ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

PegIntron 50 micrograms powder and solvent for solution for injection
PegIntron 80 micrograms powder and solvent for solution for injection
PegIntron 100 micrograms powder and solvent for solution for injection
PegIntron 120 micrograms powder and solvent for solution for injection
PegIntron 150 micrograms powder and solvent for solution for injection

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

PegIntron 50 micrograms powder and solvent for solution for injection
Each vial contains 50 micrograms of peginterferon alfa-2b as measured on a protein basis.
Each vial provides 50 micrograms/0.5 ml of peginterferon alfa-2b when reconstituted as recommended.

PegIntron 80 micrograms powder and solvent for solution for injection
Each vial contains 80 micrograms of peginterferon alfa-2b as measured on a protein basis.
Each vial provides 80 micrograms/0.5 ml of peginterferon alfa-2b when reconstituted as recommended.

PegIntron 100 micrograms powder and solvent for solution for injection
Each vial contains 100 micrograms of peginterferon alfa-2b as measured on a protein basis.
Each vial provides 100 micrograms/0.5 ml of peginterferon alfa-2b when reconstituted as recommended.

PegIntron 120 micrograms powder and solvent for solution for injection
Each vial contains 120 micrograms of peginterferon alfa-2b as measured on a protein basis.
Each vial provides 120 micrograms/0.5 ml of peginterferon alfa-2b when reconstituted as recommended.

PegIntron 150 micrograms powder and solvent for solution for injection
Each vial contains 150 micrograms of peginterferon alfa-2b as measured on a protein basis.
Each vial provides 150 micrograms/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 vial 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.

White powder.
Clear and colourless solvent.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Adults (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 Summary of Product Characteristics (SmPCs) when PegIntron is to be used in combination with these medicines.

Adults (bitherapy and monotherapy)
PegIntron is indicated for the treatment of adult patients (18 years of age and older) with CHC who are positive for hepatitis C virus RNA (HCV-RNA), including patients with compensated cirrhosis and/or co-infected with clinically stable HIV (see section 4.4).

PegIntron in combination with ribavirin (bitherapy) is indicated for the treatment of CHC infection in adult patients who are previously untreated including patients with clinically stable HIV co-infection and in adult 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 SmPC when PegIntron is to be used in combination with ribavirin.

Paediatric population (bitherapy)
PegIntron is indicated in a combination regimen with ribavirin for the treatment of children 3 years of age and older and adolescents, who have chronic hepatitis C, previously untreated, without liver decompensation, and who are positive for HCV-RNA.

When deciding not to defer treatment until adulthood, it is important to consider that the combination therapy induced a growth inhibition that may be irreversible in some patients. The decision to treat should be made on a case by case basis (see section 4.4).

Please refer to the ribavirin SmPC for capsules or oral solution 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.

Posology
PegIntron should be administered as a once weekly subcutaneous injection. The dose administered in adults 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 and paediatric patients 3 years of age and older.

Tritherapy (PegIntron with ribavirin and boceprevir): applies to adult patients with genotype 1 CHC.

Adults – 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 ribavirin 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
* Refer to the SmPC of boceprevir for details about the dose of boceprevir to be administered in tritherapy.

Adults - Duration of treatment – Naïve patients
Tritherapy: Refer to the SmPC 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.

Adults - 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 bitherapy.

Adults - Duration of treatment - Retreatment
Tritherapy: Refer to the SmPC 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.

Paediatric population (bitherapy only) – Dose to be administered
Dosing for children 3 years of age and older and adolescent patients is determined by body surface area for PegIntron and by body weight for ribavirin. The recommended dose of PegIntron is 60 μg/m^2/week subcutaneously in combination with ribavirin 15 mg/kg/day orally in two divided doses with food (morning and evening).

Paediatric population (bitherapy only) - Duration of treatment

- Genotype 1:
  The recommended duration of treatment with bitherapy is 1 year. By extrapolation from clinical data on combination therapy with standard interferon in paediatric patients (negative predictive value 96 % for interferon alfa–2b/ribavirin), patients who fail to achieve virological response at 12 weeks are highly unlikely to become sustained virological responders. Therefore, it is recommended that children and adolescent patients receiving PegIntron/ribavirin combination be discontinued from therapy if their week 12 HCV-RNA dropped < 2 $\log_{10}$ compared to pretreatment or if they have detectable HCV-RNA at treatment week 24.
- Genotype 2 or 3:
  The recommended duration of treatment with bitherapy is 24 weeks.
- Genotype 4:
  Only 5 children and adolescents with Genotype 4 were treated in the PegIntron/ribavirin clinical trial. The recommended duration of treatment with bitherapy is 1 year. It is recommended that children and adolescent patients receiving PegIntron/ribavirin combination be discontinued from therapy if their week 12 HCV-RNA dropped < 2 $\log_{10}$ compared to pretreatment or if they have detectable HCV-RNA at treatment week 24.

PegIntron monotherapy – Adults
Dose to be administered
As monotherapy the PegIntron regimen is 0.5 or 1.0 μg/kg/week. The lowest PegIntron strength available is 50 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 alternative 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/0.5 ml)**	**Administer once weekly (ml)**	**PegIntron strength (μg/0.5 ml)**	**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
107-120**	80	0.4	120	0.5

Minimum delivery for pen is 0.2 ml.
* Must use vial.
** 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
Adults: Haemoglobin in Patients with history of stable cardiac disease Children and adolescents: not applicable	≥ 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 (adults) ≥ 50 x 10^9/l, and <70 x 10^9/l (children and adolescents)	< 25 x 10^9/l (adults) < 50 x 10^9/l (children and adolescents)
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

Laboratory values	Reduce only ribavirin daily dose (see note 1) if:	Reduce only PegIntron dose (see note 2) if:	Discontinue combination therapy if:
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.
In children and adolescent patients 1st dose reduction of ribavirin is to 12 mg/kg/day, 2nd dose reduction of ribavirin is to 8 mg/kg/day.

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.
In children and adolescent patients 1st dose reduction of PegIntron is to 40 µg/m^2/week, 2nd dose reduction of PegIntron is to 20 µg/m^2/week.

Dose reduction of PegIntron in adults may be accomplished by reducing the prescribed volume or by utilizing a lower dose strength as shown in **Table 2b**. Dose reduction of PegIntron in children and adolescents is accomplished by modifying the recommended dose in a two-step process from the original starting dose of 60 µg/m^2/week, to 40 µg/m^2/week, then to 20 µg/m^2/week, if needed.

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

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	80	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

PegIntron monotherapy dose reduction guidelines in adults

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

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

Laboratory values	Reduce PegIntron to one-half dose if:	Discontinue PegIntron if:
Neutrophils	$\geq 0.5 \times 10^9$/l, and $< 0.75 \times 10^9$/l	$< 0.5 \times 10^9$/l
Platelets	$\geq 25 \times 10^9$/l, and $< 50 \times 10^9$/l	$< 25 \times 10^9$/l

For adult 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 in adults

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	25	0.25
107-120**	80	32	0.2

Minimum delivery for pen is 0.2 ml.
* Must use vial.
** 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 adult 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 3c**.

Table 3c Reduced PegIntron dose (0.5 µg/kg) for the 1.0 µg/kg monotherapy regimen in adults

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 0.2 ml.
* Must use vial.
** 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 SmPC). 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).

Paediatric population

PegIntron can be used in combination with ribavirin in paediatric patients 3 years of age and older.

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.

Paediatric population

- Existence of, or history of severe psychiatric condition, particularly severe depression, suicidal ideation or suicidal attempt.

Combination therapy

Also see SmPCs 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 adult patients with existence of history of severe psychiatric conditions, this should only be initiated after having ensured appropriate individualised diagnostic and therapeutic management of the psychiatric condition.
- The use of PegIntron in children and adolescents with existence of or history of severe psychiatric conditions is contraindicated (see section 4.3). Among children and adolescents treated with interferon alfa-2b in combination with ribavirin, suicidal ideation or attempts were reported more frequently compared to adult patients (2.4 % vs 1 %) during treatment and during the 6-month follow-up after treatment. As in adult patients, children and adolescents experienced other psychiatric adverse events (e.g. depression, emotional lability, and somnolence).

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.

Growth and development (children and adolescents)
During the course of therapy lasting up to 48 weeks in patients ages 3 through 17 years, weight loss and growth inhibition were common. Long-term data available in children treated with the combination therapy of pegylated interferon/ribavirin are indicative of substantial growth retardation. Thirty two percent (20/94) of subjects demonstrated > 15 percentile decrease in height-for-age percentile 5 years after completion of therapy (see sections 4.8 and 5.1).

Case by case benefit/risk assessment in children
The expected benefit of treatment should be carefully weighed against the safety findings observed for children and adolescents in the clinical trials (see sections 4.8 and 5.1).
- It is important to consider that the combination therapy induced a growth inhibition, that resulted in reduced height in some patients.
- This risk should be weighed against the disease characteristics of the child, such as evidence of disease progression (notably fibrosis), co-morbidities that may negatively influence the disease progression (such as HIV co-infection), as well as prognostic factors of response (HCV genotype and viral load).

Whenever possible the child should be treated after the pubertal growth spurt, in order to reduce the risk of growth inhibition. Although data are limited, no evidence of long-term effects on sexual maturation was noted in the 5-year observational follow-up study.

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, adult 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. There are no data in children or adolescents with a history of cardiac disease.

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 section 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, retinal exudates, 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, adult patients treated for chronic hepatitis C with interferon alpha have developed thyroid abnormalities, either hypothyroidism or hyperthyroidism. Approximately 21 % of children treated with PegIntron/ribavirin combination therapy developed increase in thyroid stimulating hormone (TSH). Another approximately 2 % had a transient decrease below the lower limit of normal. Prior to initiation of 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 medicine. Children and adolescents should be monitored every 3 months for evidence of thyroid dysfunction (e.g. TSH).

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 SmPC).

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 SmPCs 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.

HCV/HBV Coinfection
Cases of hepatitis B re-activation (some with severe consequences) have been reported in patients co-infected with hepatitis B and C viruses treated with interferon. The frequency of such re-activation appears to be low.
All patients should be screened for hepatitis B before starting treatment with interferon for hepatitis C. patients co-infected with hepatitis B and C must then be monitored and managed according to current clinical guidelines.

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 indicate 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

Interaction studies have only been performed in adults.

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 sections 4.3, 4.4 and 4.5 of the 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**).

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)

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)
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 thioridazine should be referred to when co-administering with the product (PegIntron)	Metabolism of thioridazine is suppressed by inhibitory action of the product (PegIntron) on CYP2D6.
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.

Medicines	Signs, Symptoms, and Treatment	Mechanism and Risk Factors
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 SmPC).

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 SmPC).

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.

4.8 Undesirable effects

Adults
Tritherapy
Refer to the SmPC 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 in adults, 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 decreased, 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 adults 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 adults in clinical trials or through post-marketing surveillance in patients treated with peginterferon 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
Not known:	Hepatitis B reactivation in HCV/HBV co-infected patients

Blood and lymphatic system disorders	
Very common:	Anaemia, neutropenia
Common:	Haemolytic anaemia, leukopenia, thrombocytopenia, 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 attempt, 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, neuropathy peripheral
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 occlusion, retinal vein occlusion, optic neuritis, papilloedema, macular oedema
Not known:	Serous retinal detachment
Ear and labyrinth disorders	
Common:	Hearing impaired/loss, tinnitus, vertigo

Uncommon	Ear pain
Cardiac disorders	
Common:	Palpitations, 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, 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, haemorrhoids, 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, 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 in adults
Most cases of neutropenia and thrombocytopenia 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 occlusion, retinal exudates, 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 < 9.4 g/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 SmPCs 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.

Paediatric population
Summary of the safety profile
In a clinical trial with 107 children and adolescent patients (3 to 17 years of age) treated with combination therapy of PegIntron and ribavirin, dose modifications were required in 25 % of patients, most commonly for anaemia, neutropenia and weight loss. In general, the adverse reactions profile in children and adolescents was similar to that observed in adults, although there is a paediatric-specific concern regarding growth inhibition. During combination therapy for up to 48 weeks with PegIntron and ribavirin, growth inhibition was observed that resulted in reduced height in some patients (see section 4.4). Weight loss and growth inhibition were very common during the treatment (at the end of treatment, mean decrease from baseline in weight and height percentile were of 17 percentiles and 8 percentiles, respectively) and growth velocity was inhibited (< 3rd percentile in 70 % of the patients).

At the end of 24 weeks post-treatment follow-up, mean decrease from baseline in weight and height percentiles were still of 3 percentiles and 7 percentiles respectively, and 20 % of the children continued to have inhibited growth (growth velocity < 3rd percentile). Ninety-four of 107 subjects enrolled in the 5 year long-term follow-up trial. The effects on growth were less in those subjects treated for 24 weeks than those treated for 48 weeks. From pre-treatment to end of long-term follow-up among subjects treated for 24 or 48 weeks, height-for-age percentiles decreased 1.3 and 9.0 percentiles, respectively. Twenty-four percent of subjects (11/46) treated for 24 weeks and 40 % of subjects (19/48) treated for 48 weeks had a > 15 percentile height-for-age decrease from pre-treatment to the end of the 5 year long-term follow-up compared to pre-treatment baseline percentile. Eleven percent of subjects (5/46) treated for 24 weeks and 13 % of subjects (6/48) treated for 48 weeks were observed to have a decrease from pre-treatment baseline of > 30 height-for-age percentiles to the end of the 5 year long-term follow-up. For weight, pre-treatment to end of long-term follow-up, weight-for-age percentiles decreased 1.3 and 5.5 percentiles among subjects treated for 24 weeks or 48 weeks, respectively. For BMI, pre-treatment to end of long-term follow-up, BMI-for-age percentiles decreased 1.6 and 7.5 percentiles among subjects treated for 24 weeks or 48 weeks, respectively. Decrease in mean height percentile at year 1 of long-term follow-up was most prominent in prepubertal age children. The decline of height, weight and BMI Z scores observed during the treatment phase in comparison to a normative population did not fully recover at the end of long-term follow-up period for children treated with 48 weeks of therapy (see section 4.4).

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

Tabulated summary of adverse reactions
The following treatment-related adverse reactions were reported in the study in children and adolescent patients treated with PegIntron in combination with ribavirin. These reactions are listed in **Table 7** 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, adverse reactions are presented in order of decreasing seriousness.

Table 7 Adverse reactions very commonly, commonly and uncommonly reported in the clinical trial in children and adolescent patients treated with PegIntron in combination with ribavirin

Infections and infestations	
Common:	Fungal infection, influenza, oral herpes, otitis media, pharyngitis streptococcal, nasopharyngitis, sinusitis
Uncommon:	Pneumonia, ascariasis, enterobiasis, herpes zoster, cellulitis, urinary tract infection, gastroenteritis
Blood and lymphatic system disorders	
Very common:	Anaemia, leucopenia, neutropenia
Common:	Thrombocytopenia, lymphadenopathy
Endocrine disorders	
Common:	Hypothyroidism
Metabolism and nutrition disorders	
Very common:	Anorexia, decreased appetite
Psychiatric disorders	
Common:	Suicidal ideation[§], suicide attempt[§], depression, aggression, affect lability, anger, agitation, anxiety, mood altered, restlessness, nervousness, insomnia
Uncommon:	Abnormal behaviour, depressed mood, emotional disorder, fear, nightmare
Nervous system disorders	
Very common:	Headache, dizziness
Common:	Dysgeusia, syncope, disturbance in attention, somnolence, poor quality sleep
Uncommon:	Neuralgia, lethargy, paraesthesia, hypoaesthesia, psychomotor hyperactivity, tremor
Eye disorders	
Common:	Eye pain
Uncommon:	Conjunctival haemorrhage, eye pruritus, keratitis, vision blurred, photophobia
Ear and labyrinth disorders	
Common:	Vertigo
Cardiac disorders	
Common:	Palpitations, tachycardia
Vascular disorders	
Common:	Flushing
Uncommon:	Hypotension, pallor
Respiratory, thoracic and mediastinal disorders	
Common:	Cough, epistaxis, pharyngolaryngeal pain
Uncommon:	Wheezing, nasal discomfort, rhinorrhoea
Gastrointestinal disorders	
Very common:	Abdominal pain, abdominal pain upper, vomiting, nausea
Common:	Diarrhoea, aphthous stomatitis, cheilosis, mouth ulceration, stomach discomfort, oral pain

Uncommon:	Dyspepsia, gingivitis
Hepatobiliary disorders	
Uncommon:	Hepatomegaly
Skin and subcutaneous tissue disorders	
Very common:	Alopecia, dry skin
Common:	Pruritus, rash, rash erythematous, eczema, acne, erythema
Uncommon:	Photosensitivity reaction, rash maculo-papular, skin exfoliation, pigmentation disorder, dermatitis atopic, skin discolouration
Musculoskeletal and connective tissue disorders	
Very common:	Myalgia, arthralgia
Common:	Musculoskeletal pain, pain in extremity, back pain
Uncommon:	Muscle contracture, muscle twitching
Renal and urinary disorders	
Uncommon:	Proteinuria
Reproductive system and breast disorders	
Uncommon:	Female: Dysmenorrhoea
General disorders and administration site conditions	
Very common:	Injection site erythema, fatigue, pyrexia, rigors, influenza-like illness, asthenia, pain, malaise, irritability
Common:	Injection site reaction, injection site pruritus, injection site rash injection site dryness, injection site pain, feeling cold
Uncommon:	Chest pain, chest discomfort, facial pain
Investigations	
Very common:	Growth rate decrease (height and/or weight decrease for age)
Common:	Blood thyroid stimulating hormone increased, thyroglobulin increased
Uncommon:	Anti-thyroid antibody positive
Injury and poisoning	
Uncommon:	Contusion

[§]class effect of interferon-alfa containing products – reported with standard interferon therapy in adult and paediatric patients; with PegIntron reported in adult patients.

