1. NAME OF THE MEDICINAL PRODUCT

Rebetol®
200 mg capsules

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each capsule contains 200 mg of ribavirin.

Excipient with known effect:
Each capsule contains 40 mg of lactose monohydrate.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Capsule
White, opaque and imprinted with blue ink.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Tritherapy:
Rebetol in combination with boceprevir and peginterferon alfa-2b is indicated for the treatment of chronic hepatitis C (CHC) genotype1 infection in adults patients (18 years of age and older) with compensated liver disease who are previously untreated or who have failed previous therapy.
Please refer to peginterferon alfa -2b and boceprevir Summary of Product Characteristics (SmPCs) when using Rebetol in combination with these medicines.

Bitherapy:
Rebetol is indicated for the treatment of chronic hepatitis C virus infection in adults 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.
Please refer to interferon alfa-2b and peginterferon alfa-2b Summary of Product Characteristics (SmPCs) when using Rebetol in combination with these medicines.

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

Previously untreated (naïve) patients
Adult patients (18 years of age or older): Rebetol is indicated for:

- tritherapy- in combination with peginterferon alfa-2b and boceprevir for the treatment of adult patients with chronic hepatitis C genotype1 infection with compensated liver disease
- bitherapy- in combination with interferon alfa-2b or peginterferon alfa-2b, for the treatment of adult patients with chronic hepatitis C, not previously treated, without liver decompensation, with elevated alanine aminotransferase (ALT), who are positive for hepatitis C viral ribonucleic acid (HCV-RNA).
- bitherapy- for the treatment of CHC infection in combination with peginterferon alfa-2b for patients with compensated cirrhosis and/or clinically stable HIV co-infection (see section 4.4).

Previously treated patients
Adult patients: Rebetol is indicated for:

- tritherapy- in combination with peginterferon alfa-2b and boceprevir for the treatment of adult patients having CHC genotype 1 infection with compensated liver disease.

- bitherapy- in combination with peginterferon alfa-2b, for the treatment of patients with chronic hepatitis C who have failed previous treatment with interferon alfa (pegylated or non-pegylated) alone or in combination with ribavirin (see section5.1).
- bitherapy-in combination with interferon alfa-2b, for the treatment of patients with chronic hepatitis C who have previously responded (with normalisation of ALT at the end of treatment) to interferon alfa monotherapy but who have subsequently relapsed.

4.2 Posology and method of administration

Treatment should be initiated, and monitored, by a physician experienced in the management of chronic hepatitis C.

Rebetol must be used in combination with either peginterferon alfa-2b or interferon alfa-2b (bitherapy), or, in adult patients with chronic hepatitis C genotype 1 infection, in combination with boceprevir and peginterferon alfa-2b (tritherapy).

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

Dose to be administered
The dose of Rebetol is based on patient body weight. Rebetol capsules are to be administered orally each day in two divided doses (morning and evening) with food.

Adult patients:
The dose of Rebetol is based on patient body weight (**Table 1**).
Rebetol must be used in combination with either peginterferon alfa-2b (1.5 micrograms/kg/week) or interferon alfa-2b (3 million international units [MIU] three times a week). The choice of combination regimen is based on the characteristics of the patient. The regimen administered should be selected based on the anticipated efficacy and safety of the combination treatment for an individual patient (see section 5.1). Refer to the SmPC for boceprevir for the details of how boceprevir is to be administered in tritherapy.

Table 1**.** Rebetol dose based on body weight for HCV monoinfected or HCV/HIV co-infected patients and whatever the genotype

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

a: 2 morning, 2 evening
b: 2 morning, 3 evening
c: 3 morning, 3 evening
d: 3 morning, 4 evening

Rebetol capsules in combination with boceprevir and peginterferon alfa-2b, or with peginterferon alfa-2b:

Duration of treatment –Naïve patients
Tritherapy:
Refer to the SmPCs for boceprevir and peginterferon alfa-2b.

Bitherapy with peginterferon alfa-2b:
Predictability of sustained virological response: Patients infected with virus genotype 1 who fail to achieve undetectable HCV-RNA or demonstrate adequate virological response at week 4 or 12 are highly unlikely to become sustained virological responders and should be evaluated for discontinuation (see also section 5.1).

- Genotype 1:
  - For patients who have undetectable HCV-RNA at treatment week 12, treatment should be continued for another nine month period (i.e., a total of 48 weeks).
  - Patients with detectable but ≥2 log decrease in HCV-RNA level from baseline at treatment week 12 should be reassessed at treatment week 24 and, if HCV-RNA is

undetectable, they should continue with full course of therapy (i.e., a total of 48 weeks). However, if HCV-RNA is still detectable at treatment week 24, discontinuation of therapy should be considered.

- In the subset of patients with genotype 1 infection and low viral load (< 600,000 IU/ml) who become HCV-RNA negative at treatment week 4 and remain HCV-RNA negative at week 24, the treatment could either be stopped after this 24 week treatment course or pursued for an additional 24 weeks (i.e. overall 48 weeks treatment duration). However, an overall 24 weeks treatment duration may be associated with a higher risk of relapse than a 48 weeks treatment duration (see section 5.1).

- Genotypes 2 or 3: It is recommended that all patients be treated with bitherapy for 24 weeks, except for HCV/HIV co-infected patients who should receive 48 weeks of treatment.
- Genotype 4**:** In general, patients infected with genotype 4 are considered harder to treat and limited study data (n=66) indicate they are compatible with a duration of treatment with bitherapy as for genotype 1.

Duration of treatment- naïve HCV/HIV co-infected patients
Bitherapy:
The recommended duration of Rebetol weight-based dosing (see **Table 1**) for HCV/HIV co-infected patients is 48 weeks with bitherapy, regardless of genotype.

Predictability of response and non-response in naïve HCV/HIV Co-infection
Early virological response by week 12, defined as a 2 log viral load decrease or undetectable levels of HCV-RNA, has been shown to be predictive for sustained response. The negative predictive value for sustained response in HCV/HIV co-infected patients treated with Rebetol in combination with peginterferon alfa-2b was 99 % (67/68; Study 1) (see section 5.1). A positive predictive value of 50% (52/104; Study 1) was observed for HCV/HIV co-infected patients receiving bitherapy.

Duration of treatment – Retreatment patients
Tritherapy:
Refer to the SmPC for boceprevir and peginterferon alfa-2b.

Bitherapy with peginterferon alfa-2b:
Predictability of sustained virological response: All patients, irrespective of genotype, who have demonstrated serum HCV-RNA below the limits of detection at week 12 should receive 48 weeks of bitherapy. Retreated patients who fail to achieve virological response (i.e. HCV-RNA below the limits of detection) at week 12 are unlikely to become sustained virological responders after 48 weeks of therapy (see also section 5.1).

Retreatment duration greater than 48 weeks in non-responder patients with genotype 1 has not been studied with pegylated interferon alfa-2b and ribavirin combination therapy.

