## SCIENTIFIC DISCUSSION

**This module reflects the initial scientific discussion for the approval of Rebetol. This scientific discussion has been updated until 5 September 2004. For information on changes after 5 September 2004 please refer to module 8B.**

### 1. Introduction

The WHO has estimated that more than 170 million persons may be infected with hepatitis C virus (HCV) world-wide. At least 85% of infected persons develop chronic infection and about 70 % go on to chronic liver disease. Treatment of chronic HCV hepatic disease has so far relied on interferon alfa. Recent evidence suggests that sustained long term improvement in hepatic histology and function only occur when there has been a reduction in HCV RNA to undetectable levels. This is included in the definition of response. A six-month course of interferon alfa monotherapy gives a response rate of 10-15%, while 12-18 months therapy may provide rates of up to 25-30%.

This application seeks marketing authorisation for ribavirin, an antiviral agent, for the treatment of hepatitis C in combination with Interferon alfa-2b.

Ribavirin is a synthetic nucleoside analogue with *in vitro* antiviral activity. While the exact mechanism of action of ribavirin against DNA and RNA viruses is unknown, there is a depletion of host cell nucleotide pools, synthesis of abnormal mRNA, and some suppressive effect on viral polymerase activity.

The current clinical applications of ribavirin are limited to inhalation treatment to respiratory syncytial virus (RSV) bronchiolitis in infants and young children and for (unlicensed) treatment of some viral haemorrhagic fevers (e.g. Lassa).

Initially (7 May 1999), Rebetol, in combination with interferon alfa-2b was indicated:

- For the treatment of adult patients with chronic hepatitis C who have previously responded (with normalisation of ALT at the end of treatment) to interferon alpha therapy but who have subsequently relapsed.
- For the treatment of adult patients with histologically proven chronic hepatitis C, not previously treated, without liver decompensation, with elevated ALT, who are positive for serum HCV-RNA and who have fibrosis or high inflammatory activity. Patients with only portal fibrosis (minimal fibrosis) should have a high inflammatory score.

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

The indication currently approved (9.9. 1999) is therefore the following:

Rebetol is indicated for the treatment of chronic hepatitis C and must only be used as part of a combination regimen with peginterferon alfa-2b or interferon alfa-2b. Rebetol monotherapy must not be used.

There is no safety or efficacy information on the use of Rebetol with other forms of interferon (i.e., not alfa-2b).

Please refer also to the peginterferon alfa-2b or interferon alfa-2b Summary of Product Characteristics (SPC) for prescribing information particular to that product.

**Naïve patients**

Rebetol is indicated, in combination with peginterferon alfa-2b or interferon alfa-2b, for the treatment of adult patients with chronic hepatitis C, not previously treated, without liver decompensation, with elevated ALT, who are positive for serum HCV-RNA (see section **4.4**).

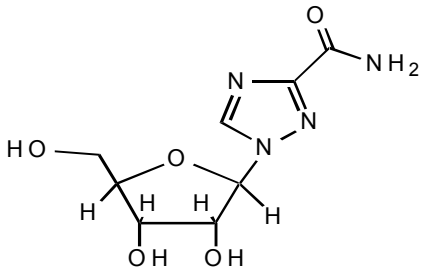
**Relapse patients**

Rebetol is indicated, in combination with peginterferon alfa-2b or interferon alfa-2b, for the treatment of adult patients with chronic hepatitis C who have previously responded (with normalisation of ALT at the end of treatment) to interferon alpha monotherapy but who have subsequently relapsed.

## 2. Part II: chemical, pharmaceutical and biological aspects

### Active substance

Ribavirin is a synthetic nucleoside analogue. Its molecular weight is 244.21. The chemical name of ribavirin is 1-β-D-Ribofuranosyl-1*H*-1, 2,4-triazole-3-carboxamide.




Ribavirin (INN name) is not a new chemical entity. It is marketed as the active ingredient in inhalation solution products and is the subject of monographs in the USP and BP.

The commercial drug substance for Rebetol will be sourced from two suppliers, Orgamol and Wenzhou. The synthetic processes for the manufacture of the active ingredient are described in their DMFs.

The drug substance complies with the BP. The batch analysis provided is satisfactory and fully supports the proposed "in house" specifications, which are considered an improvement as compared to the BP specifications.

The drug substance specification consists of description, identity, melting range, specific optical rotation, LOD, sulphated ash, heavy metals, impurities (specified and unspecified) assay and residual solvents. The reference standard is that of the British Pharmacopoeia.

The drug substance is described as freely soluble in water. Studies in support of the development of the dissolution method indicate that release of the product from the S-P dosage form is not pH dependant. It may be inferred that dissolution of the bulk drug substance reflects this.

Two polymorphic forms are possible, a low melting form II and high melting form I. There is sufficient evidence in the dossier that both synthetic routes produce exclusively form II; DSC analysis in the comparison of the three known sources of ribavirin has been provided. Additionally, the drug substance specification includes melting point limits which preclude formation and release of the higher melting form I.

Neither the BP nor USP includes melting point limits.

Wenzhou has provided adequate evidence of structure including UV and IR material. The IR spectrum produced by Orgamol for their drug substance is concordant with the IR spectrum of ribavirin published in the 1998 BP.

A comparability report is provided which critically compares the drug substance used for early studies, sourced from Heinrich Mack, with the two intended commercial suppliers (WenZhou and Orgamol). This report shows that ribavirin sourced from Orgamol and WenZhou are equivalent to each other and comparable or superior to that previously provided by Heinrich Mack, especially with respect to residual solvent levels.

A number of related substances were studied as potential ribavirin impurities arising from the synthesis of the active ingredient or formed as degradation products. Each of the named impurities has been fully characterised.

The listing of O-benzoyltribavirin as an impurity indicates that the BP monograph is based on a different route of synthesis – thus it is not considered necessary to control this impurity in the drug substances from the two sources cited in the dossier i.e. Wenzhou and Orgamol. The synthetic routes are essentially the same. In both synthetic pathways a catalyst is used. It is considered that if present this potential impurity will be controlled under the current limit for "each unspecified impurity =0.1%".

Consideration was given to the possibility of the alfa-anomer forming as a degradation product and this was critically investigated. Stress studies in aqueous acid and base and at elevated temperatures at solid state did not show evidence of anomerization. As a consequence, the specification for this synthetic impurity needs only to be given for the drug substance and is not required for the finished product.

**Other ingredients**

Ribavirin capsules consist of white opaque preservative-free hard gelatin capsules containing a drug-powder blend, manufactured in a 200 mg strength. A No. 1 size capsule with blue printing is used. The capsule contains, in addition to the drug substance, microcrystalline cellulose as a diluent, spray dried lactose monohydrate as a diluent, croscarmellose sodium as a disintegrant, and magnesium stearate as a lubricant. All of these are compendial excipients.

All materials used in the manufacturing of the product are in line with the current CPMP guideline on TSE.

**Product development and Finished product**

In REBETOL, Ribavirin is formulated as hard gelatin capsules for oral use in a 200 mg strength, packaged in blister strips of PVC/PE/PVdC and aluminium lidding.

*Pharmaceutical development*

Ribavirin capsules 200 mg are currently marketed in the US by Schering Corporation.

The initial development studies were carried out with a formulation manufactured by ICN pharmaceuticals. Schering Corporation was granted an exclusive license from ICN and a development programme was initiated to improve the formulation.

The original clinical trial formula which was obtained from ICN Pharmaceuticals differs from the current proposed commercial formula in that lactose monohydrate has been substituted for a portion of the disintegrant, croscarmellose sodium. Due to the high percentage of drug substance in the drug product, the re-formulation also involved a processing change to provide consistent fill weight at high speed filling.

Reassurance has been provided that drug substance from the different sources has the same physical characteristics and will lead to a consistently robust product. A full comparison of the characteristics of the three sources of drug substance has been provided.

*GMP inspection status*

There were no major issues relating to manufacture of the drug product, therefore a product specific inspection has been considered not necessary by the CPMP. It was considered that an inspection of the drug substance manufacturing site was not necessary. Batch release for all EU Member States is performed by SP Labo N.V. Belgium.

*Manufacture and control*

Suitable finished product specifications and stability indicating analytical procedures have been developed and validated for release and stability testing of Ribavirin capsules 200 mg. Justification of specifications is included in the dossier. Qualitatively, ribavirin is identified by comparing the HPLC retention time and the TLC Rf values of the sample versus those of the Reference Standard and a physical description is also provided. Quantitatively, the HPLC assay, dissolution, moisture content,

uniformity of mass and microbial quality specifications are acceptable for control of the content, purity and release properties of the finished product.

