SCIENTIFIC DISCUSSION

This module reflects the initial scientific discussion and scientific discussion on procedures, which have been finalised before 7 May 2002. For scientific information on procedures after this date please refer to module 8B.

1. Introduction

The active substance is a polyethylene glycol-modified ("pegylated") derivative of IntronA (human recombinant interferon alfa-2b). The modification was developed in order to decrease the systemic clearance of the active moiety. In addition, an improved benefit risk relationship was aimed for, based on the hypothesis that Cmax governs side effects, while efficacy may relate better to AUC. This is the first PEG-conjugate of a therapeutic protein for which an assessment in the centralised procedure is made.

*Therapeutic indication***.** PegIntron was initially indicated in monotherapy in case of intolerance or contraindication to ribavirin, for the treatment of adult patients with histologically proven chronic hepatitis C who have serum markers for virus C replication, e.g. those who have elevated transaminases without liver decompensation and who are positive for serum HCV-RNA or anti-HCV.

The indication was extended following the first authorisation of PegIntron further to the availability of preclinical and clinical data on the use of peginterferon alfa-2b in combination with ribavirin.

The indication currently approved is therefore the following:

PegIntron is indicated for the treatment of adult patients with histologically proven chronic hepatitis C who has elevated transaminases without liver decompensation and who are positive for serum HCV-RNA or anti-HCV.

The best way to use PegIntron in this indication is in combination with ribavirin.

This combination is indicated in naïve patients as well as in patients who have previously responded (with normalisation of ALT at the end of treatment) to interferon alpha monotherapy but who have subsequently relapsed.

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

Proposed posology**.**
Treatment should be initiated and monitored only by a physician experienced in the management of patients with hepatitis C.

PegIntron should be administered as a once weekly subcutaneous injection. The dose administered depends on whether it is used in combination with ribavirin or as monotherapy.

Combination therapy
PegIntron 1.5 micrograms/kg/week in combination with ribavirin capsules.

The dose of ribavirin to be used in combination with PegIntron is based on patient body weight (**Table 1**). Ribavirin capsules are to be administered orally each day in two divided doses with food (morning and evening).

Table 1 Ribavirin dose based on body weight		
Patient weight (kg)	**Daily ribavirin dose**	**Number of 200 mg capsules**
< 65	800 mg	4[a]
65 – 85	1,000 mg	5[b]
> 85	1,200 mg	6[c]

a: 2 morning, 2 evening
b: 2 morning, 3 evening
c: 3 morning, 3 evening

Duration of treatment: Based on the results of clinical trials, it is recommended that patients be treated for at least six months. During those clinical trials in which patients were treated for one year, patients who failed to show a virologic response after six months of treatment (HCV-RNA below lower limit of detection) were unlikely to become sustained virologic responders (HCV-RNA below lower limit of detection six months after withdrawal of treatment).

- **Genotype 1**: Treatment should be continued for another six month period (i.e., a total of one year) in patients who exhibit negative HCV-RNA after six months of treatment.
- **Genotypes Non-1**: The decision to extend therapy to one year in patients with negative HCV-RNA after six months of treatment should be based on other prognostic factors (e.g., age > 40 years, male gender, bridging fibrosis).

PegIntron monotherapy
As monotherapy the PegIntron regimen is 0.5 or 1.0 microgram/kg/week.

Duration of treatment: It is recommended that patients be treated initially for six months. In patients showing loss of HCV-RNA at six months, treatment is to be continued for an additional six months, i.e., one year of treatment.

Dose modification for all patients
If severe adverse reactions or laboratory abnormalities develop during treatment with PegIntron monotherapy or PegIntron in combination with ribavirin, modify the dosages of each product if appropriate, until the adverse reactions abate. Guidelines were developed in clinical trials for dose modification (see Dosage modification guidelines, **Table 2a** for PegIntron monotherapy and **Table 2b** for PegIntron combination therapy with ribavirin).

Table 2a Dose modification guidelines for PegIntron monotherapy		
Laboratory values	**Reduce PegIntron to one-half dose if:**	**Discontinue PegIntron if:**
Neutrophils	< 0.75 x 10^9/l	< 0.5 x 10^9/l
Platelets	< 50 x 10^9/l	< 25 x 10^9/l

Table 2b Dose modification guidelines for combination therapy (with ribavirin)			
Laboratory values	**Reduce only ribavirin dose to 600 mg/day* if:**	**Reduce only PegIntron dose to one-half dose if:**	**Discontinue combination therapy if:**
Haemoglobin	< 10 g/dl	-	< 8.5 g/dl
Haemoglobin in: Patients with history of stable cardiac disease	≥ 2 g/dl decrease in haemoglobin during any four week period during treatment (permanent dose reduction)		< 12 g/dl after four weeks of dose reduction

White blood cells	-	< 1.5 x 10^9/l	< 1.0 x 10^9/l
Neutrophils	-	< 0.75 x 10^9/l	< 0.5 x 10^9/l
Platelets	-	< 50 x 10^9/l	< 25 x 10^9/l
Bilirubin – direct	-	-	2.5 x ULN**
Bilirubin - indirect	> 5 mg/dl	-	> 4 mg/dl (for > 4 weeks)
Creatinine	-	-	> 2.0 mg/dl
ALT/AST	-	-	2 x baseline and > 10 x ULN**

* 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.

** Upper limit of normal

2. Chemical, pharmaceutical and biological aspects

Composition

PegIntron is supplied in five dosage strengths: (50 µg, 80 µg, 100 µg, 120 µg, 150 µg) as a lyophilized powder to be reconstituted in 0.7 ml water for injections before use. The label dose is contained in 0.5 ml of the reconstituted solution. The composition of the excipient matrix is the same for all dosage strengths; only the amount of the active ingredient varies. Excipients are: Sodium Phosphate DibasicAnhydrous, Sodium Phosphate Monobasic Dihydrate, Sucrose, and Polysorbate 80.

The strength is defined by weight in contrast to most Interferon medicinal products, the strengths of which are defined by bioactivity. Although the proposed definition does not allow for a conclusive direct comparison of *in vitro* activity with other products of the kind, it is preferred from a clinical point of view, taking into account the kinetics which distinguish this product from non-pegylated Interferon alfa-2b. Although not part of the labelled strength, the bioactivity of PegIntron is controlled as part of the product specifications.

The container is a 2 ml Type I flint glass vial with a butyl rubber stopper and flip-off aluminium seal.

Active substance

The active substance used to manufacture PegIntron is a conjugate of the same active substance as used for IntronA, i.e. recombinant human interferon alfa-2b produced in *E. coli*. Peginterferonalfa-2b is prepared by reacting interferon alfa-2b with activated methoxypoly(ethylene glycol) (PEG). The reaction involves the formation of a covalent bond between the mPEG and amino groups on the interferon alfa-2b molecule.