Rebetol capsules in combination with interferon alfa-2b (bitherapy only):

Duration of treatment with interferon alfa-2b:
Based on the results of clinical trials, it is recommended that patients be treated with bitherapy for at least six months. During those clinical trials in which patients were treated for one year, patients who failed to show a virological response after six months of treatment (HCV-RNA below lower limit of detection) were unlikely to become sustained virological responders (HCV-RNA below lower limit of detection six months after withdrawal of treatment).

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

Dose modification for all patients
Combination therapy:
If severe adverse reactions or laboratory abnormalities develop during combination therapy with Rebetol and peginterferon alfa-2b or interferon alfa-2b, or with Rebetol and peginterferon alfa-2b and boceprevir, modify the dosages as indicated in Table 3 if appropriate, until the adverse reactions abate. Dose reduction of boceprevir is not recommended. Guidelines were developed in clinical trials

for dose modification (see Dosage modification guidelines, **Table 3**). As adherence might be of importance for outcome of therapy, the dose should be kept as close as possible to the recommended standard dose. The potential negative impact of ribavirin dose reduction on efficacy results could not be ruled out.

Table 3 Dosage modification guidelines for combination therapy based on laboratory parameters

Laboratory Values	Reduce only Rebetol daily dose (see note 1) if:	Reduce only peginterferon alfa-2b or interferon alfa-2b dose (see note 2) if:	Discontinue combination therapy when the below test value is reported:**
Haemoglobin	< 10 g/dl	-	< 8.5 g/dl
Adults: Haemoglobin in: patients with history of stable cardiac disease	≥ 2 g/dl decrease in haemoglobin during any 4 week period during treatment (permanent dose reduction)		< 12 g/dl after 4 weeks of dose reduction
Leukocytes	-	< 1.5 x 10^9/l	< 1.0 x 10^9/l
Neutrophils	-	< 0.75 x 10^9/l	< 0.5 x 10^9/l
Platelets	-	< 50 x 10^9/l (adults)	< 25 x 10^9/l (adults)
Bilirubin – Direct	-	-	2.5 x ULN*
Bilirubin – Indirect	> 5 mg/dl	-	> 4 mg/dl (adults) (for > 4 weeks)
Serum Creatinine	-	-	> 2.0 mg/dl
Creatinine Clearance	-	-	Discontinue Rebetol if CrCl <50 ml/minute
Alanine aminotransferase (ALT) or Aspartate aminotransferase (AST)	-	-	2 x baseline and > 10 x ULN* or 2 x baseline and > 10 x ULN*

* Upper limit of normal

** Refer to the SmPC for pegylated interferon alfa-2b and interferon alfa-2b for dose modification and discontinuation.

Note 1: In adult patients, 1st dose reduction of Rebetol is by 200 mg/day (except in patients receiving the 1,400 mg, dose reduction should be by 400 mg/day). If needed, 2nd dose reduction of Rebetol is by an additional 200 mg/day.Patients whose dose of Rebetol is reduced to 600 mg daily receive one 200 mg capsule in the morning and two 200 mg capsules in the evening.

Note 2: In adult patients treated with Rebetol plus peginterferon alfa-2b, 1st dose reduction of peginterferon alfa-2b is to 1 µg/kg/week. If needed, 2nd dose reduction of peginterferon alfa-2b is to 0.5 µg/kg/week. In adult patients treated with Rebetol plus interferon alfa-2b, reduce the interferon alfa-2b dose by one-half dose.

Special populations

Use in renal impairment: The pharmacokinetics of ribavirin are altered in patients with renal dysfunction due to reduction of apparent creatinine clearance in these patients (see section 5.2). Therefore, it is recommended that renal function be evaluated in all patients prior to initiation of Rebetol. Patients with creatinine clearance < 50 ml/minute must not be treated with Rebetol (see section 4.3). Patients with impaired renal function should be more carefully monitored with respect to the development of anaemia. If serum creatinine rises to > 2.0 mg/dl (**Table 3**), Rebetol and peginterferon alfa-2b/interferon alfa-2b must be discontinued.

Use in hepatic impairment: No pharmacokinetic interaction appears between ribavirin and hepatic function (see section 5.2). Therefore, no dose adjustment of Rebetol is required in patients with hepatic impairment. The use of ribavirin is contraindicated in patients with severe hepatic impairment or decompensated cirrhosis (see section 4.3).

Use in the elderly (≥ 65 years of age): There does not appear to be a significant age-related effect on the pharmacokinetics of ribavirin. However, as in younger patients, renal function must be determined prior to administration of Rebetol (see section 5.2).

Patients co-infected with HCV/HIV: Patients taking nucleoside reverse transcriptase inhibitor (NRTI) treatment in association with ribavirin and interferon alfa-2b or peginterferon alfa-2b may be at increased risk of mitochondrial toxicity, lactic acidosis and hepatic decompensation (see section 4.4). Please refer also to the relevant product information for antiretroviral medicinal products.

Method of administration:
Rebetol should be administered orally. No special precautions for disposal or handling are required.

4.3 Contraindications

- Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.
- Pregnant women (see sections 4.4, 4.6 and 5.3). Rebetol must not be initiated until a report of a negative pregnancy test has been obtained immediately prior to initiation of therapy.
- Lactation
- A history of severe pre-existing cardiac disease, including unstable or uncontrolled cardiac disease, in the previous six months (see section 4.4).
- Patients with severe, debilitating medical conditions.
- Patients with chronic renal failure, patients with creatinine clearance < 50 ml/minute and/or on haemodialysis.
- Severe hepatic impairment (Child-Pugh Classification B or C) or decompensated cirrhosis of the liver.
- Haemoglobinopathies (e.g., thalassemia, sickle-cell anaemia).
- Initiation of peginterferon alfa-2b is contraindicated in HCV/HIV patients with cirrhosis and a Child-Pugh score ≥ 6.

Because of co-administration with peginterferon alfa-2b or interferon alfa-2b:
- Autoimmune hepatitis; or history of autoimmune disease.

4.4 Special warnings and precautions for use

Psychiatric and Central Nervous System (CNS):
Severe CNS effects, particularly depression, suicidal ideation and attempted suicide have been observed in some patients during Rebetol combination therapy with peginterferon alfa-2b or interferon alfa-2b, and even after treatment discontinuation mainly during the 6-month follow-up period. Other CNS effects including aggressive behaviour (sometimes directed against others such as homicidal ideation), bipolar disorder, mania, confusion and alterations of mental status have been observed with alfa interferons. Patients should be closely monitored for any signs or symptoms of psychiatric disorders. If such symptoms appear, the potential seriousness of these undesirable effects must be borne in mind by the prescribing physician and the need for adequate therapeutic management should be considered. If psychiatric symptoms persist or worsen, or suicidal or homicidal ideation is identified, it is recommended that treatment with Rebetol and peginterferon alfa-2b or interferon alfa-2b be discontinued, and the patient followed, with psychiatric intervention as appropriate.