Dissolution testing is performed using the basket stirring method for agitation and the dissolution medium is water. The basket is generally recognised as the preferred apparatus for capsule dosage forms.

The dissolution procedure was validated with respect to selection of the apparatus, agitation rate and medium. The dissolution medium is not pH controlled since the dissolution rate of ribavirin is not affected by the pH of the medium. A comparison of the dissolution profiles in dissolution media with and without deaeration demonstrated that deaeration is not necessary. The dissolution method was also validated with regard to precision, ruggedness and accuracy.

Studies have been conducted to demonstrate the reproducibility of the blend manufacturing and capsule filling processes. Appropriate in-process storage times both before capsule filling and before final packaging were also evaluated. Initial assay data on stability batches have demonstrated that no manufacturing overcharge is required.

*Stability*

Stability studies for Ribavirin (SCH 18908) Capsules 200 mg were conducted using the recognised ICH room temperature conditions of 25ºC/60% RH and refrigerated conditions of 4ºC/60% RH. Additional studies were performed at 30ºC/60% RH, this being considered as the ICH intermediate accelerated test condition, at 40ºC/75% RH as the accelerated condition, and at 30ºC/70% RH.

Studies were carried out on seven batches of the capsule product in two packaging systems.

The shelf life is 2 years.

**Conclusions on Part II**

The drug substance is the subject of a monograph in the BP. The applicant's test methods and specifications meet or exceed that required by the BP. Additional information regarding the drug substance is provided in the supplier DMFs.

The manufacturing process for the product, Ribavirin Capsules 200 mg, has been adequately developed to ensure consistency between batches and adherence to product specifications. All of the test methods customarily required to support the control of active and inactive ingredients in a finished pharmaceutical and for stability monitoring of the product are thoroughly validated. Product specifications are based on consistency with clinical and toxicology samples, stability data and profiles of representative batches, manufactured at the commercial site and which support the recommended two-year shelf life.

Therefore, it can be concluded that the data for ribavirin drug substance and Ribavirin Capsules 200 mg conform to the quality of a well characterised and stable product.

## 3. Part III: toxico-pharmacological aspects

The dossier relies mainly on individual data on ribavirin and interferon alfa-2b.

**Pharmacodynamics**

No animal or cell culture models for hepatitis C virus infection exist and it was not possible to test the effect on hepatitis C virus except in human patients. No preclinical studies were, therefore, performed to demonstrate anti-viral pharmacodynamic activity by ribavirin or the combination of ribavirin and interferon alfa-2b on hepatitis C virus.

**Pharmacokinetics**

The pharmacokinetics of ribavirin and interferon alfa-2b have been reasonably well characterised individually.

Data on interferon alfa-2b and ribavirin administered concomitantly is only available from two preclinical studies. Both of these studies were conducted in monkeys because interferon alfa-2b is biologically inactive in other laboratory animal species. Serum neutralising factors are elicited by interferon alfa-2b in monkeys, and dosing was therefore limited to 1 month's duration.

*Drug interactions*

No formal preclinical animal studies on drug interactions with Rebetol have been performed, except with interferon alfa-2b and antacids.

The effects of interferon alfa-2b on the phosphorylation of ribavirin were investigated in HepG2 and human PHA-stimulated peripheral blood mononuclear (PBM) cells. Interferon alfa-2b at concentrations of 10 and 100 IU $ml^{-1}$ had no effects on the phosphorylation of ribavirin at either 1 or 10 micrograms $ml^{-1}$ in both cell lines, with the triphosphate being the predominant metabolite formed.

Ribavirin indirectly affects the phosphorylation of a number of other purine and pyrimidine nucleoside analogues *in vitro*. IMP is the major phosphate donor in the initial phosphorylation of the adenosine analogue 2', 3'-dideoxyinosine and the formation of the monophosphate is stimulated by ribavirin. This appears to be due to the increased intracellular concentration of IMP that results from the inhibition of IMP dehydrogenase by ribavirin. However, the phosphorylation of zidovudine and stavudine is inhibited by ribavirin. These analogues are phosphorylated by thymidine kinase, an enzyme which is not involved in the phosphorylation of ribavirin but whose activity is under feed-back control by deoxythymidine triphosphate.

Due to this possible interaction in humans, it is recommended that plasma HIV RNA levels be closely monitored in patients treated with Rebetol concurrently with either of these two agents. The interaction can persist up to two months after interruption of Rebetol therapy (five ribavirin half-lives).

No interaction has been shown with non-nucleoside reverse-transcriptase inhibitors or protease inhibitors: Rebetol may be co-administered with these.

**Toxicology**

Ribavirin alone was evaluated in mice, rats, dogs, rabbits, cats and cynomolgus monkeys whereas interferon alfa-2b, alone or combination with ribavirin, was tested only in monkeys which is the only species responsive to interferon alfa-2b.

*Single dose toxicity*

Ribavirin was tested in the cardiovascular, gastrointestinal, renal, and central nervous systems in rats following a single oral dose of 200 mg/kg. No significant changes were found in blood pressure, heart rate, ECG, urinary excretion, gastric motility, behaviour.

*Repeated dose toxicity*

Cynomolgus monkeys received an *sc* injection of 3105 micrograms/$m^2$ interferon alfa-2b every other day in combination with 50-mg/kg/day ribavirin (3 animals *per* sex) or 100 mg/kg/day (5 animals *per* sex) for 29 days in a study which was in compliance with Good Laboratory Practices (GLP). Additional groups of 3 animals *per* sex received either 3105 µg/$m^2$ interferon alfa-2b or 50 mg/kg/day ribavirin, and a control group of 5 animals *per* sex was given a *sc* injection of saline every other day and a daily oral dose of saline. There were 2 deaths in the high dose combination group, one male and one female.

All animals treated with ribavirin and interferon alfa-2b had decreased food consumption, diarrhoea, dehydration and hypothermia. No similar clinical signs were recorded for animals on "mono-treatment", although decreased food consumption was noted in animals treated with 50-mg/kg/day ribavirin.

It was concluded that the administration of ribavirin and interferon alfa-2b in combination did not produce any unexpected toxicity. The major treatment-related change was a mild to moderate anaemia, the severity of which was greater than that produced by either drug alone.

Studies in rats, dogs and monkeys indicated that anaemia occurred with doses as low as 10 to 15 mg/kg/day of ribavirin. These studies suggested that effects of ribavirin on erythrocytes are dependent on both dose and duration of dosing and are reversible upon dose reduction or withdrawal, with considerable interspecies difference in sensitivity. Decreased erythrocyte survival at 15 mg/kg/day and normal osmotic fragility at 30 mg/kg/day in monkeys, and reticulo-endothelial

system pigmentation in dogs and monkeys at 30 mg/kg/day, were considered to be suggestive of extravascular haemolysis involving erythrophagocytosis in at least these 2 species.

The degree of *in vivo* susceptibility to erythroid effects appears to mirror the degree of retention of phosphorylated ribavirin in erythrocytes, with monkeys more affected than humans, and humans more affected than rats.

In order to assess the effects of the combination ribavirin plus peginterferon alfa-2b, one-month repeated toxicity studies in cynomolgus monkeys were performed during the post-authorisation phase. 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.

*Reproductive and development toxicity*

Ribavirin has been shown to be embryotoxic and/or teratogenic in conventional studies in all animal species investigated (rat, rabbit) at doses below those used therapeutically. The incidence and severity of the effect increases with the dose.

In repeated dose toxicity studies in male mice, both testes and sperm were affected. Recovery occurred, upon cessation of therapy, within one or two spermatogenic cycles.

There are non-clinical (monkey) and clinical indications that interferon alfa-2b may impair female fertility.

No studies have been performed using the combination product.

*Mutagenicity and Carcinogenicity*

Ribavirin has been shown to have mutagenic potential in a Balb/3T3 cell transformation assay, mouse lymphoma assay, and in a mouse micronucleus assay.

One mouse and three rat carcinogenicity studies have been completed with ribavirin. There were no evidence of any carcinogenic potential for ribavirin in the mouse study (dose up to 75 mg $kg^{-1}$ $day^{-1}$).

In the latest, and only GLP compliant, rat carcinogenicity study, the incidence of C-cell adenoma of the thyroid was increased in the high dose (40 mg $kg^{-1}$ $day^{-1}$) females (20% compared to control value of 11%). Overall, the incidences of this tumour type in both the control and high dose animals exceeded or were at the "high end" of the historical range for the strain of rat (CD) used. It was concluded that the difference in tumour incidence in high dose females was most likely due to their increased survival rate (38% compared to control value of 23%) than to a carcinogenic effect of ribavirin

Neither of the 2 earlier non-GLP rat carcinogenicity studies, both of which used higher doses than the later study, produced any indication of a carcinogenic effect. The exposure levels that could be reached were lower that the expected human exposure: plasma concentration approximated the expected therapeutic level 1x in mice and 0.1x in rat.