Appropriate molecular size characterization techniques (Mass spectroscopy, SDS-PAGE and size exclusion chromatography) were used to confirm that peginterferon alfa-2b is predominantly composed of monopegylated species with small amounts of dipegylated species and free interferon.

In the thorough characterisation of the active substance, involving high-resolution ion exchange chromatography, the monopegylated species were found to consist of a population of positional isomers of varying biological activities. This substance heterogeneity results from a purification process that removes the coupling and quenching reagents and to some extent di-peginterferon and free interferon, but does not resolve the monopegylated positional isomers. Isomer distribution data of 13 clinical batches have been submitted. The substance heterogeneity has been shown to be essentially consistent, thereby assuring a consistency of activity across the totality of the finished product.

Development pharmaceutics

A lyophilised formulation of sodium phosphate, sucrose and polysorbate 80 was developed to avoid a certain degree of depegylation that occurred with the soluble formulation used during pre-clinical and Phase I clinical studies.

The sections dealing with the conjugation chemistry, the structural elucidation and the degradation pathways are considered to represent the current state of art. Also, in general the relevant EU guidelines are met. The resolution of the separation process does not allow for base-line separation, and therefore fraction selection relies on in-process control. This was a matter of points for clarifications, which are now solved.

Line extension: PegIntron powder and solvent for solution for injection in pre-filled pen

On 6 February 2002 a Marketing Authorisation was granted for PegIntron powder and solvent for solution for injection in pre-filled pen as a line extension to the existing marketing authorisation for PegIntron. This is a new presentation for pre-filled pens with the active substance, peginterferon alfa-2b, remaining the same as that used for the vials. The product is intended for use in the same way and on the same indications as PegIntron vials. The formulations are identical but these new products are presented in two-chamber cartridges and supplied in pre-assembled single dose pen devices. The front chamber contains the lyophilised cake including the active ingredient and the rear chamber contains the solvent, 0.5 ml of water for injections.

PegIntron powder and solvent for solution for injection in pre-filled pen is presented as 50, 80, 100, 120 and 150 microgram strengths. The pen delivers 50, 80, 100, 120 and 150 microgram / 0.5 ml in doses between 0.3 and 0.5 ml and is adjustable in increments of 0.05 ml. The composition has been adequately described. The active ingredient, together with excipients is in the lyophilised powder. The excipients are Disodium phosphate, anhydrous, Sodium dihydrogen phosphate dihydrate, sucrose and polysorbate 80. The solvent, water for injections, is provided in the second chamber of the two-chamber pre-filled pen.

The PegIntron pre-filled pen is packaged in a two-chamber Type I borosilicate glass cartridge. The two chambers are separated by a gray bromobutyl rubber (Helvoet FM 457/0 Gray) plunger. The filled cartridge is permanently fitted into a plastic pen assembly. The reconstitution process is carried out when the user pushes the upper subassembly and lower body together which push the plungers so that the solvent is transferred from the rear chamber to the front bypassing the centre rubber plunger by the way of the bypass channel.

The formulation of the lyophilised powder and also the solution after reconstitution are the same as for the PegIntron vial. The development pharmaceutics refers mostly to studies done for the vial product. However, some additional development activities for the pre-filled pen such as determination of fill volume, choice of packaging components and lyophilisation cycle development is satisfactorily described.
Integrity of the container/closure system has satisfactorily been performed by microbial challenge and pressure challenge leak test according to ISO 11608-3:1997. The needle supplied is CE-marked and the sterilisation method is by irradiation.

The applicant has conducted stability studies on the finished product. The proposed shelf life of 1 year is acceptable.

The polysorbate 80, used as an excipient, can be either of bovine or vegetable origin. The applicant has provided a TSE certificate of suitability for the material of bovine origin, and thereby demonstrated compliance with Directive 1999/82/EC (i.e shown compliance with the joint CPMP/CVMP TSE guideline).

3. Toxico-pharmacological aspects

The binding of interferon to specific cell surface receptor molecules signals the cell to produce a series of antiviral proteins. Most of this act to inhibit the translation of viral proteins, but other steps in viral replication is also affected. However, no cell or animal models of chronic hepatitis C infection exist. Furthermore, the assessment is restricted by the fact that human interferon alfa-2b is inactive in rodents, and the activity is comparatively low in primates available for preclinical studies.

Pharmacodynamics

The comparisons of *in vitro* antiviral and immune system related effects between pegylated and non-pegylated interferon alfa-2b have been described. The innate biological activities of both compounds are similar.

Safety pharmacology. Cardiovascular, gastrointestinal, CNS and renal effects were studied in rats (six) and cynomolgus monkeys (three). In monkeys a significant sustained increase (doubling) of the heart rate was recorded in animals treated with a high dose, with a concomitant rise in body temperature. No other significant effects were found on electrocardiographic parameters. Additional information provided shows that the increased heart rate in injected monkeys found during the safety pharmacology studies is not specific for PegIntron but is also caused by IntronA.

Since there are no animal or cell culture models for HCV infection, no preclinical studies were performed to demonstrate the antiviral pharmacodynamic activity by the combination of ribavirin and interferon alfa-2b on hepatitis C virus.

Pharmacokinetics

The bioavailability after subcutaneous injections was 60-90 % in monkeys. The plasma half-life was 13-25 hours, as compared to about 4 h for IntronA. Distribution studies in rats indicated no localization to any specific organ or tissue; elimination (as low molecular weight radioactivity) was primarily through the kidneys.

Two mechanisms may contribute to the pharmacokinetic profile of interferon activity in plasma after the subcutaneous administration of PegIntron to rats and monkeys.

The mechanism, which appears to have a greater role, is a prolonged terminal phase half-life, indicating slower elimination of the molecule. The terminal phase half-life of interferon activity after administration of PegIntron was approximately 17-25 hours in rats and 24-35 hours in monkeys, compared to approximately 4 hours after administration of IntronA.

Another mechanism, which may contribute to the Pk profile of IFN activity in plasma, is slower absorption after subcutaneous administration. In man, the half-life for absorption of PegIntron is 4.6 hours and for IntronA is 2.3 hours.

The pharmacokinetics of ribavirin and interferon alfa-2b administered concomitantly is available from two preclinical studies conducted in monkeys. Serum Neutralizing Factors are elicited by interferon alfa-2b, and dosing was therefore limited to one-month duration.

Toxicology

Single dose toxicity studies in mice, rats and monkeys using up to several hundred times the intended clinical dose of PegIntron, indicated a low order of toxicity in these animals.

Repeated dose toxicity studies were performed in cynomolgus monkeys treated with subcutaneous doses of PegIntron every other day for one month.

Important findings included dose-related decreases in all types of blood cells, serum proteins, calcium phosphorus and potassium. The findings observed in PegIntron-dosed monkeys were similar in nature

to those produced by IntronA. There was thus no unique toxicity due to the pegylation. Greater incidence and/or severity of the findings were noted in the high-dosed monkeys compared to IntronA - dosed monkeys, which is in accordance with the prolonged exposure and higher AUC values.