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

Patients with substance use/abuse:
HCV infected patients having a co-occurring substance use disorder (alcohol, cannabis, etc) are at an increased risk of developing psychiatric disorders or exacerbation of already existing psychiatric

disorders when treated with alfa interferon. If treatment with alfa interferon is judged necessary in these patients, the presence of psychiatric co-morbidities and the potential for other substance use should be carefully assessed and adequately managed before initiating therapy. If necessary, an inter-disciplinary approach including a mental health care provider or addiction specialist should be considered to evaluate, treat and follow the patient. Patients should be closely monitored during therapy and even after treatment discontinuation. Early intervention for re-emergence or development of psychiatric disorders and substance use is recommended.

Based on results of clinical trials, the use of ribavirin as monotherapy is not effective and Rebetol must not be used alone. The safety and efficacy of combination therapy have been established only using ribavirin together with peginterferon alfa-2b or interferon alfa-2b solution for injection.

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

Haemolysis: A decrease in haemoglobin levels to < 10 g/dl was observed in up to 14 % of adult patients treated with Rebetol in combination with peginterferon alfa-2b or interferon alfa-2b in clinical trials. Although ribavirin has no direct cardiovascular effects, anaemia associated with Rebetol may result in deterioration of cardiac function, or exacerbation of the symptoms of coronary disease, or both. Thus, Rebetol must be administered with caution to patients with pre-existing cardiac disease (see section 4.3). Cardiac status must be assessed before start of therapy and monitored clinically during therapy; if any deterioration occurs, therapy must be stopped (see section 4.2).

Cardiovascular: Adult patients with a history of congestive heart failure, myocardial infarction and/or previous or current arrhythmic disorders must be closely monitored. It is recommended that those patients who have pre-existing cardiac abnormalities have electrocardiograms taken prior to and during the course of treatment. Cardiac arrhythmias (primarily supraventricular) usually respond to conventional therapy but may require discontinuation of therapy. There are no data in children or adolescents with a history of cardiac disease.

Acute hypersensitivity: If an acute hypersensitivity reaction (e.g., urticaria, angioedema, bronchoconstriction, anaphylaxis) develops, Rebetol must be discontinued immediately and appropriate medical therapy instituted. Transient rashes do not necessitate interruption of treatment.

Ocular changes: Ribavirin is used in combination therapy with alfa interferons. Retinopathy including retinal haemorrhages, retinal exudates, papilloedema, optic neuropathy and retinal artery or vein occlusion which may result in loss of vision have been reported in rare instances with combination therapy with alfa interferons. All patients should have a baseline eye examination. Any patient complaining of decrease or loss of vision must have a prompt and complete eye examination. Patients with preexisting ophthalmologic disorders (e.g., diabetic or hypertensive retinopathy) should receive periodic ophthalmologic exams during combination therapy with alfa interferons. Combination therapy with alfa interferons should be discontinued in patients who develop new or worsening ophthalmologic disorders.

Liver function: Any patient developing significant liver function abnormalities during treatment must be monitored closely. Discontinue treatment in patients who develop prolongation of coagulation markers which might indicate liver decompensation.

Potential to exacerbate immunosuppression: Pancytopenia and bone marrow suppression have been reported in the literature to occur within 3 to 7 weeks after the administration of a peginterferon and ribavirin concomitantly with azathioprine. This myelotoxicity was reversible within 4 to 6 weeks upon withdrawal of HCV antiviral therapy and concomitant azathioprine and did not recur upon reintroduction of either treatment alone (see section 4.5).

HCV/HIV Co-infection:
Mitochondrial toxicity and lactic acidosis:
Caution should be taken in HIV-positive subjects co-infected with HCV who receive nucleoside reverse transcriptase inhibitor (NRTI) treatment (especially ddI and d4T) and associated interferon

alfa-2b/ribavirin treatment. In the HIV-positive population receiving an NRTI regimen, physicians should carefully monitor markers of mitochondrial toxicity and lactic acidosis when ribavirin is administered. In particular:

- co-administration of Rebetol and didanosine is not recommended due to the risk of mitochondrial toxicity (see section 4.5).
- co-administration of Rebetol and stavudine should be avoided to limit the risk of overlapping mitochondrial toxicity.

Hepatic decompensation in HCV/HIV co-infected patients with advanced cirrhosis:
Co-infected patients with advanced cirrhosis receiving highly active anti-retroviral therapy (HAART) may be at increased risk of hepatic decompensation and death. Adding treatment with alfa interferons alone or in combination with ribavirin may increase the risk in this patient subset. Other baseline factors in co-infected patients that may be associated with a higher risk of hepatic decompensation include treatment with didanosine and elevated bilirubin serum concentrations. Co-infected patients receiving both antiretroviral (ARV) and anti-hepatitis treatment should be closely monitored, assessing their Child-Pugh score during treatment. Patients progressing to hepatic decompensation should have their anti-hepatitis treatment immediately discontinued and the ARV treatment reassessed.

Haematological abnormalities in HCV/HIV co-infected patients:
HCV/HIV co-infected patients receiving peginterferon alfa-2b/ribavirin treatment and HAART may be at increased risk to develop haematological abnormalities (as neutropenia, thrombocytopenia and anaemia) compared to HCV mono-infected patients. Although, the majority of them could be managed by dose reduction, close monitoring of haematological parameters should be undertaken in this population of patients (see section 4.2 and below “Laboratory tests” and section 4.8). Patients treated with ribavirin and zidovudine are at increased risk of developing anaemia; therefore, the concomitant use of ribavirin with zidovudine is not recommended (see section 4.5).

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

Please refer to the respective Summary of Product Characteristics of the antiretroviral medicinal products that are to be taken concurrently with HCV therapy for awareness and management of toxicities specific for each product and the potential for overlapping toxicities with Rebetol and peginterferon alfa-2b.

Dental and periodontal disorders: Dental and periodontal disorders, which may lead to loss of teeth, have been reported in patients receiving Rebetol and peginterferon alfa-2b or interferon alfa-2b combination therapy. In addition, dry mouth could have a damaging effect on teeth and mucous membranes of the mouth during long-term treatment with the combination of Rebetol and peginterferon alfa-2b or interferon alfa-2b. Patients should brush their teeth thoroughly twice daily and have regular dental examinations. In addition some patients may experience vomiting. If this reaction occurs, they should be advised to rinse out their mouth thoroughly afterwards.

Laboratory tests: Standard haematologic tests and blood chemistries (complete blood count [CBC] and differential, platelet count, electrolytes, serum creatinine, liver function tests, uric acid) must be conducted in all patients prior to initiating therapy. Acceptable baseline values that may be considered as a guideline prior to initiation of Rebetol therapy:

- Haemoglobin — Adult: $\geq$ 12 g/dl (females); $\geq$ 13 g/dl (males)
- Platelets — $\geq$ 100,000/mm^3
- Neutrophil Count — $\geq$ 1,500/mm^3

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

For females of childbearing potential: Female patients must have a routine pregnancy test performed monthly during treatment and for four months thereafter. Female partners of male patients must have

a routine pregnancy test performed monthly during treatment and for seven months thereafter (see section 4.6).

