renal impairment (creatinine clearance 30-49 ml/minute) and by a mean of 44 % in patients with severe renal impairment (creatinine clearance 15-29 ml/minute) compared to subjects with normal renal function. Based on single dose data, clearance was similar in patients with severe renal impairment not on dialysis and in patients who were receiving hemodialysis. The dose of Pegintron for monotherapy should be reduced in patients with moderate or severe renal impairment (see sections 4.2 and 4.4). Patients with creatinine clearance < 50 ml/minute must not be treated with PegIntron in combination with ribavirin (bitherapy or tritherapy) (see section 4.3).

Because of marked inter-subject variability in interferon pharmacokinetics, it is recommended that patients with severe renal impairment be closely monitored during treatment with PegIntron (see section 4.2)

Hepatic impairment
The pharmacokinetics of PegIntron have not been evaluated in patients with severe hepatic dysfunction.

Elderly (≥ 65 years of age)
The pharmacokinetics of PegIntron following a single subcutaneous dose of 1.0 microgram/kg were not affected by age. The data suggest that no alteration in PegIntron dosage is necessary based on advancing age.

Interferon neutralising factors
Interferon neutralising factor assays were performed on serum samples of patients who received PegIntron in the clinical trial. Interferon neutralising factors are antibodies which neutralise the antiviral activity of interferon. The clinical incidence of neutralising factors in patients who received PegIntron 0.5 micrograms/kg is 1.1 %.

Transfer into seminal fluid
Seminal transfer of ribavirin has been studied. Ribavirin concentration in seminal fluid is approximately two-fold higher compared to serum. However, ribavirin systemic exposure of a female

partner after sexual intercourse with a treated patient has been estimated and remains extremely limited compared to therapeutic plasma concentration of ribavirin.

5.3 Preclinical safety data

PegIntron:
Adverse events not observed in clinical trials were not seen in toxicity studies in monkeys. These studies were limited to four weeks due to the appearance of anti-interferon antibodies in most monkeys.

Reproduction studies of PegIntron have not been performed. Interferon alfa-2b has been shown to be an abortifacient in primates. PegIntron is likely to also cause this effect. Effects on fertility have not been determined. It is not known whether the components of this medicinal product are excreted into experimental animal or human milk (see section 4.6 for relevant human data on pregnancy and lactation). PegIntron showed no genotoxic potential.

The relative non-toxicity of monomethoxy-polyethylene glycol (mPEG), which is liberated from PegIntron by metabolism *in vivo* has been demonstrated in preclinical acute and subchronic toxicity studies in rodents and monkeys, standard embryo-foetal development studies and in *in vitro* mutagenicity assays.

PegIntron plus ribavirin:
When used in combination with ribavirin, PegIntron did not cause any effects not previously seen with either active substance alone. The major treatment-related change was a reversible, mild to moderate anaemia, the severity of which was greater than that produced by either active substance alone.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Powder
Sodium phosphate dibasic anhydrous, sodium phosphate monobasic dihydrate, sucrose and polysorbate 80.
Solvent
Water for injections.

Deliverable volume from pen = 0.5 ml. An overfill is also included for proper dispensing from the pen delivery system.

6.2 Incompatibilities

This medicinal product should only be reconstituted with the solvent provided (see section 6.6). In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products.

6.3 Shelf life

Before reconstitution
36 months.

After reconstitution
- Chemical and physical in-use stability has been demonstrated for 24 hours at 2°C - 8ºC.
- From a microbiological point of view, the 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 2°C - 8°C.

6.4 Special precautions for storage

Store in a refrigerator (2°C - 8°C). Do not freeze.

For storage conditions of the reconstituted medicinal product, see section 6.3.

MSD

6.5 Nature and contents of container

The powder and solvent are both contained in a two-chamber cartridge (Type I flint glass) separated by a bromobutyl rubber plunger. The cartridge is sealed at one end with a polypropylene cap containing a bromobutyl rubber liner and at the other end by a bromobutyl rubber plunger.

PegIntron 80, 100, 120, 150 micrograms are supplied as:
- 1 pen containing powder and solvent for solution for injection, 1 injection needle and 2 cleansing swabs.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

PegIntron pre-filled pen is to be removed from the refrigerator before administration to allow the solvent to reach room temperature (not more than 25°C).
Each pre-filled pen is reconstituted with the solvent provided in the two-chamber cartridge (water for injections) for administration of up to 0.5 ml of solution. A small volume is lost during preparation of PegIntron for injection when the dose is measured and injected. Therefore, each pre-filled pen contains an excess amount of solvent and PegIntron powder to ensure delivery of the labelled dose in 0.5 ml of PegIntron, solution for injection. The reconstituted solution has a concentration of 80, 100, 120, 150 micrograms in 0.5 ml.

PegIntron is injected subcutaneously after reconstituting the powder as instructed, attaching an injection needle and setting the prescribed dose. A complete and illustrated set of instructions is provided in the Annex to the Package Leaflet.

As for all parenteral medicinal products, the reconstituted solution is to be inspected visually prior to administration. The reconstituted solution should be clear and colourless. If discolouration or particulate matter is present, the reconstituted solution should not be used. After administering the dose, the PegIntron pre-filled pen and any unused solution contained in it is to be discarded..

7. MANUFACTURER:

Schering-Plough Labo N.V., Heist- op-den-Berg, Belgium.

8. LICENSE HOLDER:

Merck Sharp & Dohme (Israel-1996) Company Ltd., P.O.B. 7121, Petah-Tikva 49170.

9. LICENSE No.

PegIntron pre-filled pen 80mcg	130.34.30856.00
PegIntron pre-filled pen 100mcg	130.35.30857.00
PegIntron pre-filled pen 120mcg	130.36.30858.00
PegIntron pre-filled pen 150mcg	130.37.30859.00

The format of this leaflet was determined by the Ministry of Health and its content was checked and approved in March 2016.