Reversal of the findings were observed after several weeks of dosing, possibly due to the appearance of neutralising activity to interferon alfa in monkeys.

In order to assess the effects of the combination peginterferon alfa-2b plus ribavirin, one-month repeated toxicity studies in cynomolgus monkeys were performed. The duration of the studies was limited to one month due to occurrence of neutralising antibodies directed to interferon. The combination did not reveal unexpected new target organs but the effects were more marked with the combination compared to each individual component. Overall, there were changes in haematological parameters (reduced numbers of erythrocytes, platelets, neutrophils and lymphocytes), lymphoid organs (atrophy) and skin (inflammation, erosion and ulcers). One important aspect to consider is the reduction in neutrophil numbers that is linked to peginterferon alfa-2b treatment. This reduction could alter the host resistance to infections and may explain the few cases of mortalities reported. Neutrophil function was, however, not affected.

Reproduction studies were not performed. Interferon alfa-2b has been shown to be abortifacient in primates. PegIntron can be assumed to also have this effect, as expressed adequately in the SPC.

Genotoxicity was studied using a standard battery of tests. All findings were negative. The dosing was limited to 175 µg/plate in the Ames test, and 35 µg/ml in the chromosome aberration study, which, although below the guideline recommendations, is considered acceptable due to the (protein) nature of the test article.

Carcinogenicity studies were not performed, which is acceptable since human interferon alfa has no apparent effect in rodents, and since antibodies are rapidly formed after administration of the pegylated product.

Local tolerance. Subcutaneous injection of PegIntron and placebo to rats, both produced mild irritation, as did intramuscular injection of PegIntron to rabbits.

Free methoxypoly (ethylene glycol) (mPEG)

The relative non-toxicity of mPEG has been convincingly shown in the following studies:

Single dose toxicity. mPEG given i.v. or subcutaneously at 6480 µg/m^2 to mice and rats was non-toxic.

13-week study in rats. mPEG was given subcutaneously twice weekly in doses up to 2276 µg/m^2/week (15 animals per sex per group). No mPEG-related findings were observed at macroscopic or microscopic examinations.

13-week + 4-week recovery study in cynomolgus monkeys. mPEG was given subcutaneously twice weekly in doses up to 2276 µg/m^2/week (5 animals per sex per group). No mPEG-related findings were observed at macroscopic or microscopic examinations.

Embryo-foetal development study in rats. mPEG was given daily in doses up to 800 µg/m^2 per day on day 6 through 17 after mating (25 animals per group). No signs of toxicity, maternal or in utero effects, were noted.

Embryo-foetal development study in rabbits. mPEG was given daily in doses up to 800 µg/m^2 per day on day 7 through 19 after mating (20 animals per group). No signs of toxicity, maternal or in utero effects, were noted.

Mutagenicity. mPEG up to 5000 µg/plate ±S9 was not mutagenic in the standard battery of Salmonella and Escherichia strains.

Chromosomal aberration test. mPEG up to 5000 µg/ml of for 4 and 19 h without S9 and 4 h with S9 had no effect in a human lymphocyte chromosome aberration test.

Mouse micronucleus study. mPEG at a dose of 2 mg/kg intraperitoneally had no effect in a mouse micronucleus assay

4. Clinical aspects

Clinical Pharmacology

Pharmacodynamics. Interferon pharmacodynamics was assessed by examining changes in concentrations of effector proteins such as serum neopterin and 2'5'-oligoadenylate synthetase (2'5'-OAS). Serum neopterin levels, measured as both C_{max} and AUC, increased with dose until the maximum effect was reached at the 1.5 µg/kg dose. For 2'5'-OAS the maximal effect was attained already at 0.25 – 0.50 µg/kg.

Pharmacokinetics. The single- and multiple dose pharmacokinetics of PegIntron were evaluated in two studies, of which the multiple-dose study (0.5–2.0 µg/kg q.w.) was conducted in the target population. PegIntron was quantified using immuno- (mainly) and bioassays, the latter being a measure of the antiviral activity.

PegIntron is slowly absorbed following subcutaneous administration with the maximal serum concentrations attained within 15-44 h, which are sustained for up to 48 to 72 h post-dose. CL/F ranged from 11 to 33 ml/h/kg, which is about one-tenth of the CL/F of Intron A.

PegIntron C_{max} and AUC measurements increase in a dose-related manner. Mean apparent volume of distribution is about 1 l/kg, which is slightly less than for Intron A.

Upon multiple dosing, there is an accumulation of immunoreactive interferons. As measured by the bioassay, accumulation is less pronounced, fully in line with available safety data.

Mean PegIntron elimination half-life is approximately 30.7 hours (range 27-33 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.

A single-dose interaction study was conducted to assess the influence of PegIntron on the most important P-450 enzymes. Results of this study demonstrated no effect on the activity of cytochrome (CY) P1A2, CYP2C9, CYP2D6, and hepatic CYP3A4 or N-acetyl transferase. Caution should be advised in the interpretation of these results as the use of other forms of interferon alpha result in a 50% reduction in the clearance and thus a doubling of plasma concentrations of theophylline, a substrate of CYP1A2.

In a dose ranging, pharmacokinetic study (study I96-403), it was demonstrated that there is no pharmacokinetic interaction when peginterferon alfa-2b and ribavirin are co-administered. There was a peginterferon alfa-2b dose-related effect on viral clearance, and this effect was further enhanced by the addition of ribavirin. Peginterferon alfa-2b at the dose of 1.4 micrograms/kg/week combined with ribavirin (800 mg or 1000-1200 mg/day) had the best efficacy for clearing HCV-RNA from the serum, at weeks 1, 12 and 24, with an acceptable tolerance.

Clinical studies in special populations. Patients with decompensated liver function were not eligible in the clinical studies, therefore the pharmacokinetics of PegIntron have not been evaluated in patients with severe hepatic dysfunction.

In patients with renal impairment the exposure, as determined by the immunoassay, was doubled in the patients with the poorest renal function. Renal elimination only contributed to about 30 % of the

overall elimination of PegIntron. No further suggestions are given on additional mechanism of elimination.

There were no significant pharmacokinetic changes in elderly.

Clinical efficacy

The clinical efficacy data on which the initial application was based included two studies, which demonstrated the clinical effectiveness of PegIntron: a small dose exploration study and a large pivotal study. Each compared various dose-regimens of PegIntron with the approved dose of IntronA in patients not previously treated with an interferon.

Dose Finding Study. The dose exploration study was an open-label, active control study in which 264 patients naïve to interferon were randomized to receive treatment for 6 months with dosages of PegIntron varying from 0.25 µg/kg s.c. once weekly to 2.0 µg/kg s.c. once weekly. IntronA at the dose licensed for the treatment of CHC was chosen as comparator. Numerically favourable activity compared with IntronA was observed for PegIntron dosages between 0.5 and 2.0 µg/kg. Serum neopterin concentration increased in a dose-related manner. Neutrophil and white cell count reductions at the end of Week 4 also correlated with dose.