Uric acid may increase with Rebetol due to haemolysis; therefore, the potential for development of gout must be carefully monitored in pre-disposed patients.

Use in patients with rare hereditary disorders: Each Rebetol capsule contains 40 mg of lactose. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

4.5 Interaction with other medicinal products and other forms of interaction

Results of *in vitro* studies using both human and rat liver microsome preparations indicated no cytochrome P450 enzyme mediated metabolism of ribavirin. Ribavirin does not inhibit cytochrome P450 enzymes. There is no evidence from toxicity studies that ribavirin induces liver enzymes. Therefore, there is a minimal potential for P450 enzyme-based interactions.

Ribavirin, by having an inhibitory effect on inosine monophosphate dehydrogenase, may interfere with azathioprine metabolism possibly leading to an accumulation of 6-methylthioinosine monophosphate (6-MTIMP), which has been associated with myelotoxicity in patients treated with azathioprine. The use of pegylated alfa interferons and ribavirin concomitantly with azathioprine should be avoided. In individual cases where the benefit of administering ribavirin concomitantly with azathioprine warrants the potential risk, it is recommended that close hematologic monitoring be done during concomitant azathioprine use to identify signs of myelotoxicity, at which time treatment with these medicines should be stopped (see section 4.4).

No interaction studies have been conducted with Rebetol and other medicinal products, except for peginterferon alfa-2b, interferon alfa-2b and antacids.

Interferon alfa-2b: No pharmacokinetic interactions were noted between Rebetol and peginterferon alfa-2b or interferon alfa-2b in a multiple-dose pharmacokinetic study.

Antacid: The bioavailability of ribavirin 600 mg was decreased by co-administration with an antacid containing magnesium aluminium and simethicone; AUC_{tf} decreased 14 %. It is possible that the decreased bioavailability in this study was due to delayed transit of ribavirin or modified pH. This interaction is not considered to be clinically relevant.

Nucleoside analogs: Use of nucleoside analogs, alone or in combination with other nucleosides, has resulted in lactic acidosis. Pharmacologically, ribavirin increases phosphorylated metabolites of purine nucleosides in vitro. This activity could potentiate the risk of lactic acidosis induced by purine nucleoside analogs (e.g. didanosine or abacavir). Co-administration of Rebetol and didanosine is not recommended. Reports of mitochondrial toxicity, in particular lactic acidosis and pancreatitis, of which some fatal, have been reported (see section 4.4).
The exacerbation of anaemia due to ribavirin has been reported when zidovudine is part of the regimen used to treat HIV although the exact mechanism remains to be elucidated. The concomitant use of ribavirin with zidovudine is not recommended due to an increased risk of anaemia (see section 4.4). Consideration should be given to replacing zidovudine in a combination anti-retroviral treatment (ART) regimen if this is already established. This would be particularly important in patients with a known history of zidovudine induced anaemia.

Any potential for interactions may persist for up to two months (five half-lives for ribavirin) after cessation of Rebetol therapy due to the long half-life (see section 5.2).

There is no evidence that ribavirin interacts with non-nucleoside reverse transcriptase inhibitors or protease inhibitors.

Conflicting findings are reported in literature on co-administration between abacavir and ribavirin. Some data suggest that HIV/HCV co-infected patients receiving abacavir-containing ART may be at risk of a lower response rate to pegylated interferon/ribavirin therapy. Caution should be exercised when both medicines are co-administered.

4.6 Fertility, pregnancy and lactation

Women of childbearing potential/contraception in males and females
Female patients: Rebetol must not be used by females who are pregnant (see sections 4.3 and 5.3). Extreme care must be taken to avoid pregnancy in female patients (see section 5.3). Rebetol therapy must not be initiated until a report of a negative pregnancy test has been obtained immediately prior to initiation of therapy. Females of childbearing potential must use an effective contraceptive during treatment and for four months after treatment has been concluded; routine monthly pregnancy tests must be performed during this time. If pregnancy does occur during treatment or within four months from stopping treatment, the patient must be advised of the significant teratogenic risk of ribavirin to the foetus.

Male patients and their female partners: Extreme care must be taken to avoid pregnancy in partners of male patients taking Rebetol (see sections 4.3 and 5.3). Ribavirin accumulates intracellularly and is cleared from the body very slowly. It is unknown whether the ribavirin that is contained in sperm will exert its potential teratogenic or genotoxic effects on the human embryo/foetus. Although data on approximately 300 prospectively followed pregnancies with paternal exposure to ribavirin have not shown an increased risk of malformation compared to the general population, nor any specific pattern of malformation, either male patients or their female partners of childbearing age must be advised to use an effective contraceptive during treatment with Rebetol and for seven months after treatment. Men whose partners are pregnant must be instructed to use a condom to minimise delivery of ribavirin to the partner.

Pregnancy
The use of Rebetol is contraindicated during pregnancy.

Breast-feeding
It is not known whether ribavirin is excreted in human milk. Because of the potential for adverse reactions in breast-fed infants, breast-feeding must be discontinued prior to initiation of treatment.

Fertility
Preclinical data:
- Fertility: In animal studies, ribavirin produced reversible effects on spermatogenesis (see section 5.3).
- Teratogenicity: Significant teratogenic and/or embryocidal potential have been demonstrated for ribavirin in all animal species in which adequate studies have been conducted, occurring at doses as low as one twentieth of the recommended human dose (see section 5.3).
- Genotoxicity: Ribavirin induces genotoxicity (see section 5.3).

4.7 Effects on ability to drive and use machines

Rebetol has no or negligible influence on the ability to drive and use machines; however, peginterferon alfa-2b or interferon alfa-2b used in combination may have an effect. Thus, patients who develop fatigue, somnolence, or confusion during treatment must be cautioned to avoid driving or operating machinery.

4.8 Undesirable effects

Tritherapy
Refer to the SmPC for boceprevir.

Bitherapy
The safety of Rebetol capsules is evaluated from data from four clinical trials in patients with no previous exposure to interferon (interferon-naïve patients): two trials studied Rebetol in combination with interferon alfa-2b, two trial studied Rebetol in combination with peginterferon alfa-2b.

Patients who are treated with interferon alfa-2b and ribavirin after previous relapse from interferon therapy or who are treated for a shorter period are likely to have an improved safety profile than that described below.