Description of selected adverse reactions in children and adolescents
Most of the changes in laboratory values in the PegIntron/ribavirin clinical trial were mild or moderate. Decreases in haemoglobin, white blood cells, platelets, neutrophils and increase in bilirubin may require dose reduction or permanent discontinuation from therapy (see section 4.2). While changes in laboratory values were observed in some patients treated with PegIntron used in combination with ribavirin in the clinical trial, values returned to baseline levels within a few weeks after the end of therapy.

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. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

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 3.0 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 – Adults
Bitherapy with PegIntron, ribavirin and boceprevir
Refer to the SmPC 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 8**).

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 8**), particularly in patients infected with Genotype 1 (**Table 9**). 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 9**), while response rates in patients that received > 13.2 mg/kg ribavirin were even higher.

Table 8 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 microgram/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 9 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 %

HCV Genotype	Ribavirin dose (mg/kg)	P 1.5/R	P 0.5/R	I/R
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 micrograms/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 10**). Twenty-four % had bridging fibrosis or cirrhosis (Knodell 3/4).

Table 10 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 11**).

Table 11 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 12**).

Table 12 Predictive value of on-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)

	Negative			Positive		
	No response at treatment week	No sustained response	Negative predictive value	Response at treatment week	Sustained response	Positive predictive value
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 < 2log$_{10}$ decrease from baseline, patients to stop therapy. If week 12 HCV-RNA is positive and decreased ≥ 2log$_{10}$ 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 13.** 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 co-infected 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.

Table 13 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.

[1]Carrat 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 HCV-RNA after 12 weeks of treatment. Sustained Virologic Response (SVR) is defined as undetectable HCV-RNA at 24 weeks post-treatment (**Table 14***)*.

Table 14 Rates of response to retreatment in prior treatment failures

	Patients with undetectable HCV–RNA at treatment week 12 and SVR upon retreatment				
	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 (245/645) 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) 24.3, 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, 78.2	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) 64.2, 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-Adults
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).

Clinical efficacy and safety – paediatric population
Children and adolescents 3 to 17 years of age with compensated chronic hepatitis C and detectable HCV-RNA were enrolled in a multicentre trial and treated with ribavirin 15 mg/kg per day plus PegIntron 60 μg/m^2 once weekly for 24 or 48 weeks, based on HCV genotype and baseline viral load. All patients were to be followed for 24 weeks post-treatment. A total of 107 patients received treatment of whom 52 % were female, 89 % Caucasian, 67 % with HCV Genotype 1 and 63 % < 12 years of age. The population enrolled mainly consisted of children with mild to moderate hepatitis C. Due to the lack of data in children with severe progression of the disease, and the potential for undesirable effects**,** the benefit/risk of the combination of PegIntron with ribavirin needs to be carefully considered in this population (see sections 4.1, 4.4 and 4.8). The study results are summarized in **Table 15**.

Table 15 Sustained virological response rates (n[a,b] (%)) in previously untreated children and adolescents by genotype and treatment duration – All subjects n = 107

	24 weeks	48 weeks
All Genotypes	26/27 (96 %)	44/80 (55 %)
Genotype 1	-	38/72 (53 %)
Genotype 2	14/15 (93 %)	-
Genotype 3[c]	12/12 (100 %)	2/3 (67 %)
Genotype 4	-	4/5 (80 %)

a: Response to treatment was defined as undetectable HCV-RNA at 24 weeks post-treatment lower limit of detection=125IU/ml
b: n = number of responders/number of subjects with given genotype, and assigned treatment duration.
c: Patients with genotype 3 low viral load (< 600,000 IU/ml) were to receive 24 weeks of treatment while those with genotype 3 and high viral load (≥ 600,000 IU/ml) were to receive 48 weeks of treatment.

Long-term efficacy data - paediatric population
A five-year long-term, observational, follow-up study enrolled 94 paediatric chronic hepatitis C patients after treatment in a multicentre trial. Of these, sixty-three were sustained responders. The purpose of the study was to annually evaluate the durability of sustained virologic response (SVR) and assess the impact of continued viral negativity on clinical outcomes for patients who were sustained responders 24 weeks post-treatment with 24 or 48 weeks of peginterferon alfa-2b and ribavirin

treatment. At the end of 5 years, 85 % (80/94) of all enrolled subjects and 86 % (54/63) of sustained responders completed the study. No paediatric subjects with SVR had relapsed during the 5 years of follow-up.

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.

Paediatric population
Multiple-dose pharmacokinetic properties for PegIntron and ribavirin (capsules and oral solution) in children and adolescent patients with chronic hepatitis C have been evaluated during a clinical study.

In children and adolescent patients receiving body surface area-adjusted dosing of PegIntron at 60 μg/m^2/week, the log transformed ratio estimate of exposure during the dosing interval is predicted to be 58 % (90 % CI: 141-177 %) higher than observed in adults receiving 1.5 μg/kg/week.

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.

No studies have been conducted in juvenile animals to examine the effects of treatment with PegIntron on growth, development, sexual maturation, and behaviour. Preclinical juvenile toxicity results have demonstrated a minor, dose-related decrease in overall growth in neonatal rats dosed with ribavirin (see section 5.3 of Rebetol SmPC if PegIntron is to be administered in combination with ribavirin).

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Powder
Disodium phosphate, anhydrous
Sodium dihydrogen phosphate dihydrate
Sucrose
Polysorbate 80

Solvent
Water for injections

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
3 years.

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).

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

6.5 Nature and contents of container

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

PegIntron is supplied as:
- 1 vial of powder for solution for injection and 1 ampoule of solvent for parenteral use;
- 1 vial of powder for solution for injection, 1 ampoule of solvent for parenteral use, 1 injection syringe, 2 injection needles and 1 cleansing swab;
- 4 vials of powder for solution for injection and 4 ampoules of solvent for parenteral use;
- 4 vials of powder for solution for injection, 4 ampoules of solvent for parenteral use, 4 injection syringes, 8 injection needles and 4 cleansing swabs;
- 6 vials of powder for solution for injection and 6 ampoules of solvent for parenteral use.
- 12 vials of powder for solution for injection, 12 ampoules of solvent for parenteral use, 12 injection syringes, 24 injection needles and 12 cleansing swabs.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

PegIntron 50 micrograms powder and solvent for solution for injection
Each vial is to be reconstituted with 0.7 ml of 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 vial 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 50 micrograms/0.5 ml.

PegIntron 80 micrograms powder and solvent for solution for injection
Each vial is to be reconstituted with 0.7 ml of 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 vial 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 micrograms/0.5 ml.

PegIntron 100 micrograms powder and solvent for solution for injection
Each vial is to be reconstituted with 0.7 ml of 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 vial 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 100 micrograms/0.5 ml.

PegIntron 120 micrograms powder and solvent for solution for injection
Each vial is to be reconstituted with 0.7 ml of 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 vial 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 120 micrograms/0.5 ml.

PegIntron 150 micrograms powder and solvent for solution for injection
Each vial is to be reconstituted with 0.7 ml of 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 vial 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 150 micrograms/0.5 ml.

Using a sterilised injection syringe and injection needle, 0.7 ml of water for injections is injected into the vial of PegIntron. Dissolution of powder is completed by agitating it gently. The appropriate dose can then be withdrawn with a sterilised injection syringe and injected. A complete 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. Any unused material is to be discarded.

7. MARKETING AUTHORISATION HOLDER

Merck Sharp & Dohme B.V.
Waarderweg 39
2031 BN Haarlem
The Netherlands

8. MARKETING AUTHORISATION NUMBERS

PegIntron 50 micrograms powder and solvent for solution for injection
EU/1/00/131/001
EU/1/00/131/002
EU/1/00/131/003
EU/1/00/131/004
EU/1/00/131/005
EU/1/00/131/026

PegIntron 80 micrograms powder and solvent for solution for injection
EU/1/00/131/006
EU/1/00/131/007
EU/1/00/131/008
EU/1/00/131/009
EU/1/00/131/010
EU/1/00/131/027

PegIntron 100 micrograms powder and solvent for solution for injection
EU/1/00/131/011
EU/1/00/131/012
EU/1/00/131/013
EU/1/00/131/014
EU/1/00/131/015
EU/1/00/131/028

PegIntron 120 micrograms powder and solvent for solution for injection
EU/1/00/131/016
EU/1/00/131/017
EU/1/00/131/018
EU/1/00/131/019
EU/1/00/131/020
EU/1/00/131/029

PegIntron 150 micrograms powder and solvent for solution for injection
EU/1/00/131/021
EU/1/00/131/022
EU/1/00/131/023
EU/1/00/131/024
EU/1/00/131/025
EU/1/00/131/030

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 25 May 2000
Date of latest renewal: 25 May 2010

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the web-site of the European Medicines Agency http://www.ema.europa.eu.

1. NAME OF THE MEDICINAL PRODUCT

PegIntron 50 micrograms powder and solvent for solution for injection in pre-filled pen
PegIntron 80 micrograms powder and solvent for solution for injection in pre-filled pen
PegIntron 100 micrograms powder and solvent for solution for injection in pre-filled pen
PegIntron 120 micrograms powder and solvent for solution for injection in pre-filled pen
PegIntron 150 micrograms powder and solvent for solution for injection in pre-filled pen

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

PegIntron 50 micrograms powder and solvent for solution for injection in pre-filled pen
Each pre-filled pen contains 50 micrograms of peginterferon alfa-2b as measured on a protein basis.
Each pre-filled pen provides 50 micrograms/0.5 ml of peginterferon alfa-2b when reconstituted as recommended.

PegIntron 80 micrograms powder and solvent for solution for injection in pre-filled pen
Each pre-filled pen contains 80 micrograms of peginterferon alfa-2b as measured on a protein basis.
Each pre-filled pen provides 80 micrograms/0.5 ml of peginterferon alfa-2b when reconstituted as recommended.

PegIntron 100 micrograms powder and solvent for solution for injection in pre-filled pen
Each pre-filled pen contains 100 micrograms of peginterferon alfa-2b as measured on a protein basis.
Each pre-filled pen provides 100 micrograms/0.5 ml of peginterferon alfa-2b when reconstituted as recommended.

PegIntron 120 micrograms powder and solvent for solution for injection in pre-filled pen
Each pre-filled pen contains 120 micrograms of peginterferon alfa-2b as measured on a protein basis.
Each pre-filled pen provides 120 micrograms/0.5 ml of peginterferon alfa-2b when reconstituted as recommended.

PegIntron 150 micrograms powder and solvent for solution for injection in pre-filled pen
Each pre-filled pen contains 150 micrograms of peginterferon alfa-2b as measured on a protein basis.
Each pre-filled pen provides 150 micrograms/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

Adults (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 Summary of Product Characteristics (SmPCs) when PegIntron is to be used in combination with these medicines.

Adults (bitherapy and monotherapy)
PegIntron is indicated for the treatment of adult patients (18 years of age and older) with CHC who are positive for hepatitis C virus RNA (HCV-RNA), including patients with compensated cirrhosis and/or co-infected with clinically stable HIV (see section 4.4).

PegIntron in combination with ribavirin (bitherapy) is indicated for the treatment of CHC infection in adult patients who are previously untreated including patients with clinically stable HIV co-infection and in adult 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 SmPC when PegIntron is to be used in combination with ribavirin.

Paediatric population (bitherapy)
PegIntron is indicated in a combination regimen with ribavirin for the treatment of children 3 years of age and older and adolescents, who have chronic hepatitis C, previously untreated, without liver decompensation, and who are positive for HCV-RNA.

When deciding not to defer treatment until adulthood, it is important to consider that the combination therapy induced a growth inhibition that may be irreversible in some patients. The decision to treat should be made on a case by case basis (see section 4.4).

Please refer to the ribavirin SmPC for capsules or oral solution 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.

Posology
PegIntron should be administered as a once weekly subcutaneous injection. The dose administered in adults 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 and paediatric patients 3 years of age and older.
Tritherapy (PegIntron with ribavirin and boceprevir): applies to adult patients with genotype 1 CHC.

Adults – 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 ribavirin dose (mg)	Number of capsules (200 mg)
< 40	50	0.5	800	4
40-50	80	0.4	800	4
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
* Refer to the SmPC of boceprevir for details about the dose of boceprevir to be administered in tritherapy.

Adults - Duration of treatment – Naïve patients
Tritherapy: Refer to the SmPC 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.

Adults - 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 bitherapy.

Adults - Duration of treatment - Retreatment
Tritherapy: Refer to the SmPC 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.

Paediatric population (bitherapy only) – Dose to be administered
Dosing for children 3 years of age and older and adolescent patients is determined by body surface area for PegIntron and by body weight for ribavirin. The recommended dose of PegIntron is 60 µg/m^2/week subcutaneously in combination with ribavirin 15 mg/kg/day orally in two divided doses with food (morning and evening).

Paediatric population (bitherapy only) - Duration of treatment
- Genotype 1:
  The recommended duration of treatment with bitherapy is 1 year. By extrapolation from clinical data on combination therapy with standard interferon in paediatric patients (negative predictive value 96 % for interferon alfa–2b/ribavirin), patients who fail to achieve virological response at 12 weeks are highly unlikely to become sustained virological responders. Therefore, it is recommended that children and adolescent patients receiving PegIntron/ribavirin combination be discontinued from therapy if their week 12 HCV-RNA dropped < 2 $\log_{10}$ compared to pretreatment or if they have detectable HCV-RNA at treatment week 24.
- Genotype 2 or 3:
  The recommended duration of treatment with bitherapy is 24 weeks.
- Genotype 4:
  Only 5 children and adolescents with Genotype 4 were treated in the PegIntron/ribavirin clinical trial. The recommended duration of treatment with bitherapy is 1 year. It is recommended that children and adolescent patients receiving PegIntron/ribavirin combination be discontinued from therapy if their week 12 HCV-RNA dropped < 2 $\log_{10}$ compared to pretreatment or if they have detectable HCV-RNA at treatment week 24.

PegIntron monotherapy – Adults
Dose to be administered
As monotherapy the PegIntron regimen is 0.5 or 1.0 µg/kg/week. The lowest PegIntron strength available is 50 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/0.5 ml)**	**Administer once weekly (ml)**	**PegIntron strength (µg/0.5 ml)**	**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
107-120**	80	0.4	120	0.5

Minimum delivery for pen is 0.2 ml.

* Must use vial.

** 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
Adults: Haemoglobin in Patients with history of stable cardiac disease Children and adolescents: not applicable	≥ 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

Laboratory values	Reduce only ribavirin daily dose (see note 1) if:	Reduce only PegIntron dose (see note 2) if:	Discontinue combination therapy if:
Platelets	-	$\geq 25 \times 10^9$/l, and $< 50 \times 10^9$/l (adults) $\geq 50 \times 10^9$/l, and $<70 \times 10^9$/l (children and adolescents)	$< 25 \times 10^9$/l (adults) $< 50 \times 10^9$/l (children and adolescents)
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.
In children and adolescent patients 1st dose reduction of ribavirin is to 12 mg/kg/day, 2nd dose reduction of ribavirin is to 8 mg/kg/day.

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.
In children and adolescent patients 1st dose reduction of PegIntron is to 40 $\mu g/m^2$/week, 2nd dose reduction of PegIntron is to 20 $\mu g/m^2$/week.

Dose reduction of PegIntron in adults may be accomplished by reducing the prescribed volume or by utilizing a lower dose strength as shown in **Table 2b**. Dose reduction of PegIntron in children and adolescents is accomplished by modifying the recommended dose in a two-step process from the original starting dose of 60 $\mu g/m^2$/week, to 40 $\mu g/m^2$/week, then to 20 $\mu g/m^2$/week, if needed.

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

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

PegIntron monotherapy dose reduction guidelines in adults

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

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

Laboratory values	Reduce PegIntron to one-half dose if:	Discontinue PegIntron if:
Neutrophils	$\geq 0.5 \times 10^9$/l, and $< 0.75 \times 10^9$/l	$< 0.5 \times 10^9$/l
Platelets	$\geq 25 \times 10^9$/l, and $< 50 \times 10^9$/l	$< 25 \times 10^9$/l

For adult 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 in adults

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	25	0.25
107-120**	80	32	0.2

Minimum delivery for pen is 0.2 ml.

* Must use vial.

** 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 adult 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 3c**.

Table 3c Reduced PegIntron dose (0.5 µg/kg) for the 1.0 µg/kg monotherapy regimen in adults

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 0.2 ml.

* Must use vial.

** 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 SmPC). 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).

Paediatric population

PegIntron can be used in combination with ribavirin in paediatric patients 3 years of age and older.

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.