One pivotal confirmatory clinical study has been submitted as part of a variation application to support the extension of the use of ribavirin in combination with peginterferon alfa-2b (study C/I98-580) in patients with chronic HCV not previously treated with interferon (n = 1530).

Main Clinical Studies

The main confirmatory study on which the initial application was based is a double blind, active control, randomized study conducted in the US, Europe, and Australia. The target population comprised treatment-naive, adult subjects with CHC confirmed by positive HCV-RNA/qPCR (National Genetics Institute), a liver biopsy within the previous year compatible with chronic hepatitis and abnormal ALT levels. Compensated liver disease and essentially normal bone marrow function was required. The study was randomised, four-armed, and double blind with regard to PegIntron dose. The licensed dose of IntronA for the treatment of CHC (3 MIU s.c. thrice weekly) was compared with PegIntron 0.5, 1.0, and 1.5 µg/kg s.c. once a week for 48 weeks. For the assessment of sustained response, a 6 months follow-up after the end of therapy was conducted.

The characteristics of the patients and Baseline disease parameters were comparable across all treatment groups even though it was conducted in multiple geographic locations (Table 1). These characteristics are representative of the typical profile of a treatment-naïve patient with chronic hepatitis C.

Altogether 1224 patients were randomized and 1219 were treated.

Table 1. Baseline characteristics (Study C/I97-010)

	PegIntron 0.5 µg/kg (n=315)	PegIntron 1.0 µg/kg (n=297)	PegIntron 1.5 µg/kg (n=304)	IntronA 3 MIU (n=303)
Age (mean)	43	44	43	43
Female/male (%)	41/59	37/63	38/62	32/68
Caucasian (%)	90	91	94	89
HCV genotype(%)				
1	67	67	74	72
2	11	10	11	9
3	17	18	14	18
4	3	4	1	1
Other	3	1	1	<1

HCV/qPCR (copies/ml) mean ($x10^6$)	3.405	3.276	3.041	3.682
≤ 2 $x10^6$(%)	26	24	27	25
>2 $x10^6$ (%)	73	76	72	75
missing	<1	0	<1	<1
ALT(xULN) median	2.3	2.2	2.3	2.3
Source				
Transfusion (%)	22	26	17	20
Parenteral (%)	48	42	53	49
Sporadic/Other (%)	30	32	30	30
Yrs since exp. (mean)	18	20	19	18

The study was designed with a single measure of efficacy, but with assessments at two time points. To allow for this approach and to protect against Type 1 error, the α was split equally between the two time points (α = 0.025 x 2). The primary efficacy measure was a composite of viral response, HCV RNA <100 copies/ml (qPCR) and normalised ALT. Non-completers were classified as failures.

In long-term follow-up studies, virologic response as measured by sensitive quantitative PCR techniques has been shown to have a strong correlation with eradication of HCV-RNA and halt of disease progression. The HCV-RNA assay employed in this study is a commercially available service and is a highly sensitive validated assay. Undetectable serum HCV-RNA is highly indicative of viral clearance and predictive for the cure of chronic hepatitis C disease. Moreover, it has been demonstrated that virologic response corresponds highly with histologic improvement in the liver.

PegIntron was superior to IntronA at both time points assessed in the study, as measured by loss of serum HCV-RNA during treatment and sustained virologic response six months post treatment. Significantly more patients were negative for serum HCV-RNA with all three PegIntron regimens compared with IntronA (Table 2). There was a dose response for the PegIntron groups during treatment, however, for sustained response the 1.0 and 1.5 µg/kg groups were similar.

Table 2. Virologic Response. Study C107-010

	PegIntron 0.5 µg/kg QW (N=315)	**PegIntron 1.0 µg/kg QW (N=297)**	**PegIntron 1.5 µg/kg QW (N=304)**	**IntronA 3 MIU TIW (N=303)**
At 6 months of treatment				
Virologic Responders	104 (33%)	119 (40%)	139 (46%)	74 (24%)
p value[a]	0.018	<0.001	<0.001	
At 6 months after the end of treatment				
Virologic Responders	57 (18%)	73 (25%)	71 (23%)	37 (12%)
p value[a]	0.042	<0.001	<0.001	

[a]: Chi-Square test. Each pairwise comparison was performed with the interferon alfa-2b treatment group.

The primary endpoint of the study was a combination of loss of serum HCV-RNA plus normalization of ALT. However, sustained virologic response is the gold standard for assessing long-term response to therapy and is therefore the focus of the assessment of efficacy in this application.

As shown in **Table 3**, nearly all patients with a sustained virologic response also normalized ALT; only 10/238 (4%) had ALT levels above the upper limit or normal.

Table 3. Combined Virologic (< 100 copies/ml) and ALT Response at the End of Follow-up Study C/I97-010				
	Number (%) of Subjects			
	HCV Negative			
ALT	**PegIntron 0.5 µg/kg QW (N=315)**	**PegIntron 1.0 µg/kg QW (N=297)**	**PegIntron 1.5 µg/kg QW (N=304)**	**IntronA 3 MIU TIW (N=303)**
ALT Normal	52/57 (91) [a]	70/73 (96)	69/71 (97)	37/37 (100)
a: Subjects with normal ALT and negative HCV-RNA at FU/subjects who are PCR negative at FU.				

When used as a surrogate for response, sustained normalization of ALT was a relatively poor predictor of sustained loss of serum HCV-RNA. Only 67 to 82% of patients, who had normal ALT at the end of Follow-up, had sustained loss of serum HCV-RNA (**Table 4**).

Table 4. Correlation of Normalization of ALT with Sustained Loss of Serum HCV-RNA				
	Number (%) of Patients			
	HCV Negative			
	PegIntron 0.5 µg/kg	**PegIntron 1.0 µg**	**PegIntron 1.5 µg/kg**	**Interferon alfa-2b 3 MIU**
ALT Normal	52/77 (68)[a]	70/87 (80)	69/84 (82)	37/55 (67)
a: Patients with normal ALT and negative HCV-RNA at FU/patients who were ALT normal at FU				

Therefore, virologic response is the optimal way to assess the efficacy of PegIntron in this study as normalization of ALT is a less sensitive measure of outcome.

HCV genotype and pretreatment viral load have been shown to be predictors of response to interferons. When considered by the subgroups of HCV genotype and viral load, the response rate for all dose-regimens of PegIntron remains superior to that with IntronA (**Table 5**). As has been shown in other studies, patients with HCV genotypes 2/3 have a much higher response rate than those with genotype 1. Patients with a low (≤2 x 10^6 copies/ml) pretreatment HCV level have a higher response rate than their counterparts regardless of genotype.