The adverse reactions listed in **Table 4** are based on experience from clinical trials in adult naïve patients treated for 1 year and post-marketing use. A certain number of adverse reactions, generally attributed to interferon therapy but that have been reported in the context of hepatitis C therapy (in combination with ribavirin) are also listed for reference in **Table 4**. Also, refer to peginterferon alfa-2b and interferon alfa-2b SmPCs for adverse reactions that may be attributable to interferons monotherapy. Within the organ system classes, adverse reactions are listed under headings of frequency using the following categories: very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥ 1/10,000 to <1/1,000); very rare (<1/10,000); not known. Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

Table 4 Adverse reactions reported during clinical trials or following the marketing use of Rebetol with pegylated interferon alfa-2b or interferon alfa-2b

System Organ Class	**Adverse Reactions**
Infections and infestations	
Very common:	Viral infection, pharyngitis
Common:	Bacterial infection (including sepsis), fungal infection, influenza, respiratory tract infection, bronchitis, herpes simplex, sinusitis, otitis media, rhinitis, urinary tract infection
Uncommon	Injection site infection, lower respiratory tract infection
Rare:	Pneumonia*
Neoplasms benign, malignant and unspecified (including cysts and polyps)	
Common:	Neoplasm unspecified
Blood and lymphatic system disorders	
Very common:	Anaemia, neutropenia
Common:	Haemolitic anaemia, leukopenia, thrombocytopenia, lymphadenopathy, lymphopenia
Very rare:	Aplastic anaemia*
Not known:	Pure red cell aplasia, idiopathic thrombocytopenic purpura, thrombotic thrombocytopenic purpura
Immune system disorders	
Uncommon:	Drug hypersensitivity
Rare:	Sarcoidosis*, rheumatoid arthritis (new or aggravated)
Not known:	Vogt-Koyanagi-Harada syndrome, systemic lupus erythematosus, vasculitis, acute hypersensitivity reactions including urticaria, angioedema, bronchoconstriction, anaphylaxis
Endocrine disorders	
Common:	Hypothyroidism, hyperthyroidism
Metabolism and nutrition disorders	
Very common:	Anorexia
Common:	Hyperglycaemia, hyperuricaemia, hypocalcaemia, dehydration, increased appetite
Uncommon:	Diabetes mellitus, hypertriglyceridemia*
Psychiatric disorders	
Very common:	Depression, anxiety, emotional lability, insomnia
Common:	Suicidal ideation, psychosis, aggressive behaviour, confusion, agitation, anger, mood altered, abnormal behaviour, nervousness, sleep disorder, decreased libido apathy, abnormal dreams, crying
Uncommon:	Suicide attempts, panic attack, hallucination
Rare:	Bipolar disorder*
Very rare:	Suicide*
Not known:	Homicidal ideation*, mania*, mental status change

Table 4 Adverse reactions reported during clinical trials or following the marketing use of Rebetol with pegylated interferon alfa-2b or interferon alfa-2b

System Organ Class	Adverse Reactions
Nervous system disorders	
Very common:	Headache, dizziness, dry mouth, concentration impaired
Common:	Amnesia, memory impairment, syncope, migraine, ataxia, paraesthaesia, dysphonia, taste loss, hypoaesthesia, hyperaesthesia, hypertonia, somnolence, disturbance in attention, tremor, dysgeusia
Uncommon:	Neuropathy, peripheral neuropathy
Rare:	Seizure (convulsion)*
Very rare:	Cerebrovascular haemorrhage*, cerebrovascular ischaemia*, encephalopathy*, polyneuropathy*
Not known:	Facial palsy, mononeuropathies
Eye disorders	
Common:	Visual disturbance, blurred vision, conjunctivitis, eye irritation, eye pain, abnormal vision, lacrimal gland disorder, dry eye
Rare:	Retinal haemorrhages*, retinopathies (including macular oedema)*, retinal artery occlusion*, retinal vein occlusion*, optic neuritis*, papilloedema*, loss of visual acuity or visual field*, retinal exudates
Ear and labyrinth disorders	
Common:	Vertigo, hearing impaired/loss, tinnitus, ear pain
Cardiac disorders	
Common:	Palpitation, tachycardia
Uncommon:	Myocardial infarction
Rare:	Cardiomyopathy, arrhythmia*
Very rare:	Cardiac ischaemia*
Not known:	Pericardial effusion*, pericarditis*
Vascular disorders	
Common:	Hypotension, hypertension, flushing
Rare:	Vasculitis
Very rare:	Peripheral ischaemia*
Respiratory, thoracic and mediastinal disorders	
Very common:	Dyspnoea, coughing
Common:	Epistaxis, respiratory disorder, respiratory tract congestion, sinus congestion, nasal congestion, rhinorrhea, increased upper airway secretion, pharyngolaryngeal pain, nonproductive cough
Very rare:	Pulmonary infiltrates*, pneumonitis*, interstitial pneumonitis*
Gastro-intestinal disorders	
Very common:	Diarrhoea, vomiting, nausea, abdominal pain
Common:	Ulcerative stomatitis, stomatitis, mouth ulceration, colitis, upper right quadrant pain, dyspepsia, gastroesophoageal reflux*, glossitis, cheilitis, abdominal distension, gingival bleeding, gingivitis, loose stools, tooth disorder, constipation, flatulence
Uncommon:	Pancreatitis, oral pain
Rare:	Ischaemic colitis
Very rare:	Ulcerative colitis*
Not known:	Periodontal disorder, dental disorder, tongue pigmentation
Hepatobiliary disorders	
Common:	Hepatomegaly, jaundice, hyperbilirubinemia*
Very rare:	Hepatotoxicity (including fatalities)*

Table 4 Adverse reactions reported during clinical trials or following the marketing use of Rebetol with pegylated interferon alfa-2b or interferon alfa-2b

System Organ Class	Adverse Reactions
Skin and subcutaneous tissue disorders	
Very common:	Alopecia, pruritus, skin dry, rash
Common:	Psoriasis, aggravated psoriasis, eczema, photosensitivity reaction, maculopapular rash, erythematous rash, night sweats, hyperhidrosis, dermatitis, acne, furuncule, erythema, urticaria, skin disorder, bruise, sweating increased, abnormal hair texture, nail disorder*
Rare:	Cutaneous sarcoidosis
Very rare:	Stevens Johnson syndrome*, toxic epidermal necrolysis*, erythema multiforme*
Musculoskeletal and connective tissue disorders	
Very common:	Arthralgia, myalgia, musculoskeletal pain
Common:	Arthritis, back pain, muscle spasms, pain in extremity
Uncommon:	Bone pain, muscle weakness
Rare:	Rhabdomyolysis*, myositis*
Renal and urinary disorders	
Common:	Micturition frequency, polyuria, urine abnormality
Rare:	Renal failure, renal insufficiency*
Very rare:	Nephrotic syndrome*
Reproductive system and breast disorders	
Common:	Female: amenorrhea, menorrhagia, menstrual disorder, dysmenorrhea, breast pain, ovarian disorder, vaginal disorder. Male: impotence, prostatitis, erectile dysfunction. Sexual dysfunction (not specified)*
General disorders and administration site conditions	
Very common:	Injection site inflammation, injection site reaction, fatigue, rigors, pyrexia, influenza like illness, asthenia, irritability
Common:	Chest pain, chest discomfort, peripheral oedema, malaise, injection site pain, feeling abnormal, thirst
Uncommon:	Face oedema
Rare:	Injection site necrosis
Investigations	
Very common:	Weight decrease
Common:	Cardiac murmur

* Since ribavirin is always prescribed with an alpha interferon product, and the listed adverse drug reactions included reflecting post-marketing experience do not allow precise quantification of frequency, the frequency reported above is from clinical trials using ribavirin in combination with interferon alfa-2b (pegylated or non-pegylated).