Paediatric population
- Existence of, or history of severe psychiatric condition, particularly severe depression, suicidal ideation or suicidal attempt.

Combination therapy
Also see SmPCs 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 adult 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.
- The use of PegIntron in children and adolescents with existence of or history of severe psychiatric conditions is contraindicated (see section 4.3). Among children and adolescents treated with interferon alfa-2b in combination with ribavirin, suicidal ideation or attempts were reported more frequently compared to adult patients (2.4 % vs 1 %) during treatment and during the 6-month follow-up after treatment. As in adult patients, children and adolescents experienced other psychiatric adverse events (e.g. depression, emotional lability, and somnolence).

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.

Growth and development (children and adolescents)
During the course of therapy lasting up to 48 weeks in patients ages 3 through 17 years, weight loss and growth inhibition were common. Long-term data available in children treated with the combination therapy of pegylated interferon/ribavirin are indicative of substantial growth retardation. Thirty two percent (30/94) of subjects demonstrated > 15 percentile decrease in height-for-age percentile 5 years after completion of therapy (see sections 4.8 and 5.1).

Case by case benefit/risk assessment in children
The expected benefit of treatment should be carefully weighed against the safety findings observed for children and adolescents in the clinical trials (see sections 4.8 and 5.1).
- It is important to consider that the combination therapy induced a growth inhibition, that resulted in reduced height in some patients.
- This risk should be weighed against the disease characteristics of the child, such as evidence of disease progression (notably fibrosis), co-morbidities that may negatively influence the disease progression (such as HIV co-infection), as well as prognostic factors of response (HCV genotype and viral load).

Whenever possible the child should be treated after the pubertal growth spurt, in order to reduce the risk of growth inhibition. Although data are limited, no evidence of long-term effects on sexual maturation was noted in the 5-year observational follow-up study.

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, adult 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. There are no data in children or adolescents with a history of cardiac disease.

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 section 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, retinal exudates, 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, adult patients treated for chronic hepatitis C with interferon alpha have developed thyroid abnormalities, either hypothyroidism or hyperthyroidism. Approximately 21 % of children treated with PegIntron/ribavirin combination therapy developed increase in thyroid stimulating hormone (TSH). Another approximately 2 % had a transient decrease below the lower limit of normal. Prior to initiation of 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 medicine. Children and adolescents should be monitored every 3 months for evidence of thyroid dysfunction (e.g. TSH).

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 SmPC).

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 SmPCs 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.

<u>HCV/HBV Coinfection</u>
Cases of hepatitis B re-activation (some with severe consequences) have been reported in patients co-infected with hepatitis B and C viruses treated with interferon. The frequency of such re-activation appears to be low.
All patients should be screened for hepatitis B before starting treatment with interferon for hepatitis C; patients co-infected with hepatitis B and C must then be monitored and managed according to current clinical guidelines.

<u>Dental and periodontal disorders</u>
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.

<u>Organ transplant recipients</u>
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 indicate that interferon alpha therapy may be associated with an increased rate of kidney graft rejection. Liver graft rejection has also been reported.

<u>Other</u>
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

Interaction studies have only been performed in adults.

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 sections 4.3, 4.4 and 4.5 of the 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**).

Table 4Effect 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 thioridazine should be referred to when co-administering with the product (PegIntron)	Metabolism of thioridazine is suppressed by inhibitory action of the product (PegIntron) on CYP2D6.
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 SmPC).

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 SmPC).

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 known 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.

4.8 Undesirable effects

Adults
Tritherapy
Refer to the SmPC 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 in adults, 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 decreased, 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 adults 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 adults in clinical trials or through post-marketing surveillance in patients treated with peginterferon 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
Not known:	Hepatitis B reactivation in HCV/HBV co-infected patients
Blood and lymphatic system disorders	
Very common:	Anaemia, neutropenia
Common:	Haemolytic anaemia, leukopenia, thrombocytopenia, 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 attempt, 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, neuropathy peripheral
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 occlusion, retinal vein occlusion, optic neuritis, papilloedema, macular oedema
Not known:	Serous retinal detachment
Ear and labyrinth disorders	
Common:	Hearing impaired/loss, tinnitus, vertigo
Uncommon	Ear pain
Cardiac disorders	
Common:	Palpitations, 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, 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, haemorrhoids, 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, 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 in adults

Most cases of neutropenia and thrombocytopenia 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 occlusion, retinal exudates, 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 (11 %), 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 < 9.4 g/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 SmPCs 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.

Paediatric population

Summary of the safety profile

In a clinical trial with 107 children and adolescent patients (3 to 17 years of age) treated with combination therapy of PegIntron and ribavirin, dose modifications were required in 25 % of patients, most commonly for anaemia, neutropenia and weight loss. In general, the adverse reactions profile in children and adolescents was similar to that observed in adults, although there is a paediatric-specific concern regarding growth inhibition. During combination therapy for up to 48 weeks with PegIntron and ribavirin, growth inhibition was observed that resulted in reduced height in some patients (see section 4.4). Weight loss and growth inhibition were very common during the treatment (at the end of treatment, mean decrease from baseline in weight and height percentile were of 15 percentiles and 8 percentiles, respectively) and growth velocity was inhibited (< 3rd percentile in 70 % of the patients).

At the end of 24 weeks post-treatment follow-up, mean decrease from baseline in weight and height percentiles were still of 3 percentiles and 7 percentiles respectively, and 20 % of the children continued to have inhibited growth (growth velocity < 3rd percentile). Ninety-four of 107 subjects enrolled in the 5 year long-term follow-up trial. The effects on growth were less in those subjects treated for 24 weeks than those treated for 48 weeks. From pre-treatment to end of long-term follow-up among subjects treated for 24 or 48 weeks, height-for-age percentiles decreased 1.3 and 9.0 percentiles, respectively. Twenty-four percent of subjects (11/46) treated for 24 weeks and 40 % of subjects (19/48) treated for 48 weeks had a > 15 percentile height-for-age decrease from pre-treatment to the end of the 5 year long-term follow-up compared to pre-treatment baseline percentile. Eleven percent of subjects (5/46) treated for 24 weeks and 13 % of subjects (6/48) treated for 48 weeks were observed to have a decrease from pre-treatment baseline of > 30 height-for-age percentiles to the end of the 5 year long-term follow-up. For weight, pre-treatment to end of long-term follow-up, weight-for-age percentiles decreased 1.3 and 5.5 percentiles among subjects treated for 24 weeks or 48 weeks, respectively. For BMI, pre-treatment to end of long-term follow-up, BMI-for-age percentiles decreased 1.8 and 7.5 percentiles among subjects treated for 24 weeks or 48 weeks, respectively. Decrease in mean height percentile at year 1 of long-term follow-up was most prominent in prepubertal age children. The decline of height, weight and BMI Z scores observed during the treatment phase in comparison to a normative population did not fully recover by the end of long-term follow-up period for children treated with 48 weeks of therapy (see section 4.4).

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

Tabulated summary of adverse reactions
The following treatment-related adverse reactions were reported in the study in children and adolescent patients treated with PegIntron in combination with ribavirin. These reactions are listed in **Table 7** 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, adverse reactions are presented in order of decreasing seriousness.

Table 7 Adverse reactions very commonly, commonly and uncommonly reported in the clinical trial in children and adolescent patients treated with PegIntron in combination with ribavirin

Infections and Infestations	
Common:	Fungal infection, influenza, oral herpes, otitis media, pharyngitis streptococcal, nasopharyngitis, sinusitis
Uncommon:	Pneumonia, ascariasis, enterobiasis, herpes zoster, cellulitis, urinary tract infection, gastroenteritis
Blood and lymphatic system disorders	
Very common:	Anaemia, leucopenia, neutropenia
Common:	Thrombocytopenia, lymphadenopathy
Endocrine disorders	
Common:	Hypothyroidism
Metabolism and nutrition disorders	
Very common:	Anorexia, decreased appetite

Psychiatric disorders	
Common:	Suicidal ideation[§], suicide attempt[§], depression, aggression, affect lability, anger, agitation, anxiety, mood altered, restlessness, nervousness, insomnia
Uncommon:	Abnormal behaviour, depressed mood, emotional disorder, fear, nightmare
Nervous system disorders	
Very common:	Headache, dizziness
Common:	Dysgeusia, syncope, disturbance in attention, somnolence, poor quality sleep
Uncommon:	Neuralgia, lethargy, paraesthesia, hypoaesthesia, psychomotor hyperactivity, tremor
Eye disorders	
Common:	Eye pain
Uncommon:	Conjunctival haemorrhage, eye pruritus, keratitis, vision blurred, photophobia
Ear and labyrinth disorders	
Common:	Vertigo
Cardiac disorders	
Common:	Palpitations, tachycardia
Vascular disorders	
Common:	Flushing
Uncommon:	Hypotension, pallor
Respiratory, thoracic and mediastinal disorders	
Common:	Cough, epistaxis, pharyngolaryngeal pain
Uncommon:	Wheezing, nasal discomfort, rhinorrhoea
Gastrointestinal disorders	
Very common:	Abdominal pain, abdominal pain upper, vomiting, nausea
Common:	Diarrhoea, aphthous stomatitis, cheilosis, mouth ulceration, stomach discomfort, oral pain
Uncommon:	Dyspepsia, gingivitis
Hepatobiliary disorders	
Uncommon:	Hepatomegaly
Skin and subcutaneous tissue disorders	
Very common:	Alopecia, dry skin
Common:	Pruritus, rash, rash erythematous, eczema, acne, erythema
Uncommon:	Photosensitivity reaction, rash maculo-papular, skin exfoliation, pigmentation disorder, dermatitis atopic, skin discolouration
Musculoskeletal and connective tissue disorders	
Very common:	Myalgia, arthralgia
Common:	Musculoskeletal pain, pain in extremity, back pain
Uncommon:	Muscle contracture, muscle twitching
Renal and urinary disorders	
Uncommon:	Proteinuria
Reproductive system and breast disorders	
Uncommon:	Female: Dysmenorrhoea
General disorders and administration site conditions	
Very common:	Injection site erythema, fatigue, pyrexia, rigors, influenza-like illness, asthenia, pain, malaise, irritability
Common:	Injection site reaction, injection site pruritus, injection site rash injection site dryness, injection site pain, feeling cold
Uncommon:	Chest pain, chest discomfort, facial pain

Investigations	
Very common:	Growth rate decrease (height and/or weight decrease for age)
Common:	Blood thyroid stimulating hormone increased, thyroglobulin increased
Uncommon:	Anti-thyroid antibody positive
Injury and poisoning	
Uncommon:	Contusion

[§]class effect of interferon-alfa containing products – reported with standard interferon therapy in adult and paediatric patients; with PegIntron reported in adult patients.

Description of selected adverse reactions in children and adolescents
Most of the changes in laboratory values in the PegIntron/ribavirin clinical trial were mild or moderate. Decreases in haemoglobin, white blood cells, platelets, neutrophils and increase in bilirubin may require dose reduction or permanent discontinuation from therapy (see section 4.2). While changes in laboratory values were observed in some patients treated with PegIntron used in combination with ribavirin in the clinical trial, values returned to baseline levels within a few weeks after the end of therapy.

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. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

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 – Adults
Tritherapy with PegIntron, ribavirin and boceprevir
Refer to the SmPC 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 8**).

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 8**), particularly in patients infected with Genotype 1 (**Table 9**). 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 9**), while response rates in patients that received > 13.2 mg/kg ribavirin were even higher.

Table 8 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 9 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 micrograms/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 10**). Twenty-four % had bridging fibrosis or cirrhosis (Knodell 3/4).

Table 10 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 12 % 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 11**).

Table 11 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 12**).

Table 12 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 13.** 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 co-infected 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.

Table 13 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.

[1]Carrat F, Bani-Sadr 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 PegIntron in combination with ribavirin. This decline was significant among responders (-0.5 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 HCV-RNA after 12 weeks of treatment. Sustained Virologic Response (SVR) is defined as undetectable HCV-RNA at 24 weeks post-treatment (**Table 14***)*.

Table 14 Rates of response to retreatment in prior treatment failures

	Patients with undetectable HCV–RNA at treatment week 12 and SVR upon retreatment				
	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) 19.6, 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	18.4 (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

	Patients with undetectable HCV–RNA at treatment week 12 and SVR upon retreatment				
	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
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-Adults
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).

Clinical efficacy and safety – paediatric population
Children and adolescents 3 to 17 years of age with compensated chronic hepatitis C and detectable HCV-RNA were enrolled in a multicentre trial and treated with ribavirin 15 mg/kg per day plus PegIntron 60 μg/m^2 once weekly for 24 or 48 weeks, based on HCV genotype and baseline viral load. All patients were to be followed for 24 weeks post-treatment. A total of 107 patients received treatment of whom 52 % were female, 89 % Caucasian, 67 % with HCV Genotype 1 and 63 % < 12 years of age. The population enrolled mainly consisted of children with mild to moderate hepatitis C. Due to the lack of data in children with severe progression of the disease, and the potential for undesirable effects**,** the benefit/risk of the combination of PegIntron with ribavirin needs to be carefully considered in this population (see sections 4.1, 4.4 and 4.8). The study results are summarized in **Table 15**.

Table 15 Sustained virological response rates (n[a,b] (%)) in previously untreated children and adolescents by genotype and treatment duration – All subjects n = 107

	24 weeks	48 weeks
All Genotypes	26/27 (96 %)	44/80 (55 %)
Genotype 1	-	38/72 (53 %)
Genotype 2	14/15 (93 %)	-
Genotype 3[c]	12/12 (100 %)	2/3 (67 %)
Genotype 4	-	4/5 (80 %)

a: Response to treatment was defined as undetectable HCV-RNA at 24 weeks post-treatment lower limit of detection=125IU/ml

b: n = number of responders/number of subjects with given genotype, and assigned treatment duration.

c: Patients with genotype 3 low viral load (< 600,000 IU/ml) were to receive 24 weeks of treatment while those with genotype 3 and high viral load (≥ 600,000 IU/ml) were to receive 48 weeks of treatment.

Long-term efficacy data - paediatric population

A five-year long-term, observational, follow-up study enrolled 94 paediatric chronic hepatitis C patients after treatment in a multicentre trial. Of these, sixty-three were sustained responders. The purpose of the study was to annually evaluate the durability of sustained virologic response (SVR) and assess the impact of continued viral negativity on clinical outcomes for patients who were sustained responders 24 weeks post-treatment with 24 or 48 weeks of peginterferon alfa-2b and ribavirin treatment. At the end of 5 years, 85 % (80/94) of all enrolled subjects and 86 % (54/63) of sustained responders completed the study. No paediatric subjects with SVR had relapsed during the 5 years of follow-up.

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.

Paediatric population
Multiple-dose pharmacokinetic properties for PegIntron and ribavirin (capsules and oral solution) in children and adolescent patients with chronic hepatitis C have been evaluated during a clinical study. In children and adolescent patients receiving body surface area-adjusted dosing of PegIntron at 60 μg/m^2/week, the log transformed ratio estimate of exposure during the dosing interval is predicted to be 58 % (90 % CI: 141-177 %) higher than observed in adults receiving 1.5 μg/kg/week.

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.

No studies have been conducted in juvenile animals to examine the effects of treatment with PegIntron on growth, development, sexual maturation, and behaviour. Preclinical juvenile toxicity results have demonstrated a minor, dose-related decrease in overall growth in neonatal rats dosed with ribavirin (see section 5.3 of Rebetol SmPC if PegIntron is to be administered in combination with ribavirin).

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Powder
Disodium phosphate, anhydrous
Sodium dihydrogen phosphate dihydrate
Sucrose
Polysorbate 80

Solvent
Water for injections

6.2 Incompatibilities

In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products.

6.3 Shelf life

Before reconstitution
3 years.

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.

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 is supplied as:
- 1 pre-filled pen (CLEARCLICK) containing powder and solvent for solution for injection,
  1 needle ("Push-On Needle"),
  2 cleansing swabs;
- 4 pre-filled pens (CLEARCLICK) containing powder and solvent for solution for injection,

4 needles ("Push-On Needle"),
8 cleansing swabs;

- 12 pre-filled pens (CLEARCLICK) containing powder and solvent for solution for injection,
  12 needles ("Push-On Needle"),
  24 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).

PegIntron 50 micrograms powder and solvent for solution for injection in pre-filled pen
Each pre-filled pen (CLEARCLICK) 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 50 micrograms in 0.5 ml.

PegIntron 80 micrograms powder and solvent for solution for injection in pre-filled pen
Each pre-filled pen (CLEARCLICK) 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 micrograms in 0.5 ml.

PegIntron 100 micrograms powder and solvent for solution for injection in pre-filled pen
Each pre-filled pen (CLEARCLICK) 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 100 micrograms in 0.5 ml.

PegIntron 120 micrograms powder and solvent for solution for injection in pre-filled pen
Each pre-filled pen (CLEARCLICK) 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 120 micrograms in 0.5 ml.

PegIntron 150 micrograms powder and solvent for solution for injection in pre-filled pen
Each pre-filled pen (CLEARCLICK) 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 150 micrograms in 0.5 ml.