Table 5. Sustained Virologic Response by HCV Virus Level (copies/ml) and Genotype				
	Number (%) of Subjects			
	PegIntron 0.5 µg/kg	PegIntron 1.0 µg/kg	PegIntron 1.5 µg/kg	IntronA 3 MIU
Genotype 1				
≤2 million	14/52 (27)	16/42 (38)	19/56 (34)	10/48 (21)
>2 million	8/159 (5)	12/157 (8)	12/167 (7)	4/169 (2)
Genotypes 2/3				
≤2 million	14/24 (58)	13/21 (62)	15/22 (68)	9/25 (36)
>2 million	17/64 (27)	26/62 (42)	21/51 (41)	14/56 (25)
Genotypes 4/5/6				
≤ 2 x 10^6	2/6 (33%)	4/8 (50%)	3/4 (75%)	0/2
> 2 x 10^6	0/4	0/5	0/1	0/2

Altogether, it is concluded that non-inferiority of PegIntron in terms of efficacy has been demonstrated for the 0.5 µg/kg dose (17% sustained combined response) in relation to the licensed dose of IntronA (12%), as the 97.5% confidence interval for difference between PegIntron 0.5 µg/kg and IntronA was (-2%; +11%) (primary endpoint). In terms of the presently preferred virology endpoint the p-value "in favour of" PegIntron 0.5 µg/kg was 0.042.

With respect to higher doses of PegIntron, sustained viral response appears similar comparing PEG 1.0 and 1,5 µg/kg, 25 and 23%, respectively. It therefore seems reasonable to focus on a comparison between the 0.5 and 1.0 µg/kg regimens. In this comparison the 95% CI for difference in sustained viral response rate is about –0.2% to +13% in favour of the 1.0 µg/kg dose.

Combination peginterferon alfa-2b/ ribavirin

Relating to the proposed indication, there is a synergistic effect, whose mechanism is unknown, of the combination of ribavirin and interferon alfa-2b on the virologic sustained response and on the histologic response in both relapse and naïve patients.

The efficacy and the safety of the combination was evaluated in study (C/I98-580), a large (n = 1580 randomised, 1530 treated), randomised (stratified: genotype 1 versus non-1, cirrhosis Y/N), multicentre, open label and active control study, where patients received one of the following treatment:

- **I/R**: Interferon alfa-2b 3MIU three times weekly + ribavirin 1000/1200 mg (authorised posology)
- **PEG1.5/R**: Peginterferon alfa-2b 1.5 microgram/kg once weekly in combination with ribavirin 800 mg daily for 48 weeks. The dose of ribavirin was lower than that originally approved due to safety concerns
- **PEG0.5/R**: Peginterferon alfa-2b 1.5 microgram/kg once weekly for 4 weeks, dropping to 0.5 microgram/kg/week for a further 44 weeks in combination with ribavirin 1000/1200 mg daily

Patients were instructed to take Rebetol with food.

The primary efficacy variable was the loss of detectable serum HCV-RNA/PCR (< 100 copies/ml). Efficacy was evaluated at 24 weeks and also at follow-up (24 weeks after the end of treatment). Sustained response was determined by the proportion of subjects that were HCV-RNA negative 24 weeks after the end of treatment. Secondary endpoints were the normalisation of ALT at the end of treatment and at 24 weeks of follow-up, loss of HCV-RNA at the end of treatment, and improvement and change from baseline in biopsy scores.

Population

All patients recruited were naive and had histological evidence of chronic hepatitis, with proof of infection with hepatitis C virus (presence of serum HCV-RNA) and abnormal ALT. The patients enrolled were predominantly Caucasian, middle aged males (mean age 44 years). As it is typical with European/American population, the majority were infected with genotype 1 (~ 70%) and had a high viral load pre-study (> 2 million copies/ml). Baseline demographic and disease characteristics were consistent across all patients groups. Approximately 10 % had cirrhosis as determined by local pathologist assessment.

Of the 1580 patients randomised, 1530 were treated (50 patients were not treated mainly due to patient preference). Overall 80 % (1230/1530) of patients completed 48 weeks of treatment. Discontinuation of treatment was mainly due to adverse events (14 %, 13 % and 13 % respectively for PEG 1.5/R, PEG 0.5/R and I/R). All patients treated with at least one dose of study medication defined the ITT population.

Virological response

Final results of the study showed that for both the end of treatment and sustained virologic response 6 months after treatment, PEG 1.5/R is statistically and clinically superior to the control arm of

interferon alfa-2b + ribavirin; by contrast I/R and PEG 0.5/R produced similar sustained virologic response rates (47 %) (Table 1).

Table 1 Virologic Response

	A PEG 1.5/R (n=511)	B PEG 0.5/R (n=514)	C I/R (n=505)	A vs. C [a]	B vs. C
End of Treatment	65%	56%	54%	p<0.001 [b]	p=0.3707
End of 6 months Follow-Up	54%	47%	47%	p=0.0121 [c]	p=0.7261

a: Logistic regression
[b]: 95 % confidence interval (1.33-2.29)
[c]: 95 % confidence interval (1.08 – 1.84)

Effect of genotype on sustained response

HCV genotype is a very important predictor of response for interferon-based therapies and it had a major impact on treatment outcome in this study (Table 2). In HCV genotype 1 disease, PEG 1.5/R was significantly more effective than I/R ($p \leq 0.03$). Response rates in genotype 2/3 diseases were approximately twice that for genotype 1 and similar across treatments.

Table 2 Virologic Response by HCV Genotype

HCV Genotype	PEG 1.5/R	PEG 0.5/R	I/R	1 vs. non-1
1	42%	34%	33%	p= 0.03[a]
2/3	82%	80%	79%	
4/5/6	50%	33%	38%	

a: Logistic regression

Secondary endpoint (ALT normalisation)

With respect to the secondary endpoint of normalisation of ALT, almost all subjects who became sustained responders also normalised their ALT after completion of therapy. Among those few sustained responders who failed to normalise their ALT during follow-up, the ALT was only minimally elevated (<1.5 ULN) in the majority of the peginterferon alfa-2b treated patients.

Doses recommendation

In this study, it was shown that dosing both peginterferon alfa-2b and ribavirin by patient weight optimises sustained virologic response rates to treatment.

A logistic regression analysis of the weight effect demonstrated that weight-adjusted dosing for ribavirin maximises the sustained virologic response rate (61 %) compared to 47 % with standard I/R therapy. The sustained response rate with this regimen was improved to 48 % in the difficult to treat HCV genotype 1 patients and to 88% in patients infected with HCV genotypes 2 & 3; relapse rates were reduced in these sub-populations 17 % and 7 %, respectively. The analysis confirmed that the optimal dose of peginterferon alfa-2b is 1.5 micrograms/kg and demonstrated that the optimal dose of ribavirin, balancing for efficacy and safety, for use in combination with peginterferon alfa-2b 1.5 micrograms/kg is 13 ± 2 mg/kg for all patients; this is particularly effective for those infected with HCV genotype 1.