A reduction in haemoglobin concentrations by > 4 g/dl was observed in 30 % of patients treated with Rebetol and peginterferon alfa-2b and 37 % of patients treated with Rebetol and interferon alfa-2b. Haemoglobin levels dropped below 10 g/dl in up to 14 % of adult patients treated with Rebetol in combination with either peginterferon alfa-2b or interferon alfa-2b.

Most cases of anaemia, neutropaenia, and thrombocytopaenia were mild (WHO grades 1 or 2). There were some cases of more severe neutropenia in patients treated with Rebetol in combination with peginterferon alfa-2b (WHO grade 3: 39 of 186 [21 %]; and WHO grade 4: 13 of 186 [7 %]); WHO grade 3 leukopenia was also reported in 7 % of this treatment group.

An increase in uric acid and indirect bilirubin values associated with haemolysis was observed in some patients treated with Rebetol used in combination with peginterferon alfa-2b or interferon alfa-2b in clinical trials, but values returned to baseline levels by four weeks after the end of therapy. Among those patients with elevated uric acid levels, very few patients treated with the

combination developed clinical gout, none of which required treatment modification or discontinuation from the clinical trials.

HCV/HIV co-infected patients:
For HCV/HIV co-infected patients receiving Rebetol in combination with peginterferon alfa-2b, other adverse reactions (that were not reported in mono-infected patients) which have been reported in the studies with a frequency > 5 % were: oral candidiasis (14 %), lipodystrophy acquired (13 %), CD4 lymphocytes decreased (8 %), appetite decreased (8 %), gamma-glutamyltransferase increased (9 %), back pain (5 %), blood amylase increased (6 %), blood lactic acid increased (5 %), cytolytic hepatitis (6 %), lipase increased (6 %) and pain in limb (6 %).

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

Laboratory values for HCV/HIV co-infected patients:
Although haematological toxicities of neutropenia, thrombocytopenia and anaemia occurred more frequently in HCV/HIV co-infected patients, the majority could be managed by dose modification and rarely required premature discontinuation of treatment (see section 4.4). Haematological abnormalities were more frequently reported in patients receiving Rebetol in combination with peginterferon alfa-2b when compared to patients receiving Rebetol in combination with interferon alfa-2b. In Study 1 (see section 5.1), decrease in absolute neutrophil count levels below 500 cells/mm^3 was observed in 4 % (8/194) of patients and decrease in platelets below 50,000/mm^3 was observed in 4 % (8/194) of patients receiving Rebetol in combination with peginterferon alfa-2b. Anaemia (haemoglobin < 9.4 g/dl) was reported in 12 % (23/194) of patients treated with Rebetol in combination with peginterferon alfa-2b.

CD4 lymphocytes decrease:
Treatment with Rebetol in combination with peginterferon alfa-2b was associated with decreases in absolute CD4+ cell counts within the first 4 weeks without a reduction in CD4+ cell percentage. The decrease in CD4+ cell counts was reversible upon dose reduction or cessation of therapy. The use of Rebetol in combination with peginterferon alfa-2b had no observable negative impact on the control of HIV viraemia during therapy or follow-up. Limited safety data (N = 25) are available in co-infected patients with CD4+ cell counts < 200/µl (see section 4.4).

Please refer to the respective SmPC of the antiretroviral medicinal products that are to be taken concurrently with HCV therapy for awareness and management of toxicities specific for each product and the potential for overlapping toxicities with Rebetol in combination with peginterferon alfa-2b.

Most of the changes in laboratory values in the Rebetol/peginterferon alfa-2b clinical trial were mild or moderate. Decreases in haemoglobin, white blood cells, platelets, neutrophils and increase in bilirubin may require dose reduction or permanent discontinuation from therapy (see section 4.2). While changes in laboratory values were observed in some patients treated with Rebetol used in combination with peginterferon alfa-2b in the clinical trial, values returned to baseline levels within a few weeks after the end of therapy.

4.9 Overdose

Tritherapy
Refer to the SmPC for boceprevir.

Bitherapy
In clinical trials with Rebetol used in combination with peginterferon alfa-2b or interferon alfa-2b, the maximum overdose reported was a total dose of 10 g of Rebetol (50 x 200 mg capsules) and 39 MIU of interferon alfa-2b (13 subcutaneous injections of 3 MIU each) taken in one day by a patient in an attempt at suicide. The patient was observed for two days in the emergency room, during which time no adverse reaction from the overdose was noted.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Direct acting antivirals, nucleosides and nucleotides (excl. reverse transcriptase inhibitors), ATC code: J05A B04.

Mechanism of action
Ribavirin (Rebetol) is a synthetic nucleoside analogue which has shown *in vitro* activity against some RNA and DNA viruses. The mechanism by which Rebetol in combination with peginterferon alfa-2b or interferon alfa-2b exerts its effects against HCV is unknown. Oral formulations of Rebetol monotherapy have been investigated as therapy for chronic hepatitis C in several clinical trials. Results of these investigations showed that Rebetol monotherapy had no effect on eliminating hepatitis virus (HCV-RNA) or improving hepatic histology after 6 to 12 months of therapy and 6 months of follow-up.

Clinical trials efficacy and safety in adult subjects
Tritherapy:
Refer to the SmPC for boceprevir.

Bitherapy:
The use of Rebetol in combination treatment with peginterferon alfa-2b or interferon alfa-2b was evaluated in a number of clinical trials. Eligible patients for these trials had chronic hepatitis C confirmed by a positive HCV-RNA polymerase chain reaction assay (PCR) (> 30 IU/ml), a liver biopsy consistent with a histological diagnosis of chronic hepatitis with no other cause for the chronic hepatitis, and abnormal serum ALT.

Naïve patients
Three trials examined the use of interferon in naïve patients, two with Rebetol + interferon alfa-2b (C95-132 and I95-143) and one with Rebetol + peginterferon alfa-2b (C/I98-580). In all cases the treatment was for one year with a follow-up of six months. The sustained response at the end of follow-up was significantly increased by the addition of Rebetol to interferon alfa-2b (41 % vs 16 %, $p < 0.001$).

In clinical trials C95-132 and I95-143, Rebetol + interferon alfa-2b combination therapy proved to be significantly more effective than interferon alfa-2b monotherapy (a doubling in sustained response). Combination therapy also decreased the relapse rate. This was true for all HCV genotypes, particularly Genotype 1, in which the relapse rate was reduced by 30 % compared with interferon alfa-2b monotherapy.