**Conclusion on Part III**

In conclusion, the combination of ribavirin and interferon alfa-2b or peginterferon alfa-2b did not reveal new and unexpected target organs but amplified the effects seen with each compound alone. Target organs of ribavirin were: erythrocytes, lymphoid system and gastrointestinal tract in dogs. Ribavirin accumulates in erythrocytes of non-human primates and humans leading to a very long half life in these species compared to rodents or dogs.

Ribavirin is teratogenic and embryotoxic at doses well below the recommended human dose.

Ribavirin is mutagenic although the studies were not conducted adequately and the mechanism of action is not known. The carcinogenic potential of ribavirin was evaluated but, due to anaemia, animal

exposure could not reach multiple of the human exposure. Therefore, it is not possible to conclude on the potential carcinogenicity risk to humans.

## 4. Part IV: clinical aspects

WHO has estimated that more than 170 millions persons may be infected with hepatitis C virus (HCV) world-wide (more than 5 millions in Europe), but acute icteric manifestations are uncommon and much infection goes unrecognised. At least 85% of infected persons develop chronic infection: some have a benign and indolent infection, while twenty to thirty percent of these will eventually develop cirrhosis and its complications, haemorrhage, hepatic insufficiency and primary liver cancer.

Mortality associated with chronic hepatitis C (CHC) results mainly from the development of liver fibrosis and the subsequent occurrence of cirrhosis. Liver fibrosis progression in CHC has been clarified by a recently published study (*T. Poynard, P. Bedossa, P. Opolon et al. Natural history of liver fibrosis progression in patients with chronic hepatitis C. The Lancet 1997; **349**: 825-832*). Without treatment, 377 (33%) patients had an expected median time to cirrhosis of less than 20 years, and 356 (31%) will never progress to cirrhosis or will not progress for at least 50 years. These findings suggest the presence of at least three populations: rapid fibrosers, intermediate fibrosers and slow fibrosers.

HCV is a flavivirus which contains a positive sense RNA genome. There are six major genotypes (1-6), and a number of subtypes of each genotype (a, b, c), some of which show characteristic geographic distribution of prevalence. Viral load at commencement of therapy and the viral genotype and subtype appear to determine to some extent the response to interferon therapy.

Studies of oral ribavirin monotherapy in chronic HCV have shown no discernible effect on circulating HCV RNA levels; any biochemical improvement were not sustained (see also: *Pharmacodynamics*).

No new clinical data were included in the dossier on ribavirin alone. The data provided concern only the combination of ribavirin and interferon alfa-2b. Efficacy and safety data on the combination ribavirin/peginterferon alfa 2b were subsequently submitted during the post-authorisation phase.

The clinical trials were conducted according to GCP standards and agreed international ethical principles.

**Pharmacodynamics**

Ribavirin is a purine analogue with a broad spectrum of antiviral activity. Ribavirin exerts inhibitory but not virucidal activity *in vitro* against almost all DNA and RNA viral families. To date, neither *in vitro* nor *in vivo* resistance to ribavirin has been demonstrated.

The precise mechanisms by which ribavirin inhibits viral replication have not been fully elucidated. The drug must initially be phosphorylated within infected cells to be effective. For some viruses, the inhibition of IMP dehydrogenase by ribavirin monophosphate results in a depletion of GTP, blocking RNA-primed DNA synthesis. In addition, it has been postulated that ribavirin triphosphate can prevent capping of viral messenger RNA as well as inhibit certain viral RNA. However, ribavirin is not incorporated into either RNA or DNA and ribavirin treatment per se does not induce endogenous synthesis of alpha-interferons.

Anaemia was noted (Shulman) after 3-5 days of ribavirin at different dosages. Both marrow suppression and haemolysis were considered possible mechanisms.

Ribavirin monotherapy (Di Bisceglie *et al.,* 1995) had beneficial effects on transaminase levels during therapy but these were not sustained at 18 months, and produced small improvements in liver histology, but did not affect HCV RNA levels.

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.

**Pharmacokinetics**

Ribavirin is absorbed rapidly following oral administration (mean $T_{max}$ = 1.5 hours), followed by rapid distribution and prolonged elimination phases (single dose half-lives of absorption, distribution and elimination are 0.05, 3.73 and 79 hours, respectively). Absorption is extensive with approximately

10% of a radiolabelled dose excreted in the faeces. However, absolute bioavailability is approximately 45-65%, which appears to be due to first pass metabolism. A high intra-subject variability (30% change in AUC and $T_{max}$) has been shown, and may be due to first-pass metabolism and sequestration in non-plasma compartments.

There is a linear relationship between dose and $AUC_{hr}$, following single doses of 200-1200 mg ribavirin. Ribavirin does not bind to plasma proteins. The distribution volume of ribavirin is high: the transport in non-plasma compartments has been mainly studied in red cells, and the ratio of distribution of ribavirin among whole blood and plasma is 60:1.

Ribavirin has two pathways of metabolism: a reversible prosphorylation pathway and a degradative pathway involving deribosylation and amide hydrolysis to yield a triazole carboxylic acid metabolite. Both ribavirin and its triazole carboxiamide and triazole carboxylic acid metabolites are also excreted renally. Upon multiple dosing, ribavirin accumulates extensively in plasma with a six-fold ratio of multiple-dose to single-dose $AUC_{12hr}$. Following oral dosing with 600 mg BID, steady-state was reached by approximately 4 weeks, with mean steady state plasma concentrations approximately 2200 mg/ml. Upon discontinuation of dosing, the half-life was approximately 298 hours, which probably reflects slow elimination from non-plasma compartments.

Bioequivalence between the ICN and Schering-Plough capsules was confirmed by study C96-242. This study is critical to the application, as early development has been conducted with the ICN formulation.

The kinetics of ribavirin are altered by food (single-dose study C96-398 in 15 healthy volunteers): administration in the fed state significantly increases $C_{max}$, AUC (both increase of 70%) and $T_{max}$ (mean = 3.3 hours). In the initial clinical trials in support to this application, patients were not instructed to take Rebetol with food.

The CPMP considers that it is important that ribavirin is taken with food, in order to ensure that appropriate absorption occurs at initiation of treatment. The SPC was modified accordingly (section 4.2 Posology and method of administration). In case of toxicity, dose adjustments can be made according to what is indicated in the SPC (section 4.2 Posology and method of administration). Considering the recommendations in the SPC and the implications of reduced efficacy in the fasted state, it was agreed not to further investigate the effect of food on ribavirin's pharmacokinetics. The effect of antacids (study C96-214) is to decrease bioavailability of ribavirin. AUC is decreased by 14% if Rebetol is taken together with antacids. Given the variability of the kinetics of ribavirin, the magnitude of this effect has not been judged to be clinically relevant.

As *in vitro* studies have shown that ribavirin indirectly affects the phosphorylation of a number of other purine and pyrimidine nucleoside analogues (see: Part III), it is recommended that plasma HIV RNA levels be closely monitored in patients treated with Rebetol concurrently with zidovudine and stavudine. The interaction can persist up to two months after interruption of Rebetol therapy (five ribavirin half-lives). No interaction has been shown with non-nucleoside reverse-transcriptase inhibitors or protease inhibitors: Rebetol may be co-administered with these.

*Special populations:*

Hepatic impairment. Study C95-155 enrolled 17 patients (out of 23) with liver impairment (5 mild, 5 severe, 7 moderate – Child-Pugh's group A, C, B respectively), which received a single dose of 600 mg ribavirin. $C_{max}$ increased significantly with severity of hepatic impairment, but no significant difference was found in AUC (tf) or renal clearance. This suggests that the major site of first pass elimination are probably the tissues of the gastrointestinal tract, so hepatic dysfunction has no effect on the kinetics of ribavirin.

Renal impairment: In study C95-156 groups of patients (with CrCl >90 ml/min; 61-90; 31-60; 10-30 and in haemodialysis) were compared after administration of a single dose of ribavirin 400 mg. In the four non-dialysis groups both total and renal clearance decreased with decreasing renal function. Renal clearance strongly correlates with CrCl. The use of ribavirin for patients with CrCl <50 ml/min has been contraindicated and it is recommended that combination therapy is discontinued should serum creatinine increase above 2 mg/dl.

In addition, the use of ribavirin has been contraindicated for haemodialysis patients.

No kinetic studies have been carried out with Rebetol in children (under the age of 18) and they are excluded from its use. However, the applicant has initiated a study in paediatric patients, and this point will be reviewed when more data are available.