PegIntron is injected subcutaneously after reconstituting the powder as instructed, attaching a 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 disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

Merck Sharp & Dohme B.V.
Waarderweg 39
2031 BN Haarlem
The Netherlands

8. MARKETING AUTHORISATION NUMBERS

PegIntron 50 micrograms powder and solvent for solution for injection in pre-filled pen
EU/1/00/131/031
EU/1/00/131/032
EU/1/00/131/034

PegIntron 80 micrograms powder and solvent for solution for injection in pre-filled pen
EU/1/00/131/035
EU/1/00/131/036
EU/1/00/131/038

PegIntron 100 micrograms powder and solvent for solution for injection in pre-filled pen
EU/1/00/131/039
EU/1/00/131/040
EU/1/00/131/042

PegIntron 120 micrograms powder and solvent for solution for injection in pre-filled pen
EU/1/00/131/043
EU/1/00/131/044
EU/1/00/131/046

PegIntron 150 micrograms powder and solvent for solution for injection in pre-filled pen
EU/1/00/131/047
EU/1/00/131/048
EU/1/00/131/050

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 25 May 2000
Date of latest renewal: 25 May 2010

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the web-site of the European Medicines Agency http://www.ema.europa.eu.

ANNEX II

A. MANUFACTURER OF THE BIOLOGICAL ACTIVE SUBSTANCE AND MANUFACTURER RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

A. MANUFACTURER OF THE BIOLOGICAL ACTIVE SUBSTANCE AND MANUFACTURER RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer of the biological active substance

MSD International GmbH T/A MSD Ireland (Brinny)
Brinny
Innishannon
Co. Cork
Ireland

Name and address of the manufacturer responsible for batch release

SP Labo N.V.
Industriepark 30
B-2220 Heist-op-den-Berg
Belgium

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to restricted medical prescription (see Annex I, Summary of Product Characteristics, 4.2).

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

- **Periodic Safety Update Reports**

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

- **Risk Management Plan (RMP)**

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the Marketing Authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted
- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

Carton 50 micrograms

1. NAME OF THE MEDICINAL PRODUCT

PegIntron 50 micrograms powder and solvent for solution for injection
peginterferon alfa-2b

2. STATEMENT OF ACTIVE SUBSTANCE(S)

One vial of powder contains 50 micrograms of peginterferon alfa-2b and
provides 50 micrograms/0.5 ml of peginterferon alfa-2b when reconstituted as recommended.

3. LIST OF EXCIPIENTS

Excipients: disodium phosphate, anhydrous; sodium dihydrogen phosphate dihydrate, sucrose and polysorbate 80. One ampoule of solvent contains 0.7 ml of water for injections.

4. PHARMACEUTICAL FORM AND CONTENTS

1 vial of powder, 1 ampoule of solvent
1 vial of powder, 1 ampoule of solvent, 1 injection syringe, 2 injection needles and 1 cleansing swab
4 vials of powder, 4 ampoules of solvent
4 vials of powder, 4 ampoules of solvent, 4 injection syringes, 8 injection needles and 4 cleansing swabs
6 vials of powder, 6 ampoules of solvent
12 vials of powder, 12 ampoules of solvent, 12 injection syringes, 24 injection needles and 12 cleansing swabs
50 micrograms/0.5 ml

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Subcutaneous use.
Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

After reconstitution, use the reconstituted solution immediately or within 24 hours when stored in a refrigerator (2°C - 8°C).

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

After withdrawal of the dose, any remaining solution must be discarded.

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Merck Sharp & Dohme B.V.
Waarderweg 39
2031 BN Haarlem
The Netherlands

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/00/131/001 (1 vial of powder, 1 ampoule of solvent)
EU/1/00/131/002 (1 vial of powder, 1 ampoule of solvent, 1 injection syringe, 2 injection needles and 1 cleansing swab)
EU/1/00/131/003 (4 vials of powder, 4 ampoules of solvent)
EU/1/00/131/004 (4 vials of powder, 4 ampoules of solvent, 4 injection syringes, 8 injection needles and 4 cleansing swabs)
EU/1/00/131/005 (6 vials of powder, 6 ampoules of solvent)
EU/1/00/131/026 (12 vials of powder, 12 ampoules of solvent, 12 injection syringes, 24 injection needles and 12 cleansing swabs)

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

PegIntron 50 mcg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER – HUMAN READABLE DATA

PC:
SN:
NN:

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

PegIntron 50 micrograms – vial of powder

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

PegIntron 50 micrograms powder for injection
peginterferon alfa-2b
SC

2. METHOD OF ADMINISTRATION

Read the package leaflet before use.

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

50 mcg/0.5 ml

6. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

Carton 80 micrograms

1. NAME OF THE MEDICINAL PRODUCT

PegIntron 80 micrograms powder and solvent for solution for injection
peginterferon alfa-2b

2. STATEMENT OF ACTIVE SUBSTANCE(S)

One vial of powder contains 80 micrograms of peginterferon alfa-2b and
provides 80 micrograms/0.5 ml of peginterferon alfa-2b when reconstituted as recommended.

3. LIST OF EXCIPIENTS

Excipients: disodium phosphate, anhydrous; sodium dihydrogen phosphate dihydrate, sucrose and polysorbate 80. One ampoule of solvent contains 0.7 ml of water for injections.

4. PHARMACEUTICAL FORM AND CONTENTS

1 vial of powder, 1 ampoule of solvent
1 vial of powder, 1 ampoule of solvent, 1 injection syringe, 2 injection needles and 1 cleansing swab
4 vials of powder, 4 ampoules of solvent
4 vials of powder, 4 ampoules of solvent, 4 injection syringes, 8 injection needles and 4 cleansing swabs
6 vials of powder, 6 ampoules of solvent
12 vials of powder, 12 ampoules of solvent, 12 injection syringes, 24 injection needles and 12 cleansing swabs
80 micrograms/0.5 ml

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Subcutaneous use.
Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

After reconstitution, use the reconstituted solution immediately or within 24 hours when stored in a refrigerator (2°C - 8°C).

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

After withdrawal of the dose, any remaining solution must be discarded.

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Merck Sharp & Dohme B.V.
Waarderweg 39
2031 BN Haarlem
The Netherlands

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/00/131/006 (1 vial of powder, 1 ampoule of solvent)
EU/1/00/131/007 (1 vial of powder, 1 ampoule of solvent, 1 injection syringe, 2 injection needles and 1 cleansing swab)
EU/1/00/131/008 (4 vials of powder, 4 ampoules of solvent)
EU/1/00/131/009 (4 vials of powder, 4 ampoules of solvent, 4 injection syringes, 8 injection needles and 4 cleansing swabs)
EU/1/00/131/010 (6 vials of powder, 6 ampoules of solvent)
EU/1/00/131/027 (12 vials of powder, 12 ampoules of solvent, 12 injection syringes, 24 injection needles and 12 cleansing swabs)

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

PegIntron 80 mcg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER – HUMAN READABLE DATA

PC:
SN:
NN:

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

PegIntron 80 micrograms - vial of powder

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

PegIntron 80 micrograms powder for injection
peginterferon alfa-2b
SC

2. METHOD OF ADMINISTRATION

Read the package leaflet before use.

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

80 mcg/0.5 ml

6. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

Carton 100 micrograms

1. NAME OF THE MEDICINAL PRODUCT

PegIntron 100 micrograms powder and solvent for solution for injection
peginterferon alfa-2b

2. STATEMENT OF ACTIVE SUBSTANCE(S)

One vial of powder contains 100 micrograms of peginterferon alfa-2b and
provides 100 micrograms/0.5 ml of peginterferon alfa-2b when reconstituted as recommended.

3. LIST OF EXCIPIENTS

Excipients: disodium phosphate, anhydrous; sodium dihydrogen phosphate dihydrate, sucrose and polysorbate 80. One ampoule of solvent contains 0.7 ml of water for injections.

4. PHARMACEUTICAL FORM AND CONTENTS

1 vial of powder, 1 ampoule of solvent
1 vial of powder, 1 ampoule of solvent, 1 injection syringe, 2 injection needles and 1 cleansing swab
4 vials of powder, 4 ampoules of solvent
4 vials of powder, 4 ampoules of solvent, 4 injection syringes, 8 injection needles and 4 cleansing swabs
6 vials of powder, 6 ampoules of solvent
12 vials of powder, 12 ampoules of solvent, 12 injection syringes, 24 injection needles and 12 cleansing swabs
100 micrograms/0.5 ml

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Subcutaneous use.
Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

After reconstitution, use the reconstituted solution immediately or within 24 hours when stored in a refrigerator (2°C - 8°C).

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

After withdrawal of the dose, any remaining solution must be discarded.

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Merck Sharp & Dohme B.V.
Waarderweg 39
2031 BN Haarlem
The Netherlands

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/00/131/011 (1 vial of powder, 1 ampoule of solvent)
EU/1/00/131/012 (1 vial of powder, 1 ampoule of solvent, 1 injection syringe, 2 injection needles and 1 cleansing swab)
EU/1/00/131/013 (4 vials of powder, 4 ampoules of solvent)
EU/1/00/131/014 (4 vials of powder, 4 ampoules of solvent, 4 injection syringes, 8 injection needles and 4 cleansing swabs)
EU/1/00/131/015 (6 vials of powder, 6 ampoules of solvent)
EU/1/00/131/028 (12 vials of powder, 12 ampoules of solvent, 12 injection syringes, 24 injection needles and 12 cleansing swabs)

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

PegIntron 100 mcg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER – HUMAN READABLE DATA

PC:
SN:
NN:

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

PegIntron 100 micrograms - vial of powder

1. NAME OF THE MEDICINAL PRODUCT AND IF NECESSARY ROUTE(S) OF ADMINISTRATION

PegIntron 100 micrograms powder for injection
peginterferon alfa-2b
SC

2. METHOD OF ADMINISTRATION

Read the package leaflet before use.

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

100 mcg/0.5 ml

6. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

Carton 120 micrograms

1. NAME OF THE MEDICINAL PRODUCT

PegIntron 120 micrograms powder and solvent for solution for injection
peginterferon alfa-2b

2. STATEMENT OF ACTIVE SUBSTANCE(S)

One vial of powder contains 120 micrograms of peginterferon alfa-2b and
provides 120 micrograms/0.5 ml of peginterferon alfa-2b when reconstituted as recommended.

3. LIST OF EXCIPIENTS

Excipients: disodium phosphate, anhydrous; sodium dihydrogen phosphate dihydrate, sucrose and polysorbate 80. One ampoule of solvent contains 0.7 ml of water for injections.

4. PHARMACEUTICAL FORM AND CONTENTS

1 vial of powder, 1 ampoule of solvent
1 vial of powder, 1 ampoule of solvent, 1 injection syringe, 2 injection needles and 1 cleansing swab
4 vials of powder, 4 ampoules of solvent
4 vials of powder, 4 ampoules of solvent, 4 injection syringes, 8 injection needles and 4 cleansing swabs
6 vials of powder, 6 ampoules of solvent
12 vials of powder, 12 ampoules of solvent, 12 injection syringes, 24 injection needles and 12 cleansing swabs
120 micrograms/0.5 ml

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Subcutaneous use.
Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

After reconstitution, use the reconstituted solution immediately or within 24 hours when stored in a refrigerator (2°C - 8°C).

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

After withdrawal of the dose, any remaining solution must be discarded.

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Merck Sharp & Dohme B.V.
Waarderweg 39
2031 BN Haarlem
The Netherlands

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/00/131/016 (1 vial of powder, 1 ampoule of solvent)
EU/1/00/131/017 (1 vial of powder, 1 ampoule of solvent, 1 injection syringe, 2 injection needles and 1 cleansing swab)
EU/1/00/131/018 (4 vials of powder, 4 ampoules of solvent)
EU/1/00/131/019 (4 vials of powder, 4 ampoules of solvent, 4 injection syringes, 8 injection needles and 4 cleansing swabs)
EU/1/00/131/020 (6 vials of powder, 6 ampoules of solvent)
EU/1/00/131/029 (12 vials of powder, 12 ampoules of solvent, 12 injection syringes, 24 injection needles and 12 cleansing swabs)

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

PegIntron 120 mcg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER – HUMAN READABLE DATA

PC:
SN:
NN:

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

PegIntron 120 micrograms - vial of powder

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

PegIntron 120 micrograms powder for injection
peginterferon alfa-2b
SC

2. METHOD OF ADMINISTRATION

Read the package leaflet before use.

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

120 mcg/0.5 ml

6. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

Carton 150 micrograms

1. NAME OF THE MEDICINAL PRODUCT

PegIntron 150 micrograms powder and solvent for solution for injection
peginterferon alfa-2b

2. STATEMENT OF ACTIVE SUBSTANCE(S)

One vial of powder contains 150 micrograms of peginterferon alfa-2b and
provides 150 micrograms/0.5 ml of peginterferon alfa-2b when reconstituted as recommended.

3. LIST OF EXCIPIENTS

Excipients: disodium phosphate, anhydrous; sodium dihydrogen phosphate dihydrate, sucrose and polysorbate 80. One ampoule of solvent contains 0.7 ml of water for injections.

4. PHARMACEUTICAL FORM AND CONTENTS

1 vial of powder, 1 ampoule of solvent
1 vial of powder, 1 ampoule of solvent, 1 injection syringe, 2 injection needles and 1 cleansing swab
4 vials of powder, 4 ampoules of solvent
4 vials of powder, 4 ampoules of solvent, 4 injection syringes, 8 injection needles and 4 cleansing swabs
6 vials of powder, 6 ampoules of solvent
12 vials of powder, 12 ampoules of solvent, 12 injection syringes, 24 injection needles and 12 cleansing swabs
150 micrograms/0.5 ml

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Subcutaneous use.
Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

After reconstitution, use the reconstituted solution immediately or within 24 hours when stored in a refrigerator (2°C - 8°C).

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

After withdrawal of the dose, any remaining solution must be discarded.

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Merck Sharp & Dohme B.V.
Waarderweg 39
2031 BN Haarlem
The Netherlands

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/00/131/021 (1 vial of powder, 1 ampoule of solvent)
EU/1/00/131/022 (1 vial of powder, 1 ampoule of solvent, 1 injection syringe, 2 injection needles and 1 cleansing swab)
EU/1/00/131/023 (4 vials of powder, 4 ampoules of solvent)
EU/1/00/131/024 (4 vials of powder, 4 ampoules of solvent, 4 injection syringes, 8 injection needles and 4 cleansing swabs)
EU/1/00/131/025 (6 vials of powder, 6 ampoules of solvent)
EU/1/00/131/030 (12 vials of powder, 12 ampoules of solvent, 12 injection syringes, 24 injection needles and 12 cleansing swabs)

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

PegIntron 150 mcg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER – HUMAN READABLE DATA

PC:
SN:
NN

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

PegIntron 150 micrograms - vial of powder

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

PegIntron 150 micrograms powder for injection
peginterferon alfa-2b
SC

2. METHOD OF ADMINISTRATION

Read the package leaflet before use.

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

150 mcg/0.5 ml

6. OTHER

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

PegIntron - ampoule of solvent

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Solvent for PegIntron
Water for injections

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

0.7 ml

6. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

Carton 50 micrograms powder and solvent for solution for injection in pre-filled pen

1. NAME OF THE MEDICINAL PRODUCT

PegIntron 50 micrograms powder and solvent for solution for injection in pre-filled pen
peginterferon alfa-2b

2. STATEMENT OF ACTIVE SUBSTANCE(S)

One pre-filled pen contains a sufficient amount of peginterferon alfa-2b to provide 50 micrograms in 0.5 ml of peginterferon alfa-2b when reconstituted as recommended.

3. LIST OF EXCIPIENTS

Excipients: disodium phosphate, anhydrous; sodium dihydrogen phosphate dihydrate, sucrose and polysorbate 80. Solvent: water for injections.

4. PHARMACEUTICAL FORM AND CONTENTS

Powder and solvent for solution for injection in pre-filled pen
1 pen (CLEARCLICK), 1 injection needle and 2 cleansing swabs
4 pens (CLEARCLICK), 4 injection needles and 8 cleansing swabs
12 pens (CLEARCLICK), 12 injection needles and 24 cleansing swabs
50 micrograms/0.5 ml

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Subcutaneous use
Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

After reconstitution, use the reconstituted solution immediately or within 24 hours when stored in a refrigerator (2°C - 8°C).

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator. Do not freeze.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

After injection of the dose, discard the pen in an appropriate container.

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Merck Sharp & Dohme B.V.
Waarderweg 39
2031 BN Haarlem
The Netherlands

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/00/131/031 (1 pen, 1 injection needle and 2 cleansing swabs)
EU/1/00/131/032 (4 pens, 4 injection needles and 8 cleansing swabs)
EU/1/00/131/034 (12 pens, 12 injection needles and 24 cleansing swabs)

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

PegIntron 50 mcg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER – HUMAN READABLE DATA

PC:
SN:
NN

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

Pen label - PegIntron 50 micrograms powder and solvent for solution for injection in pre-filled pen

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

PegIntron 50 micrograms powder and solvent for injection
peginterferon alfa-2b
SC

2. METHOD OF ADMINISTRATION

Read the package leaflet before use.