In clinical trial C/I98-580, 1,530 naïve patients were treated for one year with one of the following combination regimens:
- Rebetol (800 mg/day) + peginterferon alfa-2b (1.5 micrograms/kg/week) (n = 511).
- Rebetol (1,000/1,200 mg/day) + peginterferon alfa-2b (1.5 micrograms/kg/week for one month followed by 0.5 microgram/kg/week for 11 months) (n = 514).
- Rebetol (1,000/1,200 mg/day) + interferon alfa-2b (3 MIU three times a week) (n = 505).

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

HCV genotype and baseline virus load are prognostic factors which are known to affect response rates. However, response rates in this trial were shown to be dependent also on the dose of Rebetol administered in combination with peginterferon alfa-2b or interferon alfa-2b. In those patients that received > 10.6 mg/kg Rebetol (800 mg dose in typical 75 kg patient), regardless of genotype or viral load, response rates were significantly higher than in those patients that received ≤ 10.6 mg/kg Rebetol (**Table 5**), while response rates in patients that received > 13.2 mg/kg Rebetol were even higher.

Table 5 Sustained response rates with Rebetol + peginterferon alfa-2b (by Rebetol dose [mg/kg], 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 ≤ 600,000 IU/ml	All	73 %	51 %	45 %
	≤ 10.6	74 %	25 %	33 %
	> 10.6	71 %	52 %	45 %
Genotype 1 > 600,000 IU/ml	All	30 %	27 %	29 %
	≤ 10.6	27 %	25 %	17 %
	> 10.6	37 %	27 %	29 %
Genotype 2/3	**All**	**82 %**	**80 %**	**79 %**
	≤ 10.6	79 %	73 %	50 %
	> 10.6	88 %	80 %	80 %

P1.5/R Rebetol (800 mg) + peginterferon alfa-2b (1.5 micrograms/kg)
P0.5/R Rebetol (1,000/1,200 mg) + peginterferon alfa-2b (1.5 to 0.5 microgram/kg)
I/R Rebetol (1,000/1,200 mg) + interferon alfa-2b (3 MIU)

In a separate trial, 224 patients with genotype 2 or 3 received peginterferon alfa-2b, 1.5 microgram/kg subcutaneously, once weekly, in combination with ribavirin 800 mg –1,400 mg p.o. for 6 months (based on body weight, only three patients weighing > 105 kg, received the 1,400 mg dose) (**Table 6**). Twenty-four % had bridging fibrosis or cirrhosis (Knodell 3/4).

Table 6 Virologic Response at End of Treatment, Sustained Virologic Response and Relapse by HCV Genotype and Viral Load*

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

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

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

In a non-comparative trial, 235 patients with genotype 1 and low viral load (< 600,000 IU/ml) received peginterferon alfa-2b, 1.5 microgram/kg subcutaneously, once weekly, in combination with weight adjusted Rebetol. The overall sustained response rate after a 24-week treatment duration was 50 %. Forty-one percent of subjects (97/235) had nondetectable plasma HCV-RNA levels at week 4 and week 24 of therapy. In this subgroup, there was a 92 % (89/97) sustained virological response rate. The high sustained response rate in this subgroup of patients was identified in an interim analysis (n=49) and prospectively confirmed (n=48).
Limited historical data indicate that treatment for 48 weeks might be associated with a higher sustained response rate (11/11) and with a lower risk of relapse (0/11 as compared to 7/96 following 24 weeks of treatment).

A large randomized trial compared the safety and efficacy of treatment for 48 weeks with two peginterferon alfa-2b/Rebetol regimens [peginterferon alfa-2b 1.5 µg/kg and 1 µg/kg subcutaneously once weekly both in combination with Rebetol 800 to 1,400 mg p.o. daily (in two divided doses)] and peginterferon alfa-2a 180 µg subcutaneously once weekly with ribavirin 1,000 to 1,200 mg p.o. daily (in two divided doses) in 3,070 treatment-naïve adults with chronic hepatitis C genotype 1. Response to the treatment was measured by Sustained Virologic Response (SVR) which is defined as undetectable HCV-RNA at 24 weeks post-treatment (see **Table 7**).

Table 7 Virologic response at treatment week 12, end of treatment response, relapse rate* and Sustained Virologic Response (SVR)

Treatment group	% (number) of patients		
	peginterferon alfa-2b 1.5 µg/kg + Rebetol	peginterferon alfa-2b 1 µg/kg + Rebetol	peginterferon alfa-2a 180 µg + ribavirin
Undetectable HCV-RNA at treatment week 12	40 (407/1,019)	36 (366/1,016)	45 (466/1,035)
End of treatment response*	53 (542/1,019)	49 (500/1,016)	64 (667/1,035)
Relapse*	24 (123/523)	20 (95/475)	32 (193/612)
SVR*	40 (406/1,019)	38 (386/1,016)	41 (423/1,035)
SVR in patients with undetectable HCV-RNA at treatment week 12	81 (328/407)	83 (303/366)	74 (344/466)

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

In all three treatment groups, sustained virologic response rates were similar. In patients of African American origin (which is known to be a poor prognostic factor for HCV eradication), treatment with peginterferon alfa-2b (1.5 µg/kg)/Rebetol combination therapy resulted in a higher sustained virologic response rate compared to peginterferon alfa-2b 1 µg/kg dose. At the peginterferon alfa-2b 1.5 µg/kg plus Rebetol dose, sustained virologic response rates were lower in patients with cirrhosis, in patients with normal ALT levels, in patients with a baseline viral load > 600,000 IU/ml and in patients > 40 years old. Caucasian patients had a higher sustained virologic response rate compared to the African Americans. Among patients with undetectable HCV-RNA at the end of treatment, the relapse rate was 24 %.

Predictability of sustained virological response in naïve patients
Virological response by week 12, defined as at least 2-log viral load decrease or undetectable levels of HCV RNA. Virological response by week 4 is defined as at least 1-log viral load decrease or undetectable levels of HCV-RNA. These time points (treatment week 4 and treatment week 12) have been shown to be predictive for sustained response (**Table 8**).

Table 8 Predictive Value of In-Treatment Virologic Response while on peginterferon alfa-2b 1.5 µg/kg/Rebetol 800-1,400 mg Combination Therapy		
	Negative	**Positive**

	No response at Treatment Week	No sustained Response	Predictive Value	Response at Treatment Week	Sustained Response	Predictive Value
Genotype 1*						
By Week 4*** **(n= 950)**						
HCV-RNA negative	834	539	**65%** (539/834)	116	107	**92%** (107/116)
HCV-RNA negative or ≥ 1 log decrease in viral load	220	210	**95%** (210/220)	730	392	**54%** (392/730)
By Week 12*** **(n= 915)**						
HCV-RNA negative	508	433	**85%** (433/508)	407	328	**81%** (328/407)
HCV-RNA negative or ≥ 2 log decrease in viral load	206	205	**N/A**[†]	709	402	**57%** (402/709)
Genotype 2, 3**						
By Week 12 (n=215)						
HCV-RNA negative or ≥ 2 log decrease in viral load	2	1	**50%** (1/2)	213	177	**83%** (177/213)

*Genotype 1 receive 48 weeks treatment

**Genotype 2, 3 receive 24 weeks treatment

***The presented results are from a single point of time. A patient may be missing or have had a different result for week 4 or week 12.