The use in elderly subjects (> 65 years of age) depends on adequate creatinine clearance.

In summary, ribavirin has a long half-life due to intracellular distribution. Its PK appears to be influenced mainly by, food intake (70% variability during a single-dose study), individual variability (30%), and renal impairment.

**Clinical Efficacy**

**Part A: Combination ribavirin/interferon alfa-2b**

The efficacy of the combination therapy of ribavirin and interferon alfa-2b was evaluated in:

- one phase II study (H095-058, Reichard *et al*., Lancet 1998) in naïve patients (n=100),
- two phase III studies (C95-144, I95-145) in patients who relapsed after interferon treatment (n=153 and n=192). (Part A.1)
- two phase III studies (C95-132, I95-143) in patients with chronic HCV not previously treated with interferon (n=912 and n=832), (Part A.2)

All were double blind, placebo-controlled trials, comparing interferon alfa-2b (3 MIU TIW) monotherapy with interferon alfa-2b (3 MIU t.i.w) plus ribavirin 1,000 (for weight <75 kg) or 1,200 (for weight >75 kg) mg/day.

Dose reductions were allowed in patients with abnormal laboratory findings, who could continue on treatment if the abnormality was within the cut-off value requiring discontinuation. Ribavirin dose was reduced for abnormalities in haemoglobin (<10 g/dl) and bilirubin (>5 mg/dl); interferon dose was reduced in case of decrease of white blood cells (<1.5 $10^9$/L), neutrophil (<0.75 $10^9$/L) and platelet (<50 $10^9$/l) counts.

**Part A.1: Studies of ribavirin/interferon alfa-2b in relapse patients**

The standard treatment period was 24 weeks, followed by 24 weeks of untreated follow-up. Final assessment was performed at week 48.

Regarding baseline characteristics, groups were well balanced with regard to age, gender, ALT, time since last course of interferon (max 2 years), and duration of previous therapy (mostly between 4 and 15 months). Approximately 85% of patients in study C95-144, and 65% in study I95-145 had more than 2 million copies/ml of HCV-RNA at baseline. About 54-60% (total 194 patients) patients per group had HCV genotype 1 infection, while 9-21% (total 60 patients) had genotype 2, 15-31% (total 85 patients) had type 3, and only 5 patients in the entire study had other genotypes. The baseline biopsies showed fibrous portal expansion in 72-82% of patients (total: 315), bridging fibrosis in 52 patients (11-21%), and cirrhotic changes in 9 patients (0-4%).

Overall 86% (131/153) and 95% (182/192) patients completed treatment and follow-up (48 weeks) in studies C95-144 and I95-145 respectively. There was no difference in discontinuation rate in the treatment arms.

Evaluation of the biopsies was performed by the same single pathologist in both studies. The pathologist was blinded with respect to patient identification, treatment group and time of biopsy (pre- or post-treatment).

*Response* was defined as a composite endpoint combining virological response at week 48 (loss of detectable HCV-RNA /qPCR <100 copies/ml) with improvement in the HAI score in the 48 week liver biopsy (Knodell score for sum of categories I+II+III ≥2)

Overall responders showed improvement in both parameters. Patients with missing data (missing HCV-RNA, biopsy or both) were classified as non-responders.

Relapsers were HCV RNA negative at week 24 but positive at week 48.

The following secondary endpoints were also examined:

- response rate at week 24 (HCV-RNA qPCR)
- proportion of patients with normalisation of ALT at week 24 and 48
- proportion of patients with improvement in biopsy (categories I+II+III combined scores)
- change from pre-treatment in biopsy scores (categories I+II+III combined scores)

The primary endpoint (overall response) was evaluated at week 48, end of follow-up period, together with the histologic parameters. End of follow-up virological response rate after combined therapy was 48.6% ($p < 0.0001$), compared with the significantly inferior rate of 4.7% for patients who received interferon alfa-2b monotherapy. Sustained improvement in Knodell score occurred in 63% of combination patients, compared to 41% of monotherapy. The overall response was 37.0% in the combination arms, 3.5 % in the monotherapy ($p < 0.001$).

Some secondary endpoints were evaluated at end of therapy (week 24). The ALT response was evaluated as well at week 48. End of therapy virological response rates were significantly superior with combined therapy: rates were 81% for combined and 46% for monotherapy. ALT response was 89% for combined and 57% for monotherapy at week 24; 52% for combined and 15% for monotherapy at week 48.

Each of the two studies independently demonstrated that the addition of ribavirin to interferon alfa-2b resulted in an approximately 10-fold enhancement in efficacy compared to retreatment with interferon alfa-2b alone.

Also, response induced by the combined treatment seems to be more stable: of those patients who had a virologic response at the end of treatment, 58% (83/141) in the interferon alfa-2b+ribavirin group compared to 9% (7/80) in the interferon alfa-2b+placebo group maintained the response at the end of follow-up.

In the clinical trials, patients who failed to show virological response at week 24, failed to show sustained response at week 48 (one interferon alfa-2b + ribavirin relapse patient had PCR = 200 copies/ml and became sustained responder).

An analysis of the correlation among endpoints has been made:

- Virological response and ALT level: a sustained ALT normal level is highly correlated with the eradication of detectable HCV-RNA at the end of follow-up: the number of patients with normal ALT / number of sustained virologic responders (%) is 80/83 (96%) for interferon alfa-2b + ribavirin; 8/8 (100%) for interferon alfa-2b + placebo
- Virological response and HAI Knodell score: the decrease in hepatic inflammation is highly correlated with the eradication of HCV-RNA whatever the treatment.
- Early relapses and genotype:
  - in HCV genotype1, sustained virologic response was obtained in 29% of interferon alfa-2b + ribavirin treated patients versus 3% interferon alfa-2b + placebo treated. In other HCV genotypes, a sustained virologic response was obtained in 74% interferon alfa-2b + ribavirin treated patients versus 6% interferon alfa-2b + placebo treated.
  - in the interferon alfa-2b+ribavirin group, relapse between the end of the treatment and the end of the follow-up occurred more frequently in patients infected with HCV genotype 1.
  - logistic regression analysis of sustained virologic response demonstrated that, in addition to treatment group, HCV genotype other than 1 was a significant predictor ($p<0.001$).
- Sustained virological response and high viral load: the combined treatment is associated with sustained virological responses (40-44% for interferon alfa-2b + ribavirin against 0-3% for interferon alfa-2b + placebo) also in patients with a high HCV-RNA level at baseline:

*Predictors of sustained response*

Logistic regression analysis of the pooled data using virological response as the endpoint, showed that combined treatment (interferon alfa-2b + ribavirin), HCV genotype other than 1 and baseline high

viral load were significant predictors of sustained virological response at 6 months after the end of treatment.

*Sustained Virological Response by Baseline HCV Genotype and Virus Level/Combined results for relapse patients:*

| | **Interferon alfa-2b + Ribavirin** | **Interferon alfa-2b + Placebo** |
|---|---|---|
| **Other Genotypes/< 2 million copies/ml** | 95 % (19/20) | 18 % (3/17) |
| **Other Genotypes/ > 2 million copies/ml** | 67 % (36/54) | 3 % (2/60) |
| **Genotype 1/< 2 million copies/ml** | 44 % (11/25) | 13 % (3/24) |
| **Genotype 1/ > 2 million copies/ml** | 24 % (18/74) | 0 (0/71) |

A QOL questionnaire was completed by the patients before therapy, during therapy and six months following the end of therapy. All sustained responders had improvement of QOL, whatever their treatment.

**Part A:2 Studies of ribavirin/interferon alfa-2b in naïve patients**

*Phase II trial*

The treatment period was 24 weeks, followed by 24 weeks of untreated follow-up. Final assessment was performed at week 48.

In the evaluable population, sustained response was seen in 49% of combination and 20% of interferon alfa-2b mono-therapy patients. At 24 weeks, 68% of combination and 54% of mono therapy had normal ALT, dropping to 46 % and 28 % respectively at 48 weeks.

*Phase III trials*

The trials (C95-132 and I95-143) evaluated the safety and efficacy of ribavirin plus interferon alfa-2b in patients with chronic HCV infection who had not previously been treated with IFN.

Both trials were multicentre, double-blind and placebo-controlled.

Patients were selected according to criteria similar to those employed in the IFN-experienced patient trials except that they had no past exposure to IFN nor ribavirin. Adults had to have detectable HCV-RNA by the National Genetics Institute (NGI) PCR assay, had a liver biopsy within one year which showed changes consistent with chronic hepatitis, and had elevated ALT for the past six months. Patients with decompensated cirrhosis were excluded.