On the basis of the data, the following dose recommendation for ribavirin, in combination with peginterferon alfa-2b (1.5 micrograms/kg per week) was defined:

- Patients with body weight < 65 kg, 800 mg/day
- Patients with body weight 65 - 85 kg, 1000 mg/day

- Patients with body weight > 85 kg, 1200 mg/day

Duration of treatment

The efficacy of the combination of peginterferon alfa-2b + ribavirin has been demonstrated in a large clinical study. The sustained response rate with PEG 1.5/R 6 months after the end of 1 year of treatment was significantly higher than that with I/R (54% versus 47%; p = 0.0121). It was demonstrated that the response rate was optimised when both peginterferon alfa-2b and ribavirin are dosed according to body weight. The sustained response rate increased up to 61% with PEG 1.5/R with the optimised ribavirin dose (> 10.6 mg/kg). In the subgroup of patients infected with genotype 1 the response rate was 48% (versus 33% with the regimen I/R) and for genotype2/3 patients was 88% (versus 79% with the regimen I/R) when the ribavirin dose was optimised.

The rationale for selecting a fixed treatment period of 1 year in this study was the type of patients anticipated to be enrolled (~ 70 % genotype 1/high viral load). The risk of over-treating some patients and inducing undue adverse events could not be excluded. In genotype 1 patients with a high viral load at baseline, it was shown that a treatment for 48 weeks was necessary to establish high sustained response rate. Therefore a 6 months treatment period was agreed, with the automatic extension of this treatment period to another 6 months in genotype 1 patients with high baseline viral load who exhibit negative HCV RNA after the first 6 months. For the other patients, the possibility to extend the treatment period for another 6 months can be considered.

The optimal duration of the combined treatment has not yet been fully established in subjects with non type 1 genotype infections or type 1 genotype infections with low baseline viral load. The information provided on the overall population at present indicate that the treatment should be continued at least for 24 weeks and thereafter the patients shall be re-evaluated in order to extend the treatment up to one year. It was considered that a number of prognostic factors would be involved in the clinical decision of continuing the treatment beyond 24 weeks, including the level of bridging fibrosis, the level of response in terms of viral load, age, gender, tolerability to the treatment of individual patients. The Marketing Authorisation Holder has agreed to provide the CPMP with additional information on the clinical benefit of the optimised dosing regimen of the combined treatment for specific subgroups of hepatitis C patients.

Clinical studies in special populations

Use in 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.

Patients with decompensated liver function were not eligible in the clinical studies, however the CPMP requested clarifications whether there were pharmacokinetic data available from patients with histologically proven cirrhosis at baseline. The analysis of pharmacokinetics data in cirrhotic patients (Metavir IV) from a population PK substudy of the pivotal clinical trial (C/I97-010) was made. Due to the small number of patients with Metavir scores of 4, an adequate comparison of their trough concentration data with those of patients with lower scores was not possible.

Use in renal impairment: The clearance of PegIntron is reduced in patients with significant renal impairment (creatinine clearance ≤ 50 ml/minute) (see **5.2**). It is recommended that these patients be closely monitored and that their weekly dose of PegIntron be reduced if medically appropriate.

Use in the 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 **5.2**).

Use in patients under the age of 18 years: PegIntron is not recommended for use in children or adolescents under the age of 18, as there is no experience in this group.

Clinical safety

Patient exposure

The safety assessment in this application is based primarily on data from the pivotal study in which most of the 1,219 patients completed the one-year treatment period and were followed for 6 months. Given the small number of patients (36) treated in the supportive dose exploration study, this study was of minor importance for the assessment of safety.

Altogether 940 patients in the pivotal study were exposed to PegIntron, of whom 754 received 0.5 to 1.5 microgram/kg for a year. All patients were followed for an additional 6 months post-treatment.

The most commonly reported AEs were those typically associated with interferon use, headache and myalgia, which were reported by a majority of patients (both PegIntron and IntronA).

The side effect profile observed for PegIntron was qualitatively similar to that of IntronA. The incidence and severity of adverse events reported for the lowest dose of PegIntron appeared similar to IntronA 3 MIU, while flu-like symptoms, weight loss, anorexia, dizziness and alopecia tended to be more frequently observed with higher dosages of PegIntron.

The incidences of the most common adverse events observed in monotherapy treatment are summarized in Table 6. In general, the severity of the adverse events in all treatment groups was mild to moderate and manageable by appropriate additional therapy and adjustment of the dose of the study drug.

Table 6. Adverse events reported very commonly in clinical trials (≥ 10 % of patients)

	PegIntron 0.5 microgram/kg once weekly N=315	PegIntron 1.0 microgram/kg once weekly N=297	IntronA 3 MIU three times a week N=303
Application Site Disorders			
Inflammation	34 %	42 %	16 %
Reaction	7 %	10 %	5 %
General Body Discomfort			
Asthenia	12 %	12 %	11 %
Dizziness	8 %	12 %	10 %
Fatigue	43 %	51 %	50 %
Fever	31 %	45 %	30 %
Headache	61 %	64 %	58 %
Flu-like Symptoms	18 %	22 %	19 %
Rigors	34 %	40 %	33 %
Weight Decrease	10 %	11 %	13 %
Gastro-intestinal			
Anorexia	10 %	20 %	17 %
Nausea	21 %	26 %	20 %
Diarrhoea	16 %	18 %	16 %
Abdominal Pain	14 %	15 %	11 %
Musculoskeletal			
Pain	19 %	28 %	22 %
Myalgia	48 %	54 %	53 %
Arthralgia	26 %	25 %	27 %

Psychiatric			
Depression	27 %	29 %	25 %
Anxiety	10 %	9 %	10 %
Concentration Impaired	10 %	10 %	8 %
Insomnia	17 %	23 %	23 %
Irritability	19 %	18 %	24 %
Alopecia	20 %	22 %	22 %
Pharyngitis	12 %	10 %	7 %

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

Rarely reported events include suicidal ideation and attempted suicide, hearing and retinal disorders, diabetes, hepatopathy and arrhythmia.

Granulocytopaenia ($< 0.75 \times 10^9$/l) occurred in 4 and 7 % and thrombocytopaenia ($< 70 \times 10^9$/l) in 1 and 3 % respectively of patients receiving 0.5 or 1.0 microgram/kg of PegIntron.

There was no consistent pattern with respect to discontinuation among treatment groups, but dose reduction increased with increasing PegIntron dose (Table 7).

Table 7. Proportion of Patients Dose-reducing or Discontinuing due to AEs

	PegIntron 0.5 µg/kg	PegIntron 1.0 µg/kg	PegIntron 1.5 µg/kg	IntronA 3 MIU
Dose Reduction	9%	14%	19%	6%
Discontinuation	9%	11%	9%	6%

Neutropenia and thrombocytopenia were the two most common reasons for dose reduction. Dose interruption was more common with IntronA (9%) than with PegIntron (4-6%). A relatively small proportion of subjects in each group discontinued (2-5%) or dose reduced (1-3%) due to psychiatric AEs. Depression was the most common reason for discontinuation or dose reduction due a psychiatric AE.