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

50 mcg/0.5 ml

6. OTHER

Pen (CLEARCLICK)

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

Carton 80 micrograms powder and solvent for solution for injection in pre-filled pen

1. NAME OF THE MEDICINAL PRODUCT

PegIntron 80 micrograms powder and solvent for solution for injection in pre-filled pen
peginterferon alfa-2b

2. STATEMENT OF ACTIVE SUBSTANCE(S)

One pre-filled pen contains a sufficient amount of peginterferon alfa-2b to provide 80 micrograms in 0.5 ml of peginterferon alfa-2b when reconstituted as recommended.

3. LIST OF EXCIPIENTS

Excipients: disodium phosphate, anhydrous; sodium dihydrogen phosphate dihydrate, sucrose and polysorbate 80. Solvent: water for injections.

4. PHARMACEUTICAL FORM AND CONTENTS

Powder and solvent for solution for injection in pre-filled pen
1 pen (CLEARCLICK), 1 injection needle and 2 cleansing swabs
4 pens (CLEARCLICK), 4 injection needles and 8 cleansing swabs
12 pens (CLEARCLICK), 12 injection needles and 24 cleansing swabs
80 micrograms/0.5 ml

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Subcutaneous use
Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

After reconstitution, use the reconstituted solution immediately or within 24 hours when stored in a refrigerator (2°C - 8°C).

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator. Do not freeze.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

After injection of the dose, discard the pen in an appropriate container.

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Merck Sharp & Dohme B.V.
Waarderweg 39
2031 BN Haarlem
The Netherlands

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/00/131/035 (1 pen, 1 injection needle and 2 cleansing swabs)
EU/1/00/131/036 (4 pens, 4 injection needles and 8 cleansing swabs)
EU/1/00/131/038 (12 pens, 12 injection needles and 24 cleansing swabs)

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

PegIntron 80 mcg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER – HUMAN READABLE DATA

PC:
SN:
NN

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

Pen label - PegIntron 80 micrograms powder and solvent for solution for injection in pre-filled pen

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

PegIntron 80 micrograms powder and solvent for injection
peginterferon alfa-2b
SC

2. METHOD OF ADMINISTRATION

Read the package leaflet before use.

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

80 mcg/0.5 ml

6. OTHER

Pen (CLEARCLICK)

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

Carton 100 micrograms powder and solvent for solution for injection in pre-filled pen

1. NAME OF THE MEDICINAL PRODUCT

PegIntron 100 micrograms powder and solvent for solution for injection in pre-filled pen
peginterferon alfa-2b

2. STATEMENT OF ACTIVE SUBSTANCE(S)

One pre-filled pen contains a sufficient amount of peginterferon alfa-2b to provide 100 micrograms in 0.5 ml of peginterferon alfa-2b when reconstituted as recommended.

3. LIST OF EXCIPIENTS

Excipients: disodium phosphate, anhydrous; sodium dihydrogen phosphate dihydrate, sucrose and polysorbate 80. Solvent: water for injections.

4. PHARMACEUTICAL FORM AND CONTENTS

Powder and solvent for solution for injection in pre-filled pen
1 pen (CLEARCLICK), 1 injection needle and 2 cleansing swabs
4 pens (CLEARCLICK), 4 injection needles and 8 cleansing swabs
12 pens (CLEARCLICK), 12 injection needles and 24 cleansing swabs
100 micrograms/0.5 ml

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Subcutaneous use
Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

After reconstitution, use the reconstituted solution immediately or within 24 hours when stored in a refrigerator (2°C - 8°C).

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator. Do not freeze.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

After injection of the dose, discard the pen in an appropriate container.

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Merck Sharp & Dohme B.V.
Waarderweg 39
2031 BN Haarlem
The Netherlands

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/00/131/039 (1 pen, 1 injection needle and 2 cleansing swabs)
EU/1/00/131/040 (4 pens, 4 injection needles and 8 cleansing swabs)
EU/1/00/131/042 (12 pens, 12 injection needles and 24 cleansing swabs)

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

PegIntron 100 mcg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER – HUMAN READABLE DATA

PC:
SN:
NN

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

Pen label - PegIntron 100 micrograms powder and solvent for solution for injection in pre-filled pen

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

PegIntron 100 micrograms powder and solvent for injection
peginterferon alfa-2b
SC

2. METHOD OF ADMINISTRATION

Read the package leaflet before use.

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

100 mcg/0.5 ml

6. OTHER

Pen (CLEARCLICK)

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

Carton 120 micrograms powder and solvent for solution for injection in pre-filled pen

1. NAME OF THE MEDICINAL PRODUCT

PegIntron 120 micrograms powder and solvent for solution for injection in pre-filled pen
peginterferon alfa-2b

2. STATEMENT OF ACTIVE SUBSTANCE(S)

One pre-filled pen contains a sufficient amount of peginterferon alfa-2b to provide 120 micrograms in 0.5 ml of peginterferon alfa-2b when reconstituted as recommended.

3. LIST OF EXCIPIENTS

Excipients: disodium phosphate, anhydrous; sodium dihydrogen phosphate dihydrate, sucrose and polysorbate 80. Solvent: water for injections.

4. PHARMACEUTICAL FORM AND CONTENTS

Powder and solvent for solution for injection in pre-filled pen
1 pen (CLEARCLICK), 1 injection needle and 2 cleansing swabs
4 pens (CLEARCLICK), 4 injection needles and 8 cleansing swabs
12 pens (CLEARCLICK), 12 injection needles and 24 cleansing swabs
120 micrograms/0.5 ml

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Subcutaneous use
Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

After reconstitution, use the reconstituted solution immediately or within 24 hours when stored in a refrigerator (2°C - 8°C).

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator. Do not freeze.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

After injection of the dose, discard the pen in an appropriate container.

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Merck Sharp & Dohme B.V.
Waarderweg 39
2031 BN Haarlem
The Netherlands

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/00/131/043 (1 pen, 1 injection needle and 2 cleansing swabs)
EU/1/00/131/044 (4 pens, 4 injection needles and 8 cleansing swabs)
EU/1/00/131/046 (12 pens, 12 injection needles and 24 cleansing swabs)

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

PegIntron 120 mcg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER – HUMAN READABLE DATA

PC:
SN:
NN

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

Pen label - PegIntron 120 micrograms powder and solvent for solution for injection in pre-filled pen

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

PegIntron 120 micrograms powder and solvent for injection
peginterferon alfa-2b
SC

2. METHOD OF ADMINISTRATION

Read the package leaflet before use.

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

120 mcg/0.5 ml

6. OTHER

Pen (CLEARCLICK)

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

Carton 150 micrograms powder and solvent for solution for injection in pre-filled pen

1. NAME OF THE MEDICINAL PRODUCT

PegIntron 150 micrograms powder and solvent for solution for injection in pre-filled pen
peginterferon alfa-2b

2. STATEMENT OF ACTIVE SUBSTANCE(S)

One pre-filled pen contains a sufficient amount of peginterferon alfa-2b to provide 150 micrograms in 0.5 ml of peginterferon alfa-2b when reconstituted as recommended.

3. LIST OF EXCIPIENTS

Excipients: disodium phosphate, anhydrous; sodium dihydrogen phosphate dihydrate, sucrose and polysorbate 80. Solvent: water for injections.

4. PHARMACEUTICAL FORM AND CONTENTS

Powder and solvent for solution for injection in pre-filled pen
1 pen (CLEARCLICK), 1 injection needle and 2 cleansing swabs
4 pens (CLEARCLICK), 4 injection needles and 8 cleansing swabs
12 pens (CLEARCLICK), 12 injection needles and 24 cleansing swabs
150 micrograms/0.5 ml

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Subcutaneous use
Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

After reconstitution, use the reconstituted solution immediately or within 24 hours when stored in a refrigerator (2°C - 8°C).

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator. Do not freeze.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

After injection of the dose, discard the pen in an appropriate container.

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Merck Sharp & Dohme B.V.
Waarderweg 39
2031 BN Haarlem
The Netherlands

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/00/131/047 (1 pen, 1 injection needle and 2 cleansing swabs)
EU/1/00/131/048 (4 pens, 4 injection needles and 8 cleansing swabs)
EU/1/00/131/050 (12 pens, 12 injection needles and 24 cleansing swabs)

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

PegIntron 150 mcg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER – HUMAN READABLE DATA

PC:
SN:
NN

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

Pen label - PegIntron 150 micrograms powder and solvent for solution for injection in pre-filled pen

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

PegIntron 150 micrograms powder and solvent for injection
peginterferon alfa-2b
SC

2. METHOD OF ADMINISTRATION

Read the package leaflet before use.

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

150 mcg/0.5 ml

6. OTHER

Pen (CLEARCLICK)

B. PACKAGE LEAFLET

Package leaflet: Information for the user

PegIntron 50 micrograms powder and solvent for solution for injection
PegIntron 80 micrograms powder and solvent for solution for injection
PegIntron 100 micrograms powder and solvent for solution for injection
PegIntron 120 micrograms powder and solvent for solution for injection
PegIntron 150 micrograms powder and solvent for solution for injection
peginterferon alfa-2b

Read all of this leaflet carefully before you start using this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What PegIntron is and what it is used for
2. What you need to know before you use PegIntron
3. How to use PegIntron
4. Possible side effects
5. How to store PegIntron
6. Contents of the pack and other information

1. What PegIntron is and what it is used for

The active substance in this medicine is a protein called peginterferon alfa-2b, which belongs to the class of medicines called interferons. Interferons are made by your body's immune system to help fight infections and severe diseases. This medicine is injected into your body to work with your immune system. This medicine is used for the treatment of chronic hepatitis C, a viral infection of the liver.

Adults
The combination of this medicine, ribavirin and boceprevir is recommended for use for some types of chronic hepatitis C virus infection (also called HCV infection) in adults 18 years of age and older. It may be used in adults who have not been previously treated for HCV infection or who have previously used medicines called interferons and pegylated interferons.

The combination of this medicine and ribavirin is recommended for adults 18 years of age and older who have not previously been treated with these medicines. This includes adults also infected with clinically stable HIV (Human Immunodeficiency Virus). The combination can also be used to treat adults who have already failed treatment with an interferon alpha or peginterferon alpha in combination with ribavirin or interferon alpha alone.

If you have a medical condition making use of ribavirin dangerous or if you already have had a problem taking it, your doctor will likely prescribe this medicine alone.

If you have any further questions on the use of this medicine, ask your doctor or pharmacist.

Children and adolescents
This medicine is used in combination with ribavirin in children 3 years of age and older and adolescents who have not been treated previously for chronic hepatitis C.

2. What you need to know before you use PegIntron

Do not use PegIntron
You should **tell your doctor** before starting treatment if you, or the child you are caring for:
- are **allergic** to peginterferon alfa-2b or any of the other ingredients of this medicine (listed in section 6).
- are **allergic** to any interferon.
- have had severe **heart problems**.
- have **heart disease** that has not been well controlled during the past 6 months.
- have severe medical conditions that leave you very weak.
- have autoimmune hepatitis or any other problem with your **immune system.**
- are taking medicine that suppresses (weakens) your immune system.
- have advanced, uncontrolled **liver disease** (other than hepatitis C).
- have **thyroid disease** that is not well controlled with medicines.
- have **epilepsy**, a condition that causes convulsions (seizures, or "fits").
- are being treated with **telbivudine** (see section "Other medicines and PegIntron").

You **must not use** PegIntron if any of the conditions above should apply to you, or the child you are caring for.

In addition, children and adolescents **must not use** this medicine if they have had **serious nervous or mental problems,** such as **severe depression** or **thoughts of suicide.**

Reminder: Please also read the "Do not take" section of the Package Leaflet for **ribavirin** and **boceprevir** before using them in combination with this medicine.

Warnings and precautions
Seek medical help immediately in case of a severe allergic reaction (such as difficulty in breathing, wheezing, or hives).

Talk to your doctor before taking this medicine if you, or the child you are caring for:
- have had a severe **nervous or mental disorder** or have a **history of substance abuse** (e.g. alcohol or drugs).
  The use of this medicine in children and adolescents with existence of or history of severe psychiatric conditions is not allowed (see section "Do not use PegIntron" above).
- are being treated for a **mental illness** or had treatment in the past for any other nervous or mental disorder, including **depression** (such as feelings of sadness, dejection) or **suicidal or homicidal behaviour** (see section 4 "Possible side effects").
- have ever had a **heart attack** or a **heart problem**.
- have **kidney disease**, your doctor may prescribe a lower than usual dose and monitor your kidney blood values regularly during treatment. If this medicine is used in combination with ribavirin, your doctor should monitor you, or the child you are caring for more carefully for a decrease in red blood cell count.
- have **cirrhosis** or other **liver problems** (other than hepatitis C).
- develop symptoms associated with a **cold** or other respiratory infection, such as **fever**, **cough**, or any **difficulty in breathing**.
- are **diabetic** or have **high blood pressure**, your doctor may ask you, or the child you are caring for to have an eye examination.
- have had any serious **illness affecting breathing** or **blood**.
- have the skin disorders, **psoriasis** or **sarcoidosis**, which may become worse while you are using this medicine.
- are planning to become **pregnant**, discuss this with your doctor before starting to use this medicine.
- have received an **organ transplant**, either kidney or liver, interferon treatment may increase the risk of rejection. Be sure to discuss this with your doctor.
- If you are also being treated for **HIV** (see section "Other medicines and PegIntron").

- have a current or previous infection with the hepatitis B virus, since your doctor may want to monitor you more closely.
  Reminder: Please read the "Warnings and precautions" section of the Package Leaflet for **ribavirin** before using it in combination with this medicine.

Teeth and mouth problems have been reported in patients receiving this medicine in combination with ribavirin. You may develop **gum disease,** which could lead to loss of teeth. You may develop a **dry mouth** or **vomiting,** both of which can damage your teeth. It is important to brush your teeth thoroughly twice a day, rinse your mouth out if you vomit, and have regular dental check-ups.

During treatment, some patients may experience **eye problems,** or loss of vision in rare instances. Your doctor should carry out an eye examination before starting your treatment. In case of any changes in vision, you must tell your doctor and have a prompt and complete eye examination. If you have a medical condition that may lead to future eye problems (e.g. diabetes or high blood pressure), you should receive regular eye exams during therapy. If your eye disorder becomes more severe or if you develop new eye disorders, your treatment will be discontinued.

While being treated with PegIntron, your doctor may advise to drink extra fluids to help prevent low blood pressure.

Your doctor will test your blood before you begin therapy and throughout the treatment to make sure that the therapy you are getting is safe and effective.

Children and adolescents
This medicine is not recommended for use in patients under the age of 3 years.

Other medicines and PegIntron
Please tell your doctor or pharmacist if you, or the child you are caring for:
- are taking or have recently taken any other medicines or vitamins/nutritional supplements, including medicines obtained without a prescription.
- are infected with both **Human Immunodeficiency Virus** (HIV-positive) and **Hepatitis C Virus** (HCV) and are being treated with an anti-HIV medicine(s) – [nucleoside reverse transcriptase inhibitor (**NRTI**), and/or highly active anti-retroviral therapy (**HAART**)]. Your doctor will monitor you for signs and symptoms of these conditions.
  - Taking this medicine in combination with ribavirin and an anti-HIV medicine(s) may increase the risk of lactic acidosis, liver failure, and blood abnormalities: reduction in number of red blood cells, white blood cells and blood clotting cells called platelets. Patients with advanced liver disease receiving HAART may be at increased risk of worsening liver function, therefore adding treatment with this medicine alone or in combination with ribavirin may increase their risk.
  - With **zidovudine** or **stavudine**, it is not certain if ribavirin will change the way these medicines work. Therefore, your blood will be checked regularly to be sure that the HIV infection is not getting worse. If it gets worse, your doctor will decide whether or not your ribavirin treatment needs to be changed. Additionally, patients treated with this medicine and ribavirin combination therapy and **zidovudine** could be at increased risk of developing anaemia (low number of red blood cells). Therefore the use of zidovudine with this medicine and ribavirin combination therapy is not recommended.

  Reminder: Please read the "Other medicines" section of the Package Leaflet for **ribavirin** before using it in combination with this medicine.
- are taking **telbivudine**. If you take **telbivudine** with this medicine or any type of injectable interferon product, your risk of developing peripheral neuropathy (numbness, tingling and/or burning sensations in the arms and/or legs) is higher. These events may also be more severe. Therefore, you must not take this medicine at the same time as telbivudine.

Pregnancy and breast-feeding
If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor or pharmacist for advice before taking this medicine.

Pregnancy
In studies in pregnant animals, interferons have sometimes caused miscarriage. The effect of this medicine on human pregnancy is not known. Girls or women of childbearing potential need to use effective birth control during the treatment with this medicine.

Ribavirin can be very damaging to an unborn baby. Therefore, you and your partner must take **special precautions** in sexual activity if there is any chance for pregnancy to occur:
- if you are a **girl** or a **woman** of childbearing age who is taking ribavirin:
you must have a negative pregnancy test before treatment, each month during treatment, and for the 4 months after treatment is stopped. You must use an effective birth control during the time you are taking ribavirin and for 4 months after stopping treatment. This should be discussed with your doctor.
- if you are a **man** who is taking ribavirin:
do not have sex with a pregnant woman unless you **use a condom**. If your female partner is not pregnant but is of childbearing age, she must be tested for pregnancy each month during treatment and for the 7 months after treatment has stopped. You or your partner must use an effective birth control during the time you are taking ribavirin and for 7 months after stopping treatment. This should be discussed with your doctor.