Treatment regimens and dose adjustments in patients who developed laboratory abnormalities outside of the prescribed limits were as for the previous studies. The major difference was that these trials allowed for some patients to be treated for up to 48 weeks.

*Patients in C95-132* were randomised to one of four treatment groups, which were balanced according to presence/absence of cirrhosis, pre-treatment HCV-RNA level and HCV genotype; 912 patients received treatment as follows:

- IFN alfa-2b plus ribavirin for 24 weeks 228 patients
- IFN alfa-2b plus ribavirin for 48 weeks 228 patients
- IFN alfa-2b plus placebo for 24 weeks 231 patients
- IFN alfa-2b plus placebo for 48 weeks 225 patients

In this study, fibrosis was graded with Knodell HAI score and METAVIR SCORE.

*Patients in I95-143* were similarly randomised with balancing for the same factors as in C95-132. The difference was that the IFN/placebo 24-weeks group was omitted in this study since current recommendations were to give 48 weeks IFN in naive patients: 832 patients received treatment as follows:

- IFN alfa-2b plus ribavirin for 24 weeks 277 patients
- IFN alfa-2b plus ribavirin for 48 weeks 277 patients
- IFN alfa-2b plus placebo for 48 weeks 278 patients

In this study, fibrosis was graded with Knodell HAI score and METAVIR score.

Groups were well-balanced with regard to age, sex, ALT and source and duration of infection. There were 58-70% of patients in each group who had more than 2 million copies/ml of HCV-RNA at baseline. Overall, 64-72% had HCV genotype 1 infection, while 11-17% had genotype 2, 10-20% had type 3. From biopsies 4-5% had cirrhotic changes, 15-19% showed bridging fibrosis. (These figures do not take into account the interferon alfa-2b +placebo 24 weeks group, which is not considered in the assessment of efficacy).

A 24-week post-therapy follow-up phase then ensued in all treatment groups in both trials.

The primary efficacy variable in individual study analysis was sustained virological response (undetectable HCV-RNA as measured by the NGI PCR assay, which has a cut-off limit of <100 copies/ml) at 24 weeks post-therapy.

Secondary efficacy endpoints were: improvement in liver biopsy scores at the end of follow-up, biochemical response (ALT normalisation at the end of follow-up), combined biochemical/virological response.

For the combined results, the primary efficacy endpoint was overall response, a composite endpoint defined as the association of virological and histological responses.

In both trials, there were fewer patients who completed 48 weeks therapy compared with 24 weeks therapy; however, the losses were similar for both combined and monotherapy groups and about 70% of patients assigned to 48 weeks actually completed therapy. Almost all the patients who reached the end of treatment were available for the post-therapy follow-up.

Combined results of the studies were as follows:

- End of follow-up virological response rates after combination therapy were 33% for the 24-week treatment group and 41% for the 48-week group, compared with significantly inferior rates of 6% and 16% for patients who received monotherapy for these respective treatment periods. This shows borderline superiority for 48 *vs.* 24 weeks in each individual study (p=0.053 and 0.055), and the low percentage of sustained responders in interferon monotherapy has to be noted. The treatment difference between combination 24-week and 48-week is found to be statistically significant (p=0.008) in the meta-analysis of both individual studies.
- End of therapy virological response rates were also significantly superior with combined therapy. In the 24-week treatment groups, rates were 55%; after 48 weeks of treatment, rates were 51% Monotherapy rates were 29% (24 weeks and 48 weeks).
- Combination therapy with I/R decreased relapse rates compared to I/P. Extending duration with I/R(48) further decreased the relapse rate, making I/R(48) significantly more effective than I/R(24) (p=0.008). This was true for all HCV genotypes, particularly type 1 in which relapse rates were reduced to 26% with I/R (48). Consistently higher relapse rates were noted with type 1 than with types 2 or 3.

***Relapse Rate by HCV Genotype (C95-132, I95-143)***

| | **I/R(24)** | **I/P(24)** | **I/R(48)** | **I/P(48)** |
|---|---|---|---|---|
| **All Genotypes** | **42% (118/278)[a]** | **80% (53/66)** | **21% (55/260)** | **46% (67/147)** |
| 1 | 62% (84/136) | 89% (25/28) | 26% (33/127) | 56% (37/66) |
| 2/3 | 21% (27/230) | 76% (28/37) | 15% (18/120) | 37% (29/79) |
| 4/5/6 | 58% (7/12) | 0/1 | 31% (4/13) | 50% (1/2) |

a: Patients who had positive or missing HCV-RNA at End of FU÷patients who were HCV-RNA negative at the end of treatment.

Sustained virological response rates were markedly lower for genotype 1 HCV infections compared with all non-genotype 1, whatever the treatment or duration. However, combination therapy was still superior to IFN alone against genotype 1.

- A virological response to therapy at 4 weeks strongly predicted a sustained response; the likelihood of a sustained response decreased with increased duration of therapy before a

finding of undetectable HCV RNA. None of the patients who first became negative after Week 24 became sustained responders.

Sustained Virologic Response by Time to First Negative HCV–RNA/RT–PCR.

| Time to First HCV–RNA Negative | I/R(24) | I/P(24) | I/R(48) | I/P(48) |
|---|---|---|---|---|
| **4 wks** | 83% (92/111)[a] | 48% (10/21) | 82% (94/115) | 71% (47/66) |
| **12 wks** | 44% (66/149) | 9% (3/32) | 66% (91/137) | 35% (29/84) |
| **24 wks** | 19% (8/42) | 0% (0/22) | 44% (20/45) | 15% (6/39) |
| **36 wks** | – | – | 0 (0/6) | 0 (0/11) |
| **48 wks** | – | – | 0 (0/2) | 0 (0/2) |

a: Number of sustained responders÷number of patients HCV–RNA negative for the first time in the interval.

Nevertheless in study C95-132, of the 87 patients in the 48-week combination therapy group who had a sustained virological response, 40 first became negative for HCV-RNA at week 12, and 11 others at week 24 on therapy. Also, 15/29 responders in the 48-week monotherapy group first became negative for HCV RNA after the 4-week visit (11 at 12 weeks and 4 at 24 weeks).

Delayed viral clearance was also documented in 35/70 who received 24 weeks of combination therapy and had a sustained virological response at follow-up, including 30 first negative at 12 weeks and 5 at 24 weeks.

These findings indicate that treatment should not be interrupted in non-responders at week 12, contrarily to what is currently done under interferon monotherapy. In such late responders (first negative PCR at week 24), treatment should on the contrary be continued until week 48. On the other hand, the data suggest that it is not worth continuing treatment in patients with still detectable HCV-RNA at week 24.

- Baseline viral loads and HCV genotype influenced the sustained virologic response as follows:

**Sustained Virologic Response to Treatment by HCV Genotype and Virus Levels**
(Naïve patients 24 weeks after the end of treatment)

| | **Rebetol + interferon alfa-2b 24 weeks** | **Interferon alfa-2b 24 weeks** | **Rebetol + interferon alfa-2b 48 weeks** | **Interferon alfa-2b 48 weeks** |
|---|---|---|---|---|
| **HCV Genotype 1 and ≤ 2 million copies/ml** | 32 % | 4 % | 33 % | 25 % |
| **HCV Genotype 1 and > 2 million copies/ml** | 10 % | 0.9 % | 27 % | 3 % |
| **HCV Genotype other than 1 and ≤ 2 million copies/ml** | 61 % | 25 % | 64 % | 36 % |
| **HCV Genotype other than 1 and > 2 million copies/ml** | 62 % | 11 % | 63 % | 26 % |

- Overall sustained histologic response showed for the 48 weeks therapy group a mean change in Knodell score of –2.6 in the combination groups against –1.0 in monotherapy, improvement in both groups being higher compared with 24 weeks (-1.9 and -0.6 respectively).
- The majority of the patients had disease for more than 5 years. For those patients, in study C95-132, combined therapy was clearly superior to monotherapy, but 48 weeks was not better than 24 weeks of combined treatment. In trial I95-143 response rates were markedly higher than those achieved with 24 weeks or monotherapy (61% *vs.* 39% and 24%).

The majority of patients included were mildly injured, with fibrosis score corresponding to the F1 METAVIR quotation. Nevertheless, due to the high number of patients included, the 5% cirrhosis

(F4 stage) and the 15% bridging fibrosis (F3 stage) correspond to approximately 400 patients (100 patients per arm), which seems enough to enable efficacy evaluation in this subgroup as a whole. For naive patients, it is proposed that only patients with liver fibrosis or high inflammatory activity be treated with the combination (see Section 4.1 of the SPC).