Application site disorders have been reported with the use of all alpha interferons. The incidence of injection site inflammation (erythema and/or swelling) with PegIntron at all doses was greater than that seen with IntronA (44-47% vs 21%), but was not dose related. The majority were mild in severity. No patient experienced local skin necrosis. Less common were pain or reactions (i.e. bruising, itchiness, and irritation).

Laboratory findings

As for IntronA, reduced neutrophil and platelet counts developed within a few weeks of therapy and changes thereafter were minor (Table 8).

Table 8. Haematological Abnormalities [Number (%) of subjects]

	PegIntron 0.5 µg/kg	PegIntron 1.0 µg/kg	PegIntron 1.5 µg/kg	IntronA 3MIU
Neutrophils (x 10^9/L)	N = 315	N = 297	N = 300	N = 299
1.0 - < 1.5	110 (35)	127 (43)	116 (39)	96 (32)
0.75 . < 1.0	26 (8)	55 (19)	54 (18)	18 (6)
0.5 - <0.75	10 (3)	17 (6)	27 (9)	5 (2)
< 0.5	3 (1)	3 (1)	1 (0.3)	1 (0.3)
Platelets (x 10^9/L)				
70 - < 100	34 (11)	58 (20)	54 (18)	27 (9)
50 - < 70	3 (1)	8 (3)	12 (4)	2 (0.7)
25 - < 50	0	1 (0.3)	0	1 (0.3)

Fluctuation of ALT values is characteristic of chronic hepatitis C infection. This variation is also seen during treatment with interferons. Looking at individual patients, there were 97 patients with a during-treatment ALT value greater than 2x baseline (Table 9). The majority of these ALT elevations were single occurrences or short-lived episodes during the course of treatment and was self-limiting.

Table 9. Mean serum ALT x Baseline during treatment

	PegIntron 0.5 µg/kg	PegIntron 1.0 µg/kg	PegIntron 1.5 µg/kg	IntronA 3 MIU
2 x Baseline	4 (1%)	5 (2%)	5 (2%)	3 (1%)
2.1 – 5 x	21 (7%)	24 (8%)	20 (7%)	20 (7%)
5.1 – 10 x	2 (0.6%)	1 (0.3%)	0	2 (0.7%)
>10 x	0	0	0	0

There was no specific pattern as to when the elevations of ALT occurred. With the exception of one patient, whose maximum total bilirubin was 33 µmol/l (predominantly indirect bilirubin), the ALT elevations were not associated with simultaneous increase in bilirubin or clinical signs of hepatoxicity. Forty-four PegIntron-treated patients had an elevated bilirubin value, none sufficient to cause clinical jaundice. These elevations were equally distributed across the PegIntron groups. Of these one had a concomitant elevated ALT value.

The prevalence of post-treatment binding antibody in the main clinical study was 9.1-10.2% among all PegIntron dose groups and was lower than that detected for IntronA in the same trial (15.2%). Serum neutralising antibody was also detected in small but similar proportions of subjects receiving IntronA or PegIntron (0.8-1.9%).

In general, only high titres of antibodies are supposed to influence the kinetics of proteins, and a high titre of binding antibodies normally correlates with neutralising activity. The low incidence of neutralising antibodies is therefore reassuring.

Health-Related Quality of Life (HQL) data was collected using the SF36 module as described in the clinical protocol for C/I97-010. The SF36 assesses eight domains of health; physical functioning, role physical, bodily pain, general health perceptions, vitality, social functioning, role emotional, and general mental health. Data were collected at baseline, at 12, 24, 36 and 48 weeks during treatment (treatment period), and at 12 and 24 weeks after treatment discontinuation (follow-up period). The HQL analyses were based on all randomised patients who received study drug.

In general, patients from all treatment groups showed reductions in scores for all HQL domains tested during treatment followed by a return back to baseline during follow-up. Secondary analyses showed

that patients receiving PegIntron 0.5 µg/kg experienced the least decrease in the following domain scores compared to IntronA and the higher doses of PegIntron: role-physical, bodily pain, vitality, and social functioning. At the end of follow-up, sustained responders in all PegIntron groups showed increased scores from baseline across all domains compared to non-responders who showed reductions in mean scores.

Combination peginterferon alfa-2b and ribavirin:

The safety profile of peginterferon alfa-2b in combination with ribavirin was assessed based on data from study (C/I98-580), which became available following the initial marketing authorisation.

Adverse events

Overall, the adverse events reported with the combination were as expected with interferon alfa-2b and/or ribavirin. The combination of peginterferon alfa-2b with ribavirin had a safety profile comparable to the combination of interferon alfa-2b + ribavirin.

The most common adverse events with peginterferon alfa-2b + ribavirin (fatigue, fever, headache, injection site reaction, rigors, myalgia, insomnia) were also those most frequently reported with I/R. The increase in the incidence of some flu-like symptoms with peginterferon alfa-2b 1.5 micrograms/kg was not unexpected given the higher dose of interferon alfa-2b being administered. The incidence of psychiatric adverse events was similar among groups. Few adverse events, such as injection site reaction (58% vs. 36%), fever (46% vs. 33%) and nausea (43% vs. 33%) were more common with PEG 1.5/R than with I/R (≥10% difference between groups). However, most of these events were mild to moderate in severity and did not limit treatment. Comparing peginterferon alfa-2b 1.5/R to I/R, the optimised dose of ribavirin was associated with a higher incidence of 5 adverse events for which the incidence between treatments was ≥ 10 %: injection site reaction, weight decrease, nausea, asthenia and alopecia.

Serious psychiatric adverse events are uncommon, but are recognised problem with interferon alpha treatment. During the 48-week treatment period, adverse events broadly classified as "psychiatric" were reported by approximately 75-77% of patients across all groups. The majority of these were mild or moderate and not significantly psychiatric, such as insomnia (40-41%) and irritability (34-35%). Depression was reported by 29-34% of patients, this compares with ≈28% reported in previous trials with peginterferon alfa-2b monotherapy and I/R. The incidence of depression was similar in all 3 groups and remained relatively constant during the study period (66-68% in the second 24 weeks vs. 71-73% in the first 24 weeks), demonstrating there is no increased risk of depression with longer treatment duration. There was no difference in the incidence of psychiatric adverse events between the per protocol PEG 1.5/R group and the optimised ribavirin dose group.

Severe and life-threatening adverse events

The incidence of severe AEs in every body system organ class category was similar with PEG 1.5/R and I/R, with the exception of "body as a whole" and "white cell and RES", where severe fatigue and neutropenia were more frequently reported with PEG 1.5/R than with I/R.

The frequency of life threatening AEs reported in this study was low (1 %) and was similar between the treatment groups. All were successfully managed with treatment discontinuation. There were 13 cases of neutropenia classified as WHO grade 4(life-threatening), none of which was associated with infection. For the PEG 1.5/R group there is no pattern to suggest that the optimised dose of ribavirin resulted in more life-threatening events. The incidence of suicidal attempts and suicidal ideation during treatment with the combination ribavirin/peginterferon alfa-2b was low (≤ 1.2 %) and similar in all groups. Specific reference to these life-threatening psychiatric events observed during treatment in this clinical study has been added in the SPC.