Breast-feeding
It is not known whether this medicine is present in human milk. Therefore, you should not **breast-feed** an infant if you are taking this medicine. Ask your doctor for advice.

Reminder: Please read the "Pregnancy and breast-feeding" section of the Package Leaflet for **ribavirin** before using it in combination with this medicine.

Driving and using machines
Do not drive or operate any tools or machines if you feel tired, sleepy or confused while taking this medicine.

PegIntron contains sucrose
This medicine contains sucrose. If you have an intolerance to some sugars, contact your doctor before taking this medicine.
This medicine contains less than 1 mmol sodium (23 mg) per 0.7 ml, i.e., essentially "sodium-free".

3. How to use PegIntron

Always use this medicine exactly as your doctor or pharmacist has told you. Check with your doctor or pharmacist if you are not sure.

General information about taking this medicine

Your doctor has determined the correct dose of this medicine based on how much you, or the child you are caring for weighs. If necessary, the dose may be changed during treatment.

This medicine is intended for subcutaneous use. This means that it is injected through a short injection needle into the fatty tissue just under the skin. If you are injecting this medicine yourself, you will be instructed how to prepare and give the injection. **Detailed instructions for subcutaneous administration are provided at the end of this leaflet (see section "How to self-inject PegIntron")**.

Water for injection and PegIntron powder are provided in separate ampoules. Prepare the dose by adding water for injection to PegIntron powder just before you intend to inject it and use it

immediately. Look carefully at the solution you prepared before you use it. The solution should be clear and colourless. Do not use the solution if it is discoloured (changed its colour from the original) or if there are bits of particles in the solution. Discard any solution that is left in the vial after you give yourself the injection. For disposal instructions, see section 5 "How to store PegIntron".

Inject this medicine once each week on the same day. Injecting it at the same time of day each week will help you not to forget to take it.

Always use this medicine exactly as your doctor has told you. Do not exceed the recommended dosage, and take it for as long as prescribed.

If your doctor prescribes this medicine with ribavirin or with ribavirin and boceprevir, please read the Package Leaflets of ribavirin and boceprevir before you begin combination treatment.

Use in adults – PegIntron in combination treatment
This medicine, when given with ribavirin capsules, is usually given at a dose of 1.5 microgram per kilogram of body weight once a week. If you have kidney disease, your dose may be lower, depending upon your kidney function.

Use in adults – PegIntron alone
This medicine, when given alone, is usually given at a dose of 0.5 or 1.0 microgram per kilogram of body weight once a week, for 6 months to 1 year. If you have kidney disease, your dose may be lower, depending upon your kidney function. Your doctor will determine the correct dose for you.

Use in children 3 years of age and older and adolescents
PegIntron will be given in combination with ribavirin. The dose of PegIntron is determined by a calculation accounting for both height and weight. Your doctor will determine the correct dose for you, or the child you are caring for. The duration of treatment is up to 1 year based on the doctor's judgement for you, or the child you are caring for.

All patients
If you are injecting this medicine yourself, please be sure that the dose that has been prescribed is clearly provided on the package of medicine you receive.

If you use more PegIntron than you should
Tell your doctor or healthcare professional or the doctor or healthcare professional of the child you are caring for as soon as possible.

If you forget to take PegIntron
Take/administer the dose of this medicine as soon as you remember, but only if within 1-2 days after the forgotten dose. If it is very close to your next injection, do not double the dose to make up for the forgotten dose, but continue your treatment as usual.
If you are uncertain, contact your doctor or pharmacist or the doctor or pharmacist of the child you are caring for.

Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them. Although not all of these side effects may occur, they may need medical attention if they do. When this medicine is used alone, some of these effects are less likely to occur, and some have not occurred at all.

Psychiatric and central nervous system:
Some people get depressed when taking this medicine alone or in combination treatment with ribavirin, and in some cases people have had thoughts about threatening the life of others, suicidal thoughts or aggressive behaviour (sometimes directed against others). Some patients have actually committed suicide. Seek emergency care if you notice that you are becoming depressed or have

suicidal thoughts or change in your behaviour. Ask a family member or close friend to help you stay alert to signs of depression or changes in your behaviour.

Children and adolescents are particularly prone to develop depression when being treated with this medicine and ribavirin. Immediately contact the doctor or seek emergency treatment if they display any unusual behavioural symptoms, feel depressed, or feel they want to harm themselves or others.

Growth and development (children and adolescents):
With up to one year of treatment with this medicine in combination with ribavirin, some children and adolescents did not grow or gain weight as much as expected. Some children did not reach their projected height within 1-5.5 years after completing treatment.

Contact your doctor immediately if you notice any of the following serious side effects occurring during treatment:

Very common side effects (may affect more than 1 in 10 people):
- breathing problems (including shortness of breath),
- feeling depressed,
- trouble sleeping, thinking or concentrating, dizziness,
- severe stomach pain or cramps,
- fever or chills beginning after a few weeks of treatment,
- painful or inflamed muscles (sometimes severe),

Common side effects (may affect up to 1 in 10 people):
- chest pain, changes in the way your heart beats,
- confusion,
- difficulty remaining alert, numbness or tingling feeling,
- pain in your lower back or side, difficulty or inability to pass urine,
- problems with your eyes or your eyesight or hearing,
- severe or painful reddening of your skin or mucous membrane,
- severe bleeding from your nose, gums or any other part of your body.

Uncommon side effects (may affect up to 1 in 100 people):
- wanting to harm yourself,
- hallucinations,

Rare side effects (may affect up to 1 in 1,000 people):
- convulsion ("fit"),
- blood or clots in stool (or black, tarry stool),

Unknown frequency side effects (frequency cannot be estimated from the available data):
- Wanting to harm others.

Other side effects that have been reported **<u>in adults</u>** include:

Very common side effects (may affect more than 1 in 10 people):
- feeling depressed, irritability, trouble falling asleep or staying asleep, feeling anxious or nervous, difficulty concentrating, mood swings,
- headache, dizziness, tired feeling, shaking chills, fever, flu-like symptoms, virus infection, weakness,
- difficult breathing, pharyngitis (sore throat), coughing,
- stomach pain, vomiting, nausea, diarrhoea, loss of appetite, loss of weight, dry mouth,
- hair loss, itching, dry skin, rash, irritation or redness (and rarely, skin damage) at the site of injection,
- decreases in the number of red blood cells (that may cause fatigue, shortness of breath, dizziness), decrease in certain white blood cells (that makes you more susceptible to different infections),

- pain in joints and muscles, muscle and bone pain.

Common side effects (may affect up to 1 in 10 people):
- decrease in blood clotting cells called platelets, that may result in easy bruising and spontaneous bleeding, excess of uric acid (as in gout) in the blood, low calcium level in the blood,
- decrease in thyroid gland activity (which may make you feel tired, depressed, increase your sensitivity to cold and other symptoms), increase in thyroid gland activity (which may cause nervousness, heat intolerance and excessive sweating, weight loss, palpitation, tremors), swollen glands (swollen lymph nodes), thirst,
- changed behaviour or aggressive behaviour (sometimes directed against others), agitation, nervousness, feeling sleepy, trouble sleeping, unusual dreams, lack of interest in activities, lack of interest in sex, erectile problem, increased appetite, confusion, shaky hands, poor coordination, vertigo (spinning feeling), numbness, pain or tingling feeling, increased or decreased sensitivity to touch, tense muscles, limb pain, arthritis, migraine, increased sweating,
- eye pain or infection, blurred vision, dry or teary eyes, changes in hearing/loss of hearing, ringing in ears,
- sinusitis, respiratory infections, stuffy or runny nose, difficulty in speaking, nosebleed, cold sores (herpes simplex), fungal or bacterial infections, ear infection/earache,
- indigestion (stomach upset), heartburn, redness or sores in mouth, burning sensation on tongue, red or bleeding gums, constipation, intestinal gas (flatus), bloating, hemorrhoids, sore tongue, change in taste, tooth problem, excessive loss of body water, enlarged liver,
- psoriasis, sensitivity to sunlight, rash with raised spotted lesions, redness of skin or skin disorders, puffy face, puffy hands or feet, eczema (inflamed, red, itchy and dryness of the skin with possible oozing lesions), acne, hives, abnormal hair texture, nail disorder, pain at the site of injection,
- difficult, irregular or no menstrual period, abnormally heavy and prolonged menstrual period, problem affecting ovary or vagina, pain in breast, sexual problem, irritation of prostate gland, increased need to pass urine,
- chest pain, pain on the right side around your ribs, feeling unwell, low or high blood pressure, feeling faint, flushing, palpitations (pounding heart beat), rapid heart rate.

Uncommon side effects (may affect up to 1 in 100 people):
- suicide, attempted suicide, thoughts about threatening the life of yourself, panic attack, delusions, hallucination,
- hypersensitivity reaction to the medication, heart attack, inflammation of the pancreas, pain in bone and diabetes mellitus,
- cotton wool spots (white deposits on the retina).

Rare side effects (may affect up to 1 in 1,000 people):
- diabetic ketoacidosis (medical emergency due to build-up of ketone bodies in the blood as a result of out-of-control diabetes),
- seizures (convulsions) and bipolar disorders (mood disorders characterized by alternating episodes of sadness and excitement),
- eye problems including changes in vision, damage to the retina, obstruction of the retinal artery, inflammation of the optic nerve, swelling of the eye,
- congestive heart failure, abnormal heart rhythm, pericarditis (inflammation of the lining of the heart), inflammation and degeneration of muscle tissue and peripheral nerves, kidney problems, sarcoidosis (a disease characterized by persistent fever, weight loss, joint pain and swelling, skin lesions and swollen glands).

Very rare side effects (may affect up to 1 in 10,000 people):
- aplastic anaemia, stroke (cerebrovascular events), toxic epidermal necrolysis/Stevens Johnson Syndrome/erythema multiforme (a spectrum of rashes with varying degree of severity including death which may be associated with blisters in the mouth, nose, eyes and other mucosal membranes and sloughing of the affected area of the skin).
- loss of consciousness has occurred very rarely with alpha interferons, mostly in elderly patients treated at high doses.

Side effects of unknown frequency (frequency cannot be estimated from the available data):
- pure red cell aplasia (a condition where the body stopped or reduced the production of red blood cells). This causes severe anaemia, symptoms of which would include unusual tiredness and a lack of energy.
- facial palsy (weakness and slumping on one side to the face), severe allergic reactions such as angioedema (an allergic skin disease characterized by patches of swelling involving the skin and its subcutaneous layers, the mucous membranes, and sometimes the internal organs), mania (excessive or unreasonable enthusiasm), pericardial effusion (a fluid collection that develops between the pericardium (the lining of the heart) and the heart itself), Vogt-Koyanagi-Harada syndrome (an autoimmune inflammatory disorder affecting the eyes, skin and the membranes of the ears, brain and spinal cord), change in colour of the tongue.
- thoughts about threatening the life of others.
- pulmonary fibrosis (scarring of the lungs).
- pulmonary arterial hypertension – a disease of severe narrowing of the blood vessels in the lungs resulting in high blood pressure in the blood vessels that carry blood from the heart to the lungs. This may occur in particular in patients with risk factors such as HIV infection or severe liver problems (cirrhosis). The side effect may develop at various time points during treatment, typically several months after starting treatment with PegIntron.
- hepatitis B reactivation in HCV/HBV co-infected patients (recurrence of hepatitis B disease).

If you are an **HCV/HIV co-infected adult patient receiving HAART**, the addition of this medicine and ribavirin may increase your risk of lactic acidosis, liver failure and development of blood abnormalities (reduction in number of red blood cells which carry oxygen, certain white blood cells that fight infection, and blood clotting cells called platelets).

The following other side effects (not listed above) have occurred with the combination of this medicine and ribavirin capsules (adults) in HCV/HIV co-infected patients receiving HAART:
- oral candidiasis (oral thrush),
- defective metabolism of fat,
- CD4 lymphocytes decreased,
- appetite decreased,
- back pain,
- hepatitis,
- limb pain,
- and various laboratory blood values abnormalities.

Side effects in children and adolescents
The following effects have occurred **<u>in children and adolescents:</u>**

Very common side effects (may affect more than 1 in 10 people):
- loss of appetite, dizziness, headache, vomiting, nausea, stomach pain,
- hair loss, dry skin, pain in joints and muscles, redness at the site of injection,
- feeling irritable, tired feeling, feeling unwell, pain, chills, fever, flu-like symptoms, weakness,
- decrease in rate of growth (height and weight for age),
- decreases in red blood cells that may cause fatigue, shortness of breath, dizziness.

Common side effects (may affect up to 1 in 10 people):
- fungal infection, common cold, cold sores, pharyngitis (sore throat), sinusitis, ear infection, coughing, throat pain, feeling cold, eye pain,
- decrease in blood clotting cells called platelets, that may result in easy bruising and spontaneous bleeding, swollen glands (swollen lymph nodes), blood thyroid tests abnormalities, decrease in thyroid gland activity, which may make you feel tired, depressed, increase your sensitivity to cold and other symptoms,
- wanting or attempting to harm yourself aggressive behaviour, agitation, anger, mood changes, nervousness or restlessness, depression, feeling anxious, trouble falling asleep or staying asleep, emotional instability, poor quality sleep, feeling sleepy, disturbance in attention.

- changes in taste, diarrhoea, stomach upset, oral pain,
- fainting, palpitations (pounding heart beat), rapid heart rate, flushing, nosebleed,
- sores in mouth, scaling lips and clefts in the corners of the mouth, rash, redness of skin, itching, eczema (inflamed, red, itchy and dryness of the skin with possible oozing lesions), acne,
- back pain, muscle and bone pain, limb pain, dryness, pain, rash, irritation or itching at the site of injection.

Uncommon side effects (may affect up to 1 in 100 people):
- painful or difficult urination, urinary frequency, the presence of excess protein in the urine, painful menstruation,
- itchy anal area (pinworms or ascarids), inflammation of the lining membrane of the stomach and the intestines, inflamed gums, enlarged liver,
- abnormal behaviour, emotional disorder, fear, nightmare, tremor, decreased sensitivity to touch, numbness or tingling feeling, pain radiating along the course of one or more nerves, drowsiness,
- bleeding of the mucous membrane that lines the inner surface of the eyelids, itchy eyes, eye pain, blurred vision, intolerance to light,
- low blood pressure, paleness, nasal discomfort, runny nose, wheezing, difficult breathing, chest pain or discomfort,
- redness, swelling, pain of skin, shingles, skin sensitive to sunlight, rash with raised spotted lesions, skin discolouration, peeling of skin, shortening of muscle tissue, muscle twitching, facial pain, bruising.

Reporting of side effects
If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects, you can also help provide more information on the safety of this medicine.

Reminder to adult patients prescribed combination therapy of this medicine, boceprevir and ribavirin: Please read the "Possible side effects" section of these Package Leaflets.

5. How to store PegIntron

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the carton, after EXP.

Store in a refrigerator (2°C – 8°C).

Use the reconstituted solution (solution you prepared by adding water for injection to the PegIntron powder) immediately or within 24 hours when stored in a refrigerator (2°C - 8°C).

Do not use this medicine if you notice discolouration of the powder, which should be white. The reconstituted solution should be clear and colourless. Do not use if it is discoloured or if bits of particles are present. PegIntron vials are for single use only. Discard any unused material.

Do not throw away medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What PegIntron contains

- The active substance is peginterferon alfa-2b.

PegIntron 50 micrograms powder and solvent for solution for injection
Each vial contains 50 micrograms of peginterferon alfa-2b measured on a protein basis.
Each vial provides 50 micrograms/0.5 ml of solution when reconstituted as recommended.

PegIntron 80 micrograms powder and solvent for solution for injection
Each vial contains 80 micrograms of peginterferon alfa-2b measured on a protein basis.
Each vial provides 80 micrograms/0.5 ml of solution when reconstituted as recommended.

PegIntron 100 micrograms powder and solvent for solution for injection
Each vial contains 100 micrograms of peginterferon alfa-2b measured on a protein basis.
Each vial provides 100 micrograms/0.5 ml of solution when reconstituted as recommended.

PegIntron 120 micrograms powder and solvent for solution for injection
Each vial contains 120 micrograms of peginterferon alfa-2b measured on a protein basis.
Each vial provides 120 micrograms/0.5 ml of solution when reconstituted as recommended.

PegIntron 150 micrograms powder and solvent for solution for injection
Each vial contains 150 micrograms of peginterferon alfa-2b measured on a protein basis.
Each vial provides 150 micrograms/0.5 ml of solution when reconstituted as recommended

- The other ingredients are:
  Powder: disodium phosphate; anhydrous, sodium dihydrogen phosphate dihydrate; sucrose and polysorbate 80.
  Solvent: water for injections.

What PegIntron looks like and contents of the pack

This medicine is a powder and solvent (liquid) for solution for injection.
The white powder is contained in a 2 ml glass vial and the clear and colourless solvent is presented in a 2 ml glass ampoule.