***Part A:*** **Summary and conclusions on efficacy for ribavirin in combination with interferon alfa-2b:**

*Relapse patients*

The results from the clinical trials showed that the combined treatment is significantly more potent than interferon alfa-2b alone to induce a sustained overall response in patients who previously responded to interferon alpha and subsequently relapsed.

Despite the findings of study C96-398, ribavirin has been given in the trials without regard of food. As mentioned above, the SPC has to reflect the CPMP recommendation to administer ribavirin with food, in order to achieve an optimal therapeutic index.

Even if the definition of overall response is in accordance with the consensus recommendations, a sustained virological response as well as a decrease of Knodell HAI score represent surrogates of the only relevant endpoint, which is the decreased risk of cirrhosis and hepatocellular carcinoma.

The only established predictive factor of cirrhosis is fibrosis. The trials do not show any advantage in term of decreasing fibrosis within the six months after treatment stop.

One has to consider that the treated population was moderately severe, with a median Knodell score under 7. Only 3% cirrhosis and 18% bridging fibrosis patients were included. Data on more severe and cirrhosis patients are required. The benefit of adding ribavirin to interferon is particularly significant when the viral load is high.

A virologic response at 1 and 3 months is partly predictive of sustained response but does not allow to stop the treatment if it is not reached.

The treatment duration evaluated is 24 weeks. The proposed duration of treatment seems to be pertinent in good prognostic patients (genotype non 1/ viral load < 2 million copies/ml). In patients with poor prognostic criteria (genotype 1/ viral load > 2 million copies/ml) and non responders at 24 weeks, studies testing a prolongation to 48 weeks of the combined treatment or other schedules are required to establish the optimal treatment duration.

*Naïve patients*

Data concerning the naïve patients have shown that interferon alfa-2b/ribavirin combination therapy for either 24 or 48 weeks always provides higher efficacy than interferon monotherapy with regard to virologic, biochemical and histologic endpoints.

Both a higher rate of virologic response at the end of combination therapy period associated with a subsequent decrease in relapse rate have been demonstrated.

However, sustained virologic response and decrease in inflammation scores are only surrogate markers of the clinically relevant endpoint, i.e. decreased rate of progression towards cirrhosis and hepatocellular carcinoma. On a consensus basis, it is considered that, in the course of natural history of the disease, hepatitis C is not a life-threatening pathology as long as the cirrhosis stage is not reached. To that regard, it is to be noted that the submitted data demonstrated no effect of combination therapy on fibrosis. However, the 6-month follow-up is a rather short time frame to point out an effect on such a slow progressive phenomenon.

On the contrary, recent reports (Marcellin et al., Ann. Intern. Med. 1997;127:875-881 / Lau et al., Gastroenterology 1998;114:suppl:A1284) stated that such sustained virologic responses were usually:

(i) long lasting (5 to 10 years) and

(ii) associated with progressive improvement in histologic parameters, including a decrease of fibrosis progression towards cirrhosis

These properties will have to be confirmed with a long-term follow-up (5 years) to be undertaken by the applicant.

As for predictors of sustained response, early virologic response is much less predictive of sustained response than expected from interferon monotherapy data: late clearance of HCV-RNA from serum (week 24) during bi-therapy was, contrarily to what was observed during interferon monotherapy, frequently associated with sustained virologic response.

These findings indicate that discontinuing therapy at week 12 because of persistent viremia is not indicated. However, there was no further benefit in continuing treatment in patients who failed to achieve a sustained virologic response at week 24 of therapy.

Other identified positive predictors of sustained response were genotypes 2 or 3, low viral loads, low advanced fibrosis stages and age < 40 and are associated with the highest response rates. Several of those factors probably mutually interact.

It appears that there is no longer a place for interferon alpha monotherapy in the therapeutic strategy for CHC patients when ribavirin is not contra-indicated.

There was a greater benefit of 48-week interferon alfa-2b + ribavirin therapy over 24-week interferon alfa-2b + ribavirin therapy in patients with genotype 1 and high viral load (27% sustained response with interferon alfa-2b + ribavirin (48) versus 10% with interferon alfa-2b + ribavirin (24)) and in patients with advanced fibrosis stages.

In other subgroups, a 24-week bi-therapy course provided the maximum benefit.

The 25% difference, between interferon alfa-2b + ribavirin (48) and interferon alfa-2b + ribavirin (24), in the percentage of sustained virological responses among late responders, when compared to the 8% difference observed in the overall population (41% SR for interferon alfa-2b + ribavirin (48) versus 33% SR for interferon alfa-2b + ribavirin (24), indicates that late responders may also retrieve a benefit in receiving a 48-week treatment course in order to achieve a consolidated response.

Indeed, the population of late responders probably overlays to a great extent those above-defined subgroups retrieving a benefit from being administered a 48-week therapy course (i.e. genotype1/high viral load and advanced fibrosis stage).

This needs however to be confirmed, and the Applicant should provide data on:

- disease characteristics (genotype, viral load and fibrosis stage) of late responders.
- the rates of sustained responses among late responders, broken down by genotype, viral load, fibrosis stage and treatment group.

Optimum treatment duration has been discussed taking into account all the identified positive response predictors, but it appears that

- HCV genotype
- viral load
- extent of fibrosis,
- age
- gender

should be considered as routine parameters to determine opportunity to prolong treatment to 48 weeks.

No data are currently available for patients previously non responders to interferon. Efficacy of ribavirin and interferon remains to be investigated in the following cases: cirrhosis, severe renal impairment, CH with extra-hepatic manifestations and HIV co-infected patients.

**Part B: Combination ribavirin/peginterferon alfa-2b**

Two clinical studies were submitted as part of the variation application to support the extension of the use of ribavirin in combination with peginterferon alfa-2b:

- One dose ranging and pharmacokinetic Phase II study (I96-403)
- One pivotal confirmatory study (C/I98-580) in patients with chronic HCV not previously treated with interferon (n = 1580)

*Phase II*

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.

*Phase III*

The efficacy and the safety of two PegIntron/Rebetol regimens compared to standard therapy of IntronA/Rebetol was evaluated in study C/I98-580. This was a large (n = 1580 randomised, 1530 treated), randomized (stratified: genotype 1 versus non-1, cirrhosis +/), multicentre, active-controlled, open-labelled, study where patients received one of the following treatments:

- **I/R**: Interferon alfa-2b 3MIU three times weekly + ribavirin 1000/1200 mg (authorised posology) for 48 weeks, N=505
- **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, N=511
- **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, N=514

The 48 week treatment phase was followed by 24 weeks of untreated follow-up. Patients were instructed to take Rebetol with food.

Of the 1580 patients randomised, 1530 were treated (50 patients were not treated mainly due to patient preference). The patients enrolled were predominantly Caucasian (89%), 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). There was a wide rage of subject weight: 38-181 kg. Baseline demographic and disease characteristics were consistent across all patients groups. Approximately 10 % had cirrhosis as determined by local pathologist assessment. All subjects had clinically compensated, but active, liver disease. The baseline liver histology data are summarized in Table 1.

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. Adverse events and laboratory test results were examined for safety.

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 (loss of detectable serum HCV-RNA/PCR, < 100 copies/ml) 24 weeks after the end of treatment. All other subjects, including those who discontinued before the required serum HCV-RNA/q PCR evaluations were obtained, were considered as non- responders. A subject was classified as a relapser if the subject was a responder at the end of treatment and became HCV-RNA positive at follow-up week 24. 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.

In this trial, the combination of PegIntron (1.5 micrograms/kg/week) and ribavirin was significantly more effective and clinically superior to the control arm of interferon alfa-2b + ribavirin (**Table 1**).

**Table 1** Virologic Response (% of patients HCV negative six months after cessation of treatment)

| | 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)

A logistic regression analysis of the weight effect demonstrated that weight-adjusted dosing for ribavirin maximises the sustained virologic response rate (**Table 2**). The sustained response rate increased up to 61% with PEG 1.5/R with the optimised ribavirin dose (> 10.6 mg/kg) compared to 47 % with standard I/R therapy.

HCV genotype and baseline virus load are important prognostic factors (**Table 2**). The sustained response rate with the optimised 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. Also regardless of genotype, response rates in this trial were increased if patients were able to maintain compliance. Regardless of genotype, patients who received the recommended combination regimen and maintain compliance (≥ 80 % of their treatment with Rebetol and peginterferon alfa-2b) had a higher sustained response 6 months after 1 year of treatment than those who took less (72 % vs. 46 %).

**Table 2** Sustained response rates with PegIntron + ribavirin (by ribavirin dose , genotype and viral load)

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

* 1 vs. non-1: p≤ 0.03, logistic regression

The response rates of patients with genotypes 4/5/6 were 50%, 33% and 38% for the P1.5/R, P0.5R and I/R groups, respectively.