6.6% of the relapse patients and 11% of naïve experienced severe and life-threatening events pooled from four Phase III trials. The most common are psychiatric, the category which occurred more frequently comparing I/R (2%) and I/P (1%). There were 6 deaths, 5 in the naïve patients and 1 in the relapse patient trials: two myocardial infarctions, two cases of illicit drug overdose, and an intracranial

haemorrhage. Of the 6 patients who died, 3 were randomized to combination therapy and 2 of the deaths occurred during the follow up period (16-20 weeks after dosing completion).

Laboratory values and relationship to infection

There was a clear dose-relationship in the frequency of neutropenia with peginterferon alfa-2b. There was also a dose-effect in the proportion of patients who had a dose modification due to neutropenia (18 % with PEG 1.5/R compared with 10 and 8 % for PEG 0.5/R and I/R). However, the incidence of discontinuation for neutropenia was low in all groups (0.2 –1 %). In this study, only 5 PEG 1.5/R subjects and 2 I/R subjects discontinued because of neutropenia suggesting that the dose-modification schedule included in the protocol provided adequate protection. There was a higher frequency of Grade 3/4 neutropenia when peginterferon alfa-2b was combined with the optimised of ribavirin; however, this was also seen with interferon alfa-2b. Among the subjects who had a Grade 3 or 4 neutropenia, the incidence of infections was similar: 47 % PEG 1.5/R, 39 % PEG 0.5/R; 55 % I/R. A mention on the risk of grade 3/4 neutropenia associated with peginterferon alfa-2b/ ribavirin has been added to the SPC.

Nine subjects reported serious infections. These serious infections were neither associated with neutropenia nor life threatening. The optimised dose of ribavirin did not influence the pattern of infections.

Anaemia is a well-recognised effect of ribavirin and the pattern previously observed with ribavirin in combination with interferon alfa-2b is seen in this study. A decrease in haemoglobin to less than 10 g/dl, which mandates dose modification, occurred in approximately 10% of patients; discontinuation was rare (0.2 – 0.8 %). Guidelines for dose reduction for anaemia are included in the Rebetol SPC.

As would be expected, the higher (optimised) dose of ribavirin resulted in a greater number of patients having a decrease in haemoglobin to less than 10 g/dl, with the need for dose modification. This occurred in approximately 12-14% of patients receiving the >10.6 mg/kg dose of ribavirin.

Grade 1-2 thrombocytopenia was significantly higher with PEG1.5/R than with I/R, however, no significant clinical consequences were observed during the study.

Discontinuation and dose modification

Discontinuation due to adverse events was similar among all treatment groups (13-14 %). The most frequent reasons for discontinuations in all treatment groups were flu-like symptoms (2-3 %) and psychiatric adverse events (3%).

The most common reasons for dose modification due to adverse events were anaemia and neutropenia. Dose modification for psychiatric adverse events was low in all groups (4-5 %).

5. Overall conclusions and benefit/risk assessment

From a chemical-pharmaceutical and toxicological point of view, satisfactory responses to the points for clarification have been submitted.

Taking into account both the preclinical data and the clinical exposure to peginterferon alfa-2b, it is concluded that the benefit/risk for the use in the treatment of patients with Chronic Hepatitis C (CHC) is positive. The CPMP have previously agreed that the optimum treatment for CHC is the combination of interferon alfa-2b and ribavirin. For this reason PegIntron, and all interferon monotherapies, should be used primarily in patients intolerant of ribavirin.

From an efficacy point of view, PegIntron 0.5 μg/kg has been demonstrated to be non-inferior and the 1.0 μg/kg to be superior compared with the licensed dose of IntronA. The 1.0 μg/kg dose, however, appears to be less well tolerated and dose reduction and discontinuation of therapy were more commonly encountered. It should be noted that these differences in safety do not relate to irreversible

adverse events. Dosing can be individualized taking into account expected viral response and tolerability.

When reviewing the clinical data of peginterferon alfa-2b in combination with ribavirin in naive patients, which became available after the initial granting of the marketing authorisation, the CPMP considered that the benefit/risk profile of PegIntron was still favourable.

Indeed, it was demonstrated that use in combination of peginterferon alfa-2b/ribavirin offers greater efficacy than the current standard of care interferon alfa-2b plus ribavirin without the introduction of any new adverse events, although the frequency of a few of the interferon-related events was affected. All the AEs appeared to resolve with dose-modification or discontinuation, without clinical sequelae.

Further refinement of the data analyses demonstrated also that weight adjusted dosing for both peginterferon alfa-2b and ribavirin maximises the sustained virological response rate. It was concluded that the PEG 1.5/R regimens is adopted for all patients, but with the ribavirin dose modified to take account of the impact of body weight. The peginterferon alfa-2b regimen is already weight adjusted. The ribavirin dose of 13 ± 2 mg/kg/day is the optimal dose for use in combination with peginterferon alfa-2b 1.5 µg/kg/week without compromising safety. This combination will provide an increased sustained response rate for all patients, particularly those infected with genotype 1. In addition, the optimisation of ribavirin dose had an effect on the frequency of only a few of the ribavirin-related events.

Hence, the CPMP agreed on the following dosing recommendations:

Peginterferon alfa-2b: 1.5 µg/kg/week
Ribavirin 13 ± 2 mg/kg/day as:

800 mg/day for patients weighing < 65 kg
1,000 mg/day for patients weighing 65 to 85 kg
1,200 mg/day for patients weighing > 85 kg

The optimal dose recommendations have been reconsidered and agreed upon. As far as the treatment duration is concerned, the CPMP agreed that it should last for at least six months. In genotype 1 patients with high baseline viral load, treatment should be continued for another six-month period in patients who exhibit negative HCV-RNA after the first six months treatment. For the other patients, the possibility to extend the treatment period for another 6 months can be considered on individual basis. The Marketing Authorisation Holder has agreed to provide the CPMP with additional information on the clinical benefit of the optimised dosing regimen of the combined treatment for specific subgroups of hepatitis C patients.

Based on the available data on quality, safety and efficacy, the CPMP considered that the benefit/risk profile of peginterferon alfa-2b in combination with ribavirin for the treatment of chronic hepatitis C was favourable and recommended the granting of a marketing authorisation for the following indication:

PegIntron is indicated for the treatment of adult patients with histologically proven chronic hepatitis C who has elevated transaminases without liver decompensation and who are positive for serum HCV-RNA or anti-HCV.

The best way to use PegIntron in this indication is in combination with ribavirin.

This combination is indicated in naïve patients as well as in patients who have previously responded (with normalisation of ALT at the end of treatment) to interferon alpha monotherapy but who have subsequently relapsed.

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