PegIntron is available in different pack sizes:
- 1 vial of powder for solution for injection and 1 ampoule of solvent for injection;
- 1 vial of powder for solution for injection, 1 ampoule of solvent for injection, 1 injection syringe, 2 injection needles and 1 cleansing swab;
- 4 vials of powder for solution for injection and 4 ampoules of solvent for injection;
- 4 vials of powder for solution for injection, 4 ampoules of solvent for injection, 4 injection syringes, 8 injection needles and 4 cleansing swabs;
- 6 vials of powder for solution for injection and 6 ampoules of solvent for injection;
- 12 vials of powder for solution for injection, 12 ampoules of solvent for injection, 12 injection syringes, 24 injection needles and 12 cleansing swabs.

Not all pack sizes may be marketed.

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This leaflet was last revised in MM/YYYY

Detailed information on this medicine is available on the European Medicines Agency website: http://www.ema.europa.eu.

How to self-inject PegIntron?

Your healthcare provider will instruct you how to self-inject this medicine. Do not attempt to inject yourself unless you are sure you understand the procedure and requirements of self-injection. The following instructions explain how to inject this medicine yourself. Please read the instructions carefully and follow them step by step.

Preparation

Collect the necessary items before you begin:

- a vial of PegIntron powder for injection;
- an ampoule of water for injections solvent to prepare PegIntron injection;
- a 1 ml syringe;
- a long needle (for example 0.8 × 40 mm [21 gauge 1.5 inch]) to be used to add water for injections to the PegIntron powder vial;
- a short needle (for example 0.3 × 13 mm [30 gauge 0.5 inch]) for the subcutaneous injection;
- a cleansing swab.

Wash your hands carefully.

Reconstituting PegIntron powder for injection

Before reconstitution, this medicine may appear either as a white tablet-shaped solid that is whole or in pieces, or as a white powder.

When the total amount of solvent is combined with the full amount of PegIntron powder, the solution will be at the correct concentration to measure your dose (i.e., the labelled amount is contained in 0.5 ml).

A small volume is lost during preparation of this medicine for injection and when the dose is measured and injected. Therefore, each vial contains an extra amount of solvent and PegIntron powder to ensure delivery of the labeled dose in 0.5 ml of PegIntron, solution for injection.

- Remove the protective cap from the PegIntron vial.
- Clean the rubber top of the vial with a cleansing swab. You can save the swab to clean the skin area where you will inject the dose.
- Remove the syringe from the wrapping and **do not touch the tip of the syringe**.
- Take the long needle and place it firmly on to the tip of the syringe.
- Remove the needle guard without touching the needle and keep the syringe with the needle in your hand.
- Tap the top of the ampoule of solvent gently to make sure that all the liquid is at the bottom of the ampoule.
- Break off the top of the ampoule of solvent.
- Insert the needle in the ampoule of solvent and withdraw the total amount of solvent.
- Then insert the needle through the rubber top of the PegIntron vial. Gently place the needle tip against the glass wall of the vial without touching the cleaned top of the vial with your hands.
- Inject the solvent **SLOWLY,** aiming the stream of liquid at the glass wall of the vial. Do not aim the stream directly at the white solid or powder, or inject the liquid quickly, as this causes a greater amount of bubbles. The solution may appear cloudy or bubbly for a few minutes. This is to be expected and is not a cause for concern.
- Dissolve the entire contents by swirling the PegIntron vial with a gentle rotary motion leaving the needle and attached syringe in the vial.
  Do not shake, but gently turn the vial upside down until any powder at the top of the vial is dissolved.
- The contents should now be completely dissolved.
- Stand the vial upright and let any bubbles present in the solution rise to the top of the solution. Once 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. Use this solution immediately. If it cannot be used immediately, the solution may be refrigerated for up to 24 hours.

Measuring the dose of PegIntron 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 PegIntron 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 (change in the original colour of the solution) 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. These are thigh, outer surface of the upper arm (you may need the assistance of another person to use this site) and 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 inserted, 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 intended for single use must be discarded. Dispose of the syringe and needles safely in a closed container.

Package leaflet: Information for the user

PegIntron 50 micrograms powder and solvent for solution for injection in pre-filled pen
PegIntron 80 micrograms powder and solvent for solution for injection in pre-filled pen
PegIntron 100 micrograms powder and solvent for solution for injection in pre-filled pen
PegIntron 120 micrograms powder and solvent for solution for injection in pre-filled pen
PegIntron 150 micrograms powder and solvent for solution for injection in pre-filled pen
peginterferon alfa-2b

Read all of this leaflet carefully before you start using this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What PegIntron is and what it is used for
2. What you need to know before you use PegIntron
3. How to use PegIntron
4. Possible side effects
5. How to store PegIntron
6. Contents of the pack and other information

1. What PegIntron is and what it is used for

The active substance in this medicine is a protein called peginterferon alfa-2b, which belongs to the class of medicines called interferons. Interferons are made by your body's immune system to help fight infections and severe diseases. This medicine is injected into your body to work with your immune system. This medicine is used for the treatment of chronic hepatitis C, a viral infection of the liver.

Adults
The combination of this medicine, ribavirin and boceprevir is recommended for use for some types of chronic hepatitis C virus infection (also called HCV infection) in adults 18 years of age and older. It may be used in adults who have not been previously treated for HCV infection or who have previously used medicines called interferons and pegylated interferons.

The combination of this medicine and ribavirin is recommended for adults 18 years of age and older who have not previously been treated with these medicines. This includes adults also infected with clinically stable HIV (Human Immunodeficiency Virus). The combination can also be used to treat adults who have already failed treatment with an interferon alpha or peginterferon alpha in combination with ribavirin or interferon alpha alone.

If you have a medical condition making use of ribavirin dangerous or if you already have had a problem taking it, your doctor will likely prescribe this medicine alone.

If you have any further questions on the use of this medicine, ask your doctor or pharmacist.

Children and adolescents
This medicine is used in combination with ribavirin in children 3 years of age and older and adolescents who have not been treated previously for chronic hepatitis C.

2. What you need to know before you use PegIntron

Do not use PegIntron
You should **tell your doctor** before starting treatment if you, or the child you are caring for:
- are **allergic** to peginterferon alfa-2b or any of the other ingredients of this medicine (listed in section 6).
- are **allergic** to any interferon.
- have had severe **heart problems**.
- have **heart disease** that has not been well controlled during the past 6 months.
- have severe medical conditions that leave you very weak.
- have autoimmune hepatitis or any other problem with your **immune system.**
- are taking medicine that suppresses (weakens) your immune system.
- have advanced, uncontrolled **liver disease** (other than hepatitis C).
- have **thyroid disease** that is not well controlled with medicines.
- have **epilepsy**, a condition that causes convulsions (seizures, or "fits").
- are being treated with **telbivudine** (see section "Other medicines and PegIntron").

You **must not use** PegIntron if any of the conditions above should apply to you, or the child you are caring for.

In addition, children and adolescents **must not use** this medicine if they have had **serious nervous or mental problems,** such as **severe depression** or **thoughts of suicide.**

Reminder: Please also read the "Do not take" section of the Package Leaflet for **ribavirin** and **boceprevir** before using them in combination with this medicine.

Warnings and precautions
Seek medical help immediately in case of a severe allergic reaction (such as difficulty in breathing, wheezing, or hives).

Talk to your doctor before taking this medicine if you, or the child you are caring for:
- have had a severe **nervous or mental disorder** or have a **history of substance abuse** (e.g. alcohol or drugs).
  The use of this medicine in children and adolescents with existence of or history of severe psychiatric conditions is not allowed (see section "Do not use PegIntron" above).
- are being treated for a **mental illness** or had treatment in the past for any other nervous or mental disorder, including **depression** (such as feelings of sadness, dejection) or **suicidal or homicidal behaviour** (see section 4 "Possible side effects").
- have ever had a **heart attack** or a **heart problem**.
- have **kidney disease**, your doctor may prescribe a lower than usual dose and monitor your kidney blood values regularly during treatment. If this medicine is used in combination with ribavirin, your doctor should monitor you, or the child you are caring for more carefully for a decrease in red blood cell count.
- have **cirrhosis** or other **liver problems** (other than hepatitis C).
- develop symptoms associated with a **cold** or other respiratory infection, such as **fever**, **cough**, or any **difficulty in breathing**.
- are **diabetic** or have **high blood pressure**, your doctor may ask you, or the child you are caring for to have an eye examination.
- have had any serious **illness affecting breathing** or **blood**.
- have the skin disorders, **psoriasis** or **sarcoidosis**, which may become worse while you are using this medicine.
- are planning to become **pregnant**, discuss this with your doctor before starting to use this medicine.
- have received an **organ transplant**, either kidney or liver, interferon treatment may increase the risk of rejection. Be sure to discuss this with your doctor.
- If you are also being treated for **HIV** (see section "Other medicines and PegIntron").

- have a current or previous infection with the hepatitis B virus, since your doctor may want to monitor you more closely.
  Reminder: Please read the "Warnings and precautions" section of the Package Leaflet for **ribavirin** before using it in combination with this medicine.

Teeth and mouth problems have been reported in patients receiving this medicine in combination with ribavirin. You may develop **gum disease,** which could lead to loss of teeth. You may develop a **dry mouth** or **vomiting,** both of which can damage your teeth. It is important to brush your teeth thoroughly twice a day, rinse your mouth out if you vomit, and have regular dental check-ups.

During treatment, some patients may experience **eye problems,** or loss of vision in rare instances. Your doctor should carry out an eye examination before starting your treatment. In case of any changes in vision, you must tell your doctor and have a prompt and complete eye examination. If you have a medical condition that may lead to future eye problems (e.g. diabetes or high blood pressure), you should receive regular eye exams during therapy. If your eye disorder becomes more severe or if you develop new eye disorders, your treatment will be discontinued.

While being treated with PegIntron, your doctor may advise to drink extra fluids to help prevent low blood pressure.

Your doctor will test your blood before you begin therapy and throughout the treatment to make sure that the therapy you are getting is safe and effective.

Children and adolescents
This medicine is not recommended for use in patients under the age of 3 years.

Other medicines and PegIntron
Please tell your doctor or pharmacist if you, or the child you are caring for:
- are taking or have recently taken any other medicines or vitamins/nutritional supplements, including medicines obtained without a prescription.
- are infected with both **Human Immunodeficiency Virus** (HIV-positive) and **Hepatitis C Virus** (HCV) and are being treated with an anti-HIV medicine(s) – [nucleoside reverse transcriptase inhibitor (**NRTI**), and/or highly active anti-retroviral therapy (**HAART**)]. Your doctor will monitor you for signs and symptoms of these conditions.
  - Taking this medicine in combination with ribavirin and an anti-HIV medicine(s) may increase the risk of lactic acidosis, liver failure, and blood abnormalities: reduction in number of red blood cells, white blood cells and blood clotting cells called platelets. Patients with advanced liver disease receiving HAART may be at increased risk of worsening liver function, therefore adding treatment with this medicine alone or in combination with ribavirin may increase their risk.
  - With **zidovudine** or **stavudine**, it is not certain if ribavirin will change the way these medicines work. Therefore, your blood will be checked regularly to be sure that the HIV infection is not getting worse. If it gets worse, your doctor will decide whether or not your ribavirin treatment needs to be changed. Additionally, patients treated with this medicine and ribavirin combination therapy and **zidovudine** could be at increased risk of developing anaemia (low number of red blood cells). Therefore the use of zidovudine with this medicine and ribavirin combination therapy is not recommended.

  Reminder: Please read the "Other medicines" section of the Package Leaflet for **ribavirin** before using it in combination with this medicine.
- are taking **telbivudine**. If you take **telbivudine** with this medicine or any type of injectable interferon product, your risk of developing peripheral neuropathy (numbness, tingling and/or burning sensations in the arms and/or legs) is higher. These events may also be more severe. Therefore, you must not take this medicine at the same time as telbivudine.

Pregnancy and breast-feeding
If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor or pharmacist for advice before taking this medicine.

Pregnancy
In studies in pregnant animals, interferons have sometimes caused miscarriage. The effect of this medicine on human pregnancy is not known. Girls or women of childbearing potential need to use effective birth control during the treatment with this medicine.

Ribavirin can be very damaging to an unborn baby. Therefore, you and your partner must take **special precautions** in sexual activity if there is any chance for pregnancy to occur:
- if you are a **girl** or a **woman** of childbearing age who is taking ribavirin:
you must have a negative pregnancy test before treatment, each month during treatment, and for the 4 months after treatment is stopped. You must use an effective birth control during the time you are taking ribavirin and for 4 months after stopping treatment. This should be discussed with your doctor.
- if you are a **man** who is taking ribavirin:
do not have sex with a pregnant woman unless you **use a condom**. If your female partner is not pregnant but is of childbearing age, she must be tested for pregnancy each month during treatment and for the 7 months after treatment has stopped. You or your partner must use an effective birth control during the time you are taking ribavirin and for 7 months after stopping treatment. This should be discussed with your doctor.

Breast-feeding
It is not known whether this medicine is present in human milk. Therefore, you should not **breast-feed** an infant if you are taking this medicine. Ask your doctor for advice.

Reminder: Please read the "Pregnancy and breast-feeding" section of the Package Leaflet for **ribavirin** before using it in combination with this medicine.

Driving and using machines
Do not drive or operate any tools or machines if you feel tired, sleepy or confused while taking this medicine.

PegIntron contains sucrose
This medicine contains sucrose. If you have an intolerance to some sugars, contact your doctor before taking this medicine.
This medicine contains less than 1 mmol sodium (23 mg) per 0.7 ml, i.e., essentially "sodium-free".

3. How to use PegIntron

Always use this medicine exactly as your doctor or pharmacist has told you. Check with your doctor or pharmacist if you are not sure.

General information about taking this medicine

Your doctor has determined the correct dose of this medicine based on how much you, or the child you are caring for weighs. If necessary, the dose may be changed during treatment.

This medicine is intended for subcutaneous use. This means that it is injected through a short needle into the fatty tissue just under the skin. If you are injecting this medicine yourself, you will be instructed how to prepare and give the injection. **Detailed instructions for subcutaneous administration are provided at the end of this leaflet (see ANNEX TO THE PACKAGE LEAFLET "How to use the PegIntron pre-filled pen")**.

Prepare the dose just before you intend to inject it and use it immediately. Look carefully at the solution you prepared before you use it. The solution should be clear and colourless. Do not use the

solution if it is discoloured (changed its colour from the original) or if there are bits of particles in the solution. Discard the PegIntron pre-filled pen (CLEARCLICK) with any solution that is left in it after you give yourself the injection. For disposal instructions, see section 5 "How to store PegIntron".

Inject this medicine once each week on the same day. Injecting it at the same time of day each week will help you not to forget to take it.

Always use this medicine exactly as your doctor has told you. Do not exceed the recommended dosage, and take it for as long as prescribed.

If your doctor prescribes this medicine with ribavirin or with ribavirin and boceprevir, please read the Package Leaflets of ribavirin and boceprevir before you begin combination treatment.

Use in adults – PegIntron in combination treatment
This medicine, when given with ribavirin capsules, is usually given at a dose of 1.5 microgram per kilogram of body weight once a week. If you have kidney disease, your dose may be lower, depending upon your kidney function.

Use in adults – PegIntron alone
This medicine, when given alone, is usually given at a dose of 0.5 or 1.0 microgram per kilogram of body weight once a week, for 6 months to 1 year. If you have kidney disease, your dose may be lower, depending upon your kidney function. Your doctor will determine the correct dose for you.

Use in children 3 years of age and older and adolescents
PegIntron will be given in combination with ribavirin. The dose of PegIntron is determined by a calculation accounting for both height and weight. Your doctor will determine the correct dose for you, or the child you are caring for. The duration of treatment is up to 1 year based on the doctor's judgement for you, or the child you are caring for.

All patients
If you are injecting this medicine yourself, please be sure that the dose that has been prescribed is clearly provided on the package of medicine you receive.

If you use more PegIntron than you should
Tell your doctor or healthcare professional or the doctor or healthcare professional of the child you are caring for as soon as possible.

If you forget to take PegIntron
Take/administer the dose of this medicine as soon as you remember, but only if within 1-2 days after the forgotten dose. If it is very close to your next injection, do not double the dose to make up for the forgotten dose, but continue your treatment as usual.
If you are uncertain, contact your doctor or pharmacist or the doctor or pharmacist of the child you are caring for.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them. Although not all of these side effects may occur, they may need medical attention if they do. When this medicine is used alone, some of these effects are less likely to occur, and some have not occurred at all.

Psychiatric and central nervous system:
Some people get depressed when taking this medicine alone or in combination treatment with ribavirin, and in some cases people have had thoughts about threatening the life of others, suicidal thoughts or aggressive behaviour (sometimes directed against others). Some patients have actually committed suicide. Seek emergency care if you notice that you are becoming depressed or have

suicidal thoughts or change in your behaviour. Ask a family member or close friend to help you stay alert to signs of depression or changes in your behaviour.

Children and adolescents are particularly prone to develop depression when being treated with this medicine and ribavirin. Immediately contact the doctor or seek emergency treatment if they display any unusual behavioural symptoms, feel depressed, or feel they want to harm themselves or others.

Growth and development (children and adolescents):
With up to one year of treatment with this medicine in combination with ribavirin, some children and adolescents did not grow or gain weight as much as expected. Some children did not reach their projected height within 1-5.5 years after completing treatment.