In addition, 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*

The data 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. 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 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. However in genotype 1 patients with a low baseline viral load the optimal duration of combined treatment, as evaluated with interferon alfa-2b and ribavirin, is debated.

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.

***Part B:*** **Summary and conclusions on efficacy for ribavirin in combination with peginterferon alfa-2b:**
In this trial, the combination of PegIntron (1.5 micrograms/kg/week) and ribavirin was significantly more effective and clinically superior to the control arm of interferon alfa-2b + ribavirin. This effect was further enhanced 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 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 Safety**

The safety database consists of:

- Data from two ribavirin/interferon alfa-2b phase III studies (C95-144, I95-145) in patients who relapsed after interferon treatment (n=153 and n=192). Part A

- Data from the two ribavirin/interferon alfa-2b phase III placebo controlled studies in naïve patients (C95-132 and I95-143; n=912 and n=832), Part A

- Data from one ribavirin/peginterferon alfa-2b phase 3 active controlled study in naïve patients (C/I98-580; n=1530). This data was provided following the initial marketing authorization. Part B
- Postmarketing Assessments, Part C

Part A: Ribavirin in combination with Interferon alfa-2b

The pattern of adverse events reporting across the relapse and naïve populations were similar, and reflect the safety profiles of Interferon alfa-2b and ribavirin administered alone.

The most common adverse events reported in both treatment groups and both populations (relapse and naïve) were flu-like symptoms including headache, fatigue, myalgia, fever and rigors. These symptoms typically occurred upon initiation of therapy and decreased with continued treatment. Cough and pharyngitis were reported more frequently in the combination treatment population.

Respiratory system disorders (coughing, dyspnoea, and pharyngitis), skin disorders (pruritus, rash, dry skin), asthenia/fatigue, anorexia/nausea, and insomnia were more common in patients who received Ribavirin + interferon alfa-2b than in those who received interferon alfa-2b and placebo.

Together with haemolysis, these are the defining toxicities of ribavirin use.

Haemolysis is the defining toxicity of the combination therapy and appears to be related to ribavirin.

Among patients treated with the combination, 74% experienced a drop in haemoglobin >2g/dl versus 9% with interferon alone. A decrease in haemoglobin levels below 10 g/dl was observed in up to 14% of the patients.

Some degree of neutropenia occurred in both groups, in about half of all patients. Possibility of immunosuppression is an aspect that the applicant has to monitor with the follow-up measures.

The moderate and mild cardio-vascular events are similar in both treatment groups.

Due to the possibility of cardio-vascular adverse events secondary to ribavirin-associated anaemia, cardiac adverse events were minimised and successfully managed by provisions made in the protocols for 1) the exclusion of patients with a severe cardiac history, 2) the requirement of a minimum Hb level at entry, 3) the increased monitoring of patients whose Hb levels decreased, and 4) the strict criteria for dose discontinuation and modification.

Few patients discontinued due to anaemia, suggesting that the criteria for management of decrease in haemoglobin concentration were largely successful. Close monitoring of patients with history of cardiac disease is required, and the criteria for dose adjustment must be strictly followed.

Anaemia/decrease in haemoglobin concentration was the most frequent reason for dose reduction with I/R (7%-8%) relative to I/P (0%), and occurred with similar incidence regardless of treatment duration.

There may be an increase in uric acid levels, due to haemolysis. The potential for development of gout must be carefully monitored in pre-disposed patients.

Thyroid function abnormalities (change in TSH values) requiring clinical intervention occurred in 3 % of patients with no previous thyroid disorder.

Depression and irritability increased during treatment in both treatment groups. There is a trend toward a slight increase in the overall incidence of neuro-psychiatric events in the combined treatment arm. When occurring the depressions were more severe, with several suicide attempts and suicidal ideation, in patients treated with ribavirin. More patients discontinued the treatment or reduced their doses for neuro-psychiatric reasons in the ribavirin treatment groups.

The proportion of discontinuations due to psychiatric events was higher with I/R(48) (9%) than with the other treatments (2%-4%).

Distribution of depression events over time suggests a linear accumulation over time.

No psychiatric AE was particularly notable for causing discontinuation or dose reduction among patients assigned I/R (24) or I/P (24) (≤1%). With I/R (48) on the contrary, depression caused more discontinuation (3%) or dose reduction (2%) than any other AE, also when compared to I/P(48). Anxiety and suicidal ideation were also more frequent reasons for discontinuation among patients who received I/R (48) when compared to I/R (24) and I/P (48).

These findings suggest that Rebetol therapy should be contra-indicated in patients with a pre-existing history of severe psychiatric disorders (i.e. severe depression, history of suicidal ideation/attempt).

Other patients receiving extended therapy with I/R should receive careful monitoring by the prescribing physician for depression, suicidal thoughts or ideation because of the potentially serious consequences. If symptoms persist or worsen, the patient should discontinue I/R therapy.

The data submitted by the applicant not refer to the immunological consequences of the co-administration of ribavirin and interferon alfa-2b. These data indicate that the follow-up of lymphocytes subsets cannot alone ensure the absence of immunosuppressive effects of a co-administration of interferon alfa-2b and ribavirin.

*Dosage reductions*

Dosage reductions or interruptions because of adverse events occurred in 12 % of patients in the interferon-relapse population treated for 24 weeks and 21 % of patients in the interferon-naive population treated with the combination for 48 weeks.

Anaemia was the primary reason for dosage reduction. Therapy was discontinued due to adverse events in 6 % of patients in the interferon-relapse population treated for 24 weeks and 20 % of patients in the interferon-naive population treated for 48 weeks.

*Severe AE*

Severe and life-threatening events pooled from the four phase III trials were experienced by 6.6% of relapse patients and 11% of naive. The most common were psychiatric, the category which occurred more frequently comparing I/R (2%) with I/P (1%). There were 6 deaths, 5 in the naive patients and 1 in the relapse patients trials: two myocardial infarctions, two cases of illicit drug overdose, and an intracranial haemorrhage. Of the 6 patients who died, 3 were randomised to combination therapy and 2 of the 3 deaths occurred during the follow-up period (16-20 weeks after dosing completion).

*Duration of therapy*

Careful consideration has been given to the question whether extension of therapy duration to 48 weeks modifies the safety profile when compared to the 24 week regimen.

AE were reported more frequently in the 48 week treatment groups. From these, psychiatric events, nausea and weight decrease, which are, in the exception of insomnia, classically associated with interferon alfa-2b use, appear to be more frequent when ribavirin is added to interferon, as shown by the Δ I/R (48) versus I/P (48).

Extended treatment with I/R (48) resulted in an increase in treatment discontinuations as compared to

- treatment with interferon monotherapy I/P(48), **and**
- 6-month treatment with ribavirin I/R (24) (10% of treatment discontinuations during the first 6 months, another 10% discontinuation during the following 6 months of treatment).

There are three groups of AEs that appear to reflect the impact of extending the duration of treatment of ribavirin and interferon alfa-2b: psychiatric events (irritability, depression, insomnia, anxiety), general malaise (infection viral, musculo-skeletal pain etc…) and gastrointestinal disorders.

In naive patients, there is an additional risk of serious psychiatric events associated with extended ribavirin therapy when compared to 6-month ribavirin therapy. The proportion of discontinuations due

to psychiatric events was higher with I/R (48) (9%) than with the other treatments (2%-4%), mainly due to depression (3%).

Pregnancies

Ribavirin is a known teratogen and as such, all patients and their partners have to avoid pregnancy and take the precautions detailed in section 4.6 of the SPC. In the four controlled studies, 12 pregnancies were reported, four in female patients, and eight in partners of male patients. Three of the four patients did not receive ribavirin. The fourth miscarried. Of the eight partners, two miscarried (treatment group remained blinded), three gave birth to healthy babies (one of the three had received ribavirin + interferon), and three outcomes are unknown.

Concomitant medications

Significant increases in some categories of medications used in the pre-treatment period compared to those used during treatment were noted, especially analgesics/antipyretics, nonsteroidal anti-inflammatory agents, and antihistamines. These increases were similar with both interferon alfa-2b + ribavirin and with interferon-2b + placebo.

During the post-marketing surveillance phase, two new undesirable effects have been reported in the first Periodic Safety Update Report covering the period from 8 May 1999 to 7 November 1999: pancreatitis and aggressive behaviour. Cases of pancreatitis, some of them possibly related to the combination ribavirin/interferon alfa 2b, and aggressive behaviour have been reported. Although the frequency of these effects is unknown, it was considered acceptable to update the SPC accordingly. Very rarely, cases of aplastic anaemia have also been reported when ribavirin is used in combination with interferon alfa-2b. Further to evaluation of the data presented in the Periodic Safety Update Reports, it was agreed to include an adequate statement in the Summary of the Product Characteristics.

**Summary and conclusions on clinical safety with ribavirin and interferon alfa-2b:**

Overall, AE reporting was more frequent in the naive population when compared to the relapse population. Given that their previous experience and tolerance to interferon had selected the relapse population, this difference is not surprising. No new types of AE have been reported in the naive population, or in the compassionate studies, as compared to the relapse population.

There was a global decrease of treatment tolerance in patients treated with the combination compared with those treated with interferon + placebo, as showed by the increase of concomitant emergent drugs, treatment discontinuations and dose reductions due to adverse events.

Anaemia and decrease in haemoglobin occurred more frequently with interferon alfa-2b + ribavirin than with interferon alfa-2b + placebo. Severe anaemias occurred preferentially in ribavirin treated patients. Cardio-vascular events were correlated with large haemoglobin drops.

Severe and life threatening cardiovascular complications occurred slightly more frequently in patients who received the combined treatment. These adverse events were observed although patients with a severe cardiac history have been excluded. Using the strict dosage modifications defined in the protocols, there were seldom discontinuations due to decrease in Hb. The contribution of an Hb decrease in the other adverse events such as cardio-vascular, respiratory, psychiatric and general ones cannot be excluded.

The CPMP requests the applicant to further investigate the mechanism of haemolysis.

Neuro-psychiatric events, in particular depressions were more frequently observed in patients who received the combined treatment, in whom severe complications such as suicide attempts and overdose of illicit drugs were reported.

Regarding the effect of extending therapy duration to 48 weeks, distribution of depression events over time suggests a linear accumulation over time.

On the contrary, dose reductions because of anaemia generally occur during the first two months of treatment and are maintained thereafter, indicating that there is no further risk in extending therapy to 48 weeks with regard to anaemia.

Interestingly, no decrease in treatment efficacy was shown when ribavirin doses were reduced, indicating that the minimum efficient dose remains to be confirmed.

It can be concluded that:

1. The safety profile of ribavirin and interferon combination therapy in naive and relapse patients are close. This implies the need of:
    - careful management of haemolysis and anaemia, particularly in patients with a history of cardiovascular problems,
    - careful monitoring of depression and suicidal ideas, also in the follow-up period,
2. extending therapy from 24 to 48 weeks markedly worsen the safety profile, not because of anaemia, the defining toxicity of ribavirin, but due to increased risk of serious depression and suicide, together with increased risk of weight decrease due to general malaise and gastrointestinal disorders.

In view of those findings, it is recommended that the risk to benefit ratio should be thoroughly evaluated by the prescribing physician:

- before initiating ribavirin and interferon alfa-2b combination therapy in naive patients,
- before deciding to extend therapy to 48 weeks

**Part B: Ribavirin in Combination with peginterferon alfa-2b**

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. The optimised dose of ribavirin resulted in a greater fall in hemoglobin levels when compared to those subjects not receiving the optimized dose. Neutropenia is interferon dose related and is slightly increased by co-administration of the optimised dose of ribavirin.

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.

*Dosage Modifications and Discontinuations*
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 %).

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 (5%).

*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.

*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.

**Part B: Summary and conclusions on clinical safety with ribavirin and peginterferon alfa-2b**

With respect to the combination peginterferon alfa-2b + ribavirin, there are no unique adverse events observed in study C/I98-580 that have not already been reported with interferon alfa-2b + ribavirin. With the exception of injection site reactions and some flu-like symptoms, the frequency of the common adverse events was essentially the same with the two combinations. Furthermore, the optimisation of the ribavirin dose did not appear to adversely affect the safety profile. Anaemia is

ribavirin dose-related and, as would be expected, the higher optimised dose of ribavirin resulted in a greater fall in the haemoglobin level but this was easily managed by dose-modification of the ribavirin. Neutropenia is interferon dose-related, and was increased by the co-administration of optimised dose of ribavirin. But, as with anaemia, it was easily managed by dose-modification and did not appear to have clinical sequelae.

**Part C: Postmarketing Assessment**

Based on review of the postmarketing database, the following text was recommended and approved for inclusion in the SPC:

Combination NRTI regimen and Ribavirin:

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

## 5. Overall Conclusions and benefit/risk assessment

It has been demonstrated that the addition of ribavirin to interferon alfa-2b resulted in an approximately 10-fold enhancement in efficacy in the relapse population compared to re-treatment with interferon alfa-2b alone. The enhancement compared to treatment with interferon alfa-2b alone was 3-fold in the naive population.

The efficacy demonstrated with ribavirin in combination with interferon alfa-2b was surpassed when peginterferon alfa-2b was used with ribavirin. 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.

**Conclusion**

A positive benefit/risk ratio has been determined for Rebetol in the following populations:

I) *Naive patients with the following characteristics*: adult patients with histologically proven chronic hepatitis C without liver decompensation, with elevated ALT, who are positive for serum HCV-RNA and who have fibrosis or high inflammatory activity. Patients with only portal fibrosis (minimal fibrosis) should have a high inflammatory score.

II) *Relapse patients with the following characteristics:* adult patients with chronic hepatitis C who have previously responded (with normalisation of ALT at the end of treatment) to interferon alpha therapy but who have subsequently relapsed.

The optimal treatment duration was not established, however the following was indicated, according to the results of the clinical trials with interferon alfa-2b and ribavirin:

I) *Relapse patients*: a course of treatment of 24 weeks is recommended.

II) *Naive patients:* it is recommended that patients be treated for at least 24 weeks. Treatment should be continued for another 24-week period (i.e. a total of 48 weeks) in patients who exhibit negative HCV-RNA at week 24, *and* with viral genotype 1 (as determined in a pre-treatment sample) and high pre-treatment viral load

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

When reviewing the clinical data of ribavirin in combination with peginterferon alfa-2b in naive patients, which became later available, the CPMP considered that the benefit/risk profile of Rebetol was still favourable. Indeed, it was demonstrated that 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 regimen 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.

Therefore on the basis of the available efficacy and safety data available, the CPMP recommended the following indication for Rebetol:

> "Rebetol is indicated for the treatment of chronic hepatitis C and must only be used as part of a combination regimen with peginterferon alfa-2b or interferon alfa-2b. Rebetol monotherapy must not be used.
> There is no safety or efficacy information on the use of Rebetol with other forms of interferon (i.e., not alfa-2b).
> Please refer also to the peginterferon alfa-2b or interferon alfa-2b Summary of Product Characteristics (SPC) for prescribing information particular to that product.
>
> Naïve patients
> Rebetol is indicated, in combination with peginterferon alfa-2b or interferon alfa-2b, for the treatment of adult patients with histologically proven chronic hepatitis C, not previously treated, without liver decompensation, with elevated ALT, who are positive for serum HCV-RNA and who have fibrosis or high inflammatory activity. Patients with only portal fibrosis (minimal fibrosis) should have a high inflammatory score.
>
> Relapse patients
> Rebetol is indicated, in combination with peginterferon alfa-2b or interferon alfa-2b, for the treatment of adult patients with chronic hepatitis C who have previously responded (with normalisation of ALT at the end of treatment) to interferon alpha monotherapy but who have subsequently relapsed".

**Renewal of the Marketing Authorisation for Rebetol**.
Based on the CPMP review of the available information, the CPMP on 22/04/2004 was of the opinion that the quality, the safety and the efficacy of this medicinal product continues to be adequately and sufficiently demonstrated and therefore considered by consensus that the benefit/risk profile of Rebetol continues to be favourable for the following indication:

Rebetol is indicated for the treatment of chronic hepatitis C and must only be used as part of a combination regimen with peginterferon alfa-2b or interferon alfa-2b. Rebetol monotherapy must not be used.

There is no safety or efficacy information on the use of Rebetol with other forms of interferon (i.e., not alfa-2b).

Please refer also to the peginterferon alfa-2b or interferon alfa-2b Summary of Product Characteristics (SPC) for prescribing information particular to that product.

**Naïve patients**
Rebetol is indicated, in combination with peginterferon alfa-2b or interferon alfa-2b, for the treatment of adult patients with chronic hepatitis C, not previously treated, without liver decompensation, with elevated ALT, who are positive for serum HCV-RNA (see section **4.4**).

**Relapse patients**
Rebetol is indicated, in combination with peginterferon alfa-2b or interferon alfa-2b, for the treatment of adult patients with chronic hepatitis C who have previously responded (with normalisation of ALT at the end of treatment) to interferon alpha monotherapy but who have subsequently relapsed.