Contact your doctor immediately if you notice any of the following serious side effects occurring during treatment:
Very common side effects (may affect more than 1 in 10 people):
- breathing problems (including shortness of breath),
- feeling depressed,
- trouble sleeping, thinking or concentrating, dizziness,
- severe stomach pain or cramps,
- fever or chills beginning after a few weeks of treatment,
- painful or inflamed muscles (sometimes severe),

Common side effects (may affect up to 1 in 10 people):
- chest pain, changes in the way your heart beats,
- confusion,
- difficulty remaining alert, numbness or tingling feeling,
- pain in your lower back or side, difficulty or inability to pass urine,
- problems with your eyes or your eyesight or hearing,
- severe or painful reddening of your skin or mucous membrane,
- severe bleeding from your nose, gums or any other part of your body.

Uncommon side effects (may affect up to 1 in 100 people):
- wanting to harm yourself,
- hallucinations,

Rare side effects (may affect up to 1 in 1,000 people):
- convulsion ("fit"),
- blood or clots in stool (or black, tarry stool),

Unknown frequency side effects (frequency cannot be estimated from the available data):
- Wanting to harm others.

Other side effects that have been reported **in adults** include:

Very common side effects (may affect more than 1 in 10 people):
- feeling depressed, irritability, trouble falling asleep or staying asleep, feeling anxious or nervous, difficulty concentrating, mood swings,
- headache, dizziness, tired feeling, shaking chills, fever, flu-like symptoms, virus infection, weakness,
- difficult breathing, pharyngitis (sore throat), coughing,
- stomach pain, vomiting, nausea, diarrhoea, loss of appetite, loss of weight, dry mouth,
- hair loss, itching, dry skin, rash, irritation or redness (and rarely, skin damage) at the site of injection,
- decreases in the number of red blood cells (that may cause fatigue, shortness of breath, dizziness), decrease in certain white blood cells (that makes you more susceptible to different infections),
- pain in joints and muscles, muscle and bone pain.

Common side effects (may affect up to 1 in 10 people):
- decrease in blood clotting cells called platelets, that may result in easy bruising and spontaneous bleeding, excess of uric acid (as in gout) in the blood, low calcium level in the blood,
- decrease in thyroid gland activity (which may make you feel tired, depressed, increase your sensitivity to cold and other symptoms), increase in thyroid gland activity (which may cause nervousness, heat intolerance and excessive sweating, weight loss, palpitation, tremors), swollen glands (swollen lymph nodes), thirst,
- changed behaviour or aggressive behaviour (sometimes directed against others), agitation, nervousness, feeling sleepy, trouble sleeping, unusual dreams, lack of interest in activities, lack of interest in sex, erectile problem, increased appetite, confusion, shaky hands, poor coordination, vertigo (spinning feeling), numbness, pain or tingling feeling, increased or decreased sensitivity to touch, tense muscles, limb pain, arthritis, migraine, increased sweating,
- eye pain or infection, blurred vision, dry or teary eyes, changes in hearing/loss of hearing, ringing in ears,
- sinusitis, respiratory infections, stuffy or runny nose, difficulty in speaking, nosebleed, cold sores (herpes simplex), fungal or bacterial infections, ear infection/earache,
- indigestion (stomach upset), heartburn, redness or sores in mouth, burning sensation on tongue, red or bleeding gums, constipation, intestinal gas (flatus), bloating, hemorrhoids, sore tongue, change in taste, tooth problem, excessive loss of body water, enlarged liver,
- psoriasis, sensitivity to sunlight, rash with raised spotted lesions, redness of skin or skin disorders, puffy face, puffy hands or feet, eczema (inflamed, red, itchy and dryness of the skin with possible oozing lesions), acne, hives, abnormal hair texture, nail disorder, pain at the site of injection,
- difficult, irregular or no menstrual period, abnormally heavy and prolonged menstrual period, problem affecting ovary or vagina, pain in breast, sexual problem, irritation of prostate gland, increased need to pass urine,
- chest pain, pain on the right side around your ribs, feeling unwell, low or high blood pressure, feeling faint, flushing, palpitations (pounding heart beat), rapid heart rate.

Uncommon side effects (may affect up to 1 in 100 people):
- suicide, attempted suicide, thoughts about threatening the life of yourself, panic attack, delusions, hallucination,
- hypersensitivity reaction to the medication, heart attack, inflammation of the pancreas, pain in bone and diabetes mellitus,
- cotton wool spots (white deposits on the retina).

Rare side effects (may affect up to 1 in 1,000 people):
- diabetic ketoacidosis (medical emergency due to build-up of ketone bodies in the blood as a result of out-of-control diabetes),
- seizures (convulsions) and bipolar disorders (mood disorders characterized by alternating episodes of sadness and excitement),
- eye problems including changes in vision, damage to the retina, obstruction of the retinal artery, inflammation of the optic nerve, swelling of the eye,
- congestive heart failure, abnormal heart rhythm, pericarditis (inflammation of the lining of the heart), inflammation and degeneration of muscle tissue and peripheral nerves, kidney problems, sarcoidosis (a disease characterized by persistent fever, weight loss, joint pain and swelling, skin lesions and swollen glands).

Very rare side effects (may affect up to 1 in 10,000 people):
- aplastic anaemia, stroke (cerebrovascular events), toxic epidermal necrolysis/Stevens Johnson Syndrome/erythema multiforme (a spectrum of rashes with varying degree of severity including death which may be associated with blisters in the mouth, nose, eyes and other mucosal membranes and sloughing of the affected area of the skin).
- loss of consciousness has occurred very rarely with alpha interferons, mostly in elderly patients treated at high doses.

Side effects of unknown frequency (frequency cannot be estimated from the available data):
- pure red cell aplasia (a condition where the body stopped or reduced the production of red blood cells). This causes severe anaemia, symptoms of which would include unusual tiredness and a lack of energy.
- facial palsy (weakness and slumping on one side to the face), severe allergic reactions such as angioedema (an allergic skin disease characterized by patches of swelling involving the skin and its subcutaneous layers, the mucous membranes, and sometimes the internal organs), mania (excessive or unreasonable enthusiasm), pericardial effusion (a fluid collection that develops between the pericardium (the lining of the heart) and the heart itself), Vogt-Koyanagi-Harada syndrome (an autoimmune inflammatory disorder affecting the eyes, skin and the membranes of the ears, brain and spinal cord), change in colour of the tongue.
- thoughts about threatening the life of others.
- pulmonary fibrosis (scarring of the lungs).
- pulmonary arterial hypertension – a disease of severe narrowing of the blood vessels in the lungs resulting in high blood pressure in the blood vessels that carry blood from the heart to the lungs. This may occur in particular in patients with risk factors such as HIV infection or severe liver problems (cirrhosis). The side effect may develop at various time points during treatment, typically several months after starting treatment with PegIntron.
- hepatitis B reactivation in HCV/HBV co-infected patients (recurrence of hepatitis B disease).

If you are an **HCV/HIV co-infected adult patient receiving HAART**, the addition of this medicine and ribavirin may increase your risk of lactic acidosis, liver failure, and development of blood abnormalities (reduction in number of red blood cells which carry oxygen, certain white blood cells that fight infection, and blood clotting cells called platelets).

The following other side effects (not listed above) have occurred with the combination of this medicine and ribavirin capsules (adults) in HCV/HIV co-infected patients receiving HAART:
- oral candidiasis (oral thrush),
- defective metabolism of fat,
- CD4 lymphocytes decreased,
- appetite decreased,
- back pain,
- hepatitis,
- limb pain,
- and various laboratory blood values abnormalities.

Side effects in children and adolescents
The following effects have occurred **<u>in children and adolescents:</u>**

Very common side effects (may affect more than 1 in 10 people):
- loss of appetite, dizziness, headache, vomiting, nausea, stomach pain,
- hair loss, dry skin, pain in joints and muscles, redness at the site of injection,
- feeling irritable, tired feeling, feeling unwell, pain, chills, fever, flu-like symptoms, weakness,
- decrease in rate of growth (height and weight for age),
- decreases in red blood cells that may cause fatigue, shortness of breath, dizziness.

Common side effects (may affect up to 1 in 10 people):
- fungal infection, common cold, cold sores, pharyngitis (sore throat), sinusitis, ear infection, coughing, throat pain, feeling cold, eye pain,
- decrease in blood clotting cells called platelets, that may result in easy bruising and spontaneous bleeding, swollen glands (swollen lymph nodes), blood thyroid tests abnormalities, decrease in thyroid gland activity, which may make you feel tired, depressed, increase your sensitivity to cold and other symptoms,
- wanting or attempting to harm yourself, aggressive behaviour, agitation, anger, mood changes, nervousness or restlessness, depression, feeling anxious, trouble falling asleep or staying asleep, emotional instability, poor quality sleep, feeling sleepy, disturbance in attention.
- changes in taste, diarrhoea, stomach upset, oral pain,

- fainting, palpitations (pounding heart beat), rapid heart rate, flushing, nosebleed,
- sores in mouth, scaling lips and clefts in the corners of the mouth, rash, redness of skin, itching, eczema (inflamed, red, itchy and dryness of the skin with possible oozing lesions), acne,
- back pain, muscle and bone pain, limb pain, dryness, pain, rash, irritation or itching at the site of injection.

Uncommon side effects (may affect up to 1 in 100 people):
- painful or difficult urination, urinary frequency, the presence of excess protein in the urine, painful menstruation,
- itchy anal area (pinworms or ascarids), inflammation of the lining membrane of the stomach and the intestines, inflamed gums, enlarged liver,
- abnormal behaviour, emotional disorder, fear, nightmare, tremor, decreased sensitivity to touch, numbness or tingling feeling, pain radiating along the course of one or more nerves, drowsiness,
- bleeding of the mucous membrane that lines the inner surface of the eyelids, itchy eyes, eye pain, blurred vision, intolerance to light,
- low blood pressure, paleness, nasal discomfort, runny nose, wheezing, difficult breathing, chest pain or discomfort,
- redness, swelling, pain of skin, shingles, skin sensitive to sunlight, rash with raised spotted lesions, skin discolouration, peeling of skin, shortening of muscle tissue, muscle twitching, facial pain, bruising.

Reporting of side effects
If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects, you can also help provide more information on the safety of this medicine.

Reminder to adult patients prescribed combination therapy of this medicine, boceprevir and ribavirin: Please read the "Possible side effects" section of these Package Leaflets.

5. How to store PegIntron

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the carton, after EXP.

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

Use the reconstituted solution (solution you prepared by mixing the powder and the liquid in the pre-filled pen) immediately or within 24 hours when stored in a refrigerator (2°C - 8°C).

Do not use this medicine if you notice discolouration of the powder, which should be white. The reconstituted solution should be clear and colourless. Do not use if it is discoloured or if bits of particles are present. After administering the dose, discard the PegIntron pre-filled pen (CLEARCLICK) and any unused solution contained in it.

Do not throw away medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What PegIntron contains

- The active substance is peginterferon alfa-2b.

PegIntron 50 micrograms powder and solvent for solution for injection in pre-filled pen
Each pre-filled pen contains 50 micrograms of peginterferon alfa-2b measured on a protein basis.
Each pre-filled pen provides 50 micrograms/0.5 ml of solution when reconstituted as recommended.

PegIntron 80 micrograms powder and solvent for solution for injection in pre-filled pen
Each pre-filled pen contains 80 micrograms of peginterferon alfa-2b measured on a protein basis.
Each pre-filled pen provides 80 micrograms/0.5 ml of solution when reconstituted as recommended.

PegIntron 100 micrograms powder and solvent for solution for injection in pre-filled pen
Each pre-filled pen contains 100 micrograms of peginterferon alfa-2b measured on a protein basis.
Each pre-filled pen provides 100 micrograms/0.5 ml of solution when reconstituted as recommended.

PegIntron 120 micrograms powder and solvent for solution for injection in pre-filled pen
Each pre-filled pen contains 120 micrograms of peginterferon alfa-2b measured on a protein basis.
Each pre-filled pen provides 120 micrograms/0.5 ml of solution when reconstituted as recommended.

PegIntron 150 micrograms powder and solvent for solution for injection in pre-filled pen
Each pre-filled pen contains 150 micrograms of peginterferon alfa-2b measured on a protein basis.
Each pre-filled pen provides 150 micrograms/0.5 ml of solution when reconstituted as recommended.

- The other ingredients are:
  Powder: disodium phosphate, anhydrous; sodium dihydrogen phosphate dihydrate; sucrose and polysorbate 80.
  Solvent: water for injections.

What PegIntron looks like and contents of the pack

This medicine is a powder and solvent (liquid) for solution for injection in a pre-filled pen (CLEARCLICK).
The white powder and the clear and colourless solvent are both contained in a two-chamber glass cartridge assembled into a single use pre-filled pen.

PegIntron is available in different pack sizes:
- 1 pre-filled pen containing powder and solvent for solution for injection,
  1 needle ("Push-On Needle"),
  2 cleansing swabs;
- 4 pre-filled pens containing powder and solvent for solution for injection,
  4 needles ("Push-On Needle"),
  8 cleansing swabs;
- 12 pre-filled pens containing powder and solvent for solution for injection,
  12 needles ("Push-On Needle"),
  24 cleansing swabs.

Not all pack sizes may be marketed.

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This leaflet was last revised in MM/YYYY

Detailed information on this medicine is available on the European Medicines Agency website: http://www.ema.europa.eu.

ANNEX TO THE PACKAGE LEAFLET

How to use the PegIntron pre-filled pen
The following instructions explain how to use the pre-filled pen to inject yourself. Please read the instructions carefully and follow them step by step. Your healthcare provider will instruct you on how to give the injections. Do not attempt to administer an injection until you are sure you understand how to use the pre-filled pen. Each pre-filled pen is for single use only.

Getting ready
- Find a well-lit, clean flat work surface such as a table.
- Take the pre-filled pen out of the refrigerator. Look at the date printed on the carton after EXP to make sure that the expiration date has not passed. Do not use if the expiration date has passed.
- Remove the pre-filled pen from the carton.
- Lay the pre-filled pen on a flat clean surface and wait until it reaches room temperature (but not more than 25°C). This may take up to 20 minutes.
- Wash your hands well with soap and warm water. Keep your work area, your hands, and the injection site clean to decrease the risk of infection.

You will need the following supplies that are included in the package:

- a pre-filled pen (CLEARCLICK)
- a needle ("Push-On Needle")
- 2 alcohol swabs

1. Mix
- Hold the pre-filled pen upright with the dial on the bottom.
- Turn the dial to number 1 (see Figure 1). You may hear a "click" sound.

Figure 1

- DO NOT SHAKE TO MIX. Gently turn the pre-filled pen up-side-down two times to mix (see Figure 2).

Figure 2

- Look in the window. The solution should be clear and colourless before use. Some bubbles may be present, but this is normal. Do not use if it is discoloured or if particles are present.

2. Add needle

- Turn the dial to number 2 (see Figure 3). You may hear a "click" sound.

Figure 3

- Wipe the top of the pre-filled pen where the needle is going to be attached with an alcohol swab (see Figure 4).

Figure 4

- Remove the yellow paper from the needle cap before attaching the needle ("Push-On Needle") to the pre-filled pen (see Figure 5),

Figure 5

- Support the pre-filled pen in upright position and push the needle straight down firmly (see Figure 6). You might hear a soft sound when pushing on the needle.

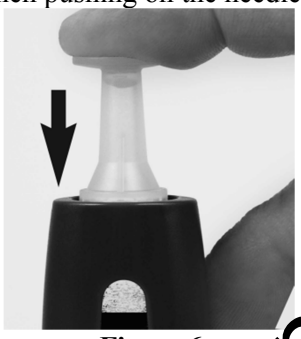

Figure 6

- Remove the needle cap. You may see some liquid trickle out of the needle (see Figure 7). This is normal.

Figure 7

3. Dial dose

- Turn the dial to **your prescribed dose** (see Figure 8). You may hear clicking sounds as you dial. Note: The needle shield will automatically SNAP UP as you dial (see Figure 9). You may dial up or down to any dose prior to injection.

Figure 8

Figure 9

You are ready to inject

- Choose an injection site on your stomach area (abdomen) or thigh. Avoid your belly button (navel) and waistline. If you are very thin, you should only use the thigh for injection. You should use a different place each time you give yourself an injection. Do not inject PegIntron into an area where the skin is irritated, red, bruised, infected, or has scars, stretch marks, or lumps.
- Wipe the injection site with a new alcohol swab. Let the skin air dry.
- Pinch a fold of loose skin in the area you have cleaned for injection.
- Press the pre-filled pen against the skin as shown in Figure 10. The shield will automatically glide back to allow the needle to inject the medicine.
- **Hold the pre-filled pen against the skin for 15 seconds.** Note: The pre-filled pen will make a clicking sound for up to 10 seconds – depending on your dose. Additional 5 seconds ensures complete dose delivery.
  Note: Once the pre-filled pen is removed from the skin, the needle shield will lock in place.

Figure 10: Thigh injection

Disposal of the injection materials

The pre-filled pen, needle and all injection materials are intended for single use and must be discarded after the injection. Dispose of the used pre-filled pen safely in a closed container. Ask your healthcare provider or pharmacist for an appropriate container.