[†] These criteria were used in the protocol: If week 12 HCV-RNA is positive and < 2 $\log_{10}$ decrease from baseline, patients to stop therapy. If week 12 HCV-RNA is positive and decreased ≥ 2 $\log_{10}$ from baseline, then retest HCV-RNA at week 24 and if positive, patients to stop therapy.

HCV/HIV Co-infected patients

Two trials have been conducted in patients co-infected with HIV and HCV. The response to treatment in both of these trials is presented in **Table 9**. Study 1 (RIBAVIC; P01017) was a randomized, multicentre study which enrolled 412 previously untreated adult patients with chronic hepatitis C who were co-infected with HIV. Patients were randomized to receive either Rebetol (800 mg/day) plus peginterferon alfa-2b (1.5 µg/kg/week) or Rebetol (800 mg/day) plus interferon alfa-2b (3 MIU TIW) for 48 weeks with a follow-up period of 6 months. Study 2 (P02080) was a randomized, single centre study that enrolled 95 previously untreated adult patients with chronic hepatitis C who were co-infected with HIV. Patients were randomized to receive either Rebetol (800-1,200 mg/day based on weight) plus peginterferon alfa-2b (100 or 150 µg/week based on weight) or Rebetol (800-1,200 mg/day based on weight) plus interferon alfa-2b (3 MIU TIW). The duration of therapy was 48 weeks with a follow-up period of 6 months except for patients infected with genotypes 2 or 3 and viral load < 800,000 IU/ml (Amplicor) who were treated for 24 weeks with a 6 month follow-up period.

Table 9 Sustained virological response based on genotype after Rebetol in combination with peginterferon alfa-2b in HCV/HIV co-infected patients

	Study 1[1]			**Study 2**[2]		
	Rebetol (800 mg/day) + peginterferon	Rebetol (800 mg/day) + Interferon	p value[a]	Rebetol (800-1,200 mg/day)[d] + peginterferon	Rebetol (800-1,200 mg/day)[d] + Interferon alfa-	p value[b]

	alfa-2b (1.5 µg /kg/ week)	alfa-2b (3 MIU TIW)		alfa-2b (100 or 150[c] µg/week)	2b (3 MIU TIW)	
All	27 % (56/205)	20 % (41/205)	0.047	44 % (23/52)	21 % (9/43)	0.017
Genotype 1, 4	17 % (21/125)	6 % (8/129)	0.006	38 % (12/32)	7 % (2/27)	0.007
Genotype 2, 3	44 % (35/80)	43 % (33/76)	0.88	53 % (10/19)	47 % (7/15)	0.730

MIU = million international units; TIW = three times a week.
a: p value based on Cochran-Mantel Haenszel Chi square test.
b: p value based on chi-square test.
c: subjects < 75 kg received 100 µg/week peginterferon alfa-2b and subjects ≥ 75 kg received 150 µg/week peginterferon alfa-2b .
d: Rebetol dosing was 800 mg for patients < 60 kg, 1,000 mg for patients 60-75 kg, and 1,200 mg for patients > 75 kg.

[1]Carrat F, Bani-Sadr F, Pol S et al. JAMA 2004; 292(23): 2839-2848.
[2] Laguno M, Murillas J, Blanco J.L et al. AIDS 2004; 18(13): F27-F36.

Histological response
Liver biopsies were obtained before and after treatment in Study 1 and were available for 210 of the 412 subjects (51 %). Both the Metavir score and Ishak grade decreased among subjects treated with Rebetol in combination with peginterferon alfa-2b. This decline was significant among responders (-0.3 for Metavir and -1.2 for Ishak) and stable (-0.1 for Metavir and -0.2 for Ishak) among non-responders. In terms of activity, about one-third of sustained responders showed improvement and none showed worsening. There was no improvement in terms of fibrosis observed in this study. Steatosis was significantly improved in patients infected with HCV Genotype 3.

Previously treated patients
- Retreatment of prior treatment failures (relapse and nonresponder patients) with peginterferon alfa-2b in combination with Rebetol:
In a non-comparative trial, 2,293 patients with moderate to severe fibrosis who failed previous treatment with combination alfa interferon/ribavirin were retreated with peginterferon alfa 2b, 1.5 microgram/kg subcutaneously, once weekly, in combination with weight adjusted Rebetol. Failure to prior therapy was defined as relapse or non-response (HCV-RNA positive at the end of a minimum of 12 weeks of treatment).

Patients who were HCV-RNA negative at Treatment week 12 continued treatment for 48 weeks and were followed for 24 weeks post-treatment. Responseweek 12 was defined as undetectable HCV-RNA after 12 weeks of treatment. Sustained Virologic Response (SVR) is defined as undetectable HCV-RNA at 24 weeks post-treatment (**Table 10***)*.

Table 10 Rates of Response to retreatment in prior treatment failures

	Patients with undetectable HCV–RNA at treatment week 12 and SVR upon retreatement				
	interferon alpha/ribavirin		peginterferon alpha/ribavirin		Overall Population*
	Response week 12 % (n/N)	SVR % (n/N) 99% CI	Response week 12 % (n/N)	SVR % (n/N) 99% CI	SVR % (n/N) 99 % CI
Overall	38.6 (549/1,423)	59.4 (326/549) 54.0,64.8	31.5 (272/863)	50.4 (137/272) 42.6, 58.2	21.7 (497/2,293) 19.5, 23.9
Prior Response					
Relapse	67.7 (203/300)	59.6 (121/203) 50.7, 68.5	58.1 (200/344)	52.5 (105/200) 43.4, 61.6	37.7 (243/645) 32.8, 42.6

Table 10 Rates of Response to retreatment in prior treatment failures					
	Patients with undetectable HCV–RNA at treatment week 12 and SVR upon retreatement				
	interferon alpha/ribavirin		peginterferon alpha/ribavirin		Overall Population*
	Response week 12 % (n/N)	SVR % (n/N) 99% CI	Response week 12 % (n/N)	SVR % (n/N) 99% CI	SVR % (n/N) 99 % CI
Genotype 1/4	59.7 (129/216)	51.2 (66/129) 39.8, 62.5	48.6 (122/251)	44.3 (54/122) 32.7, 55.8	28.6 (134/468) 23.3, 34.0
Genotype 2/3	88.9 (72/81)	73.6 (53/72) (60.2, 87.0)	83.7 (77/92)	64.9 (50/77) 50.9, 78.9	61.3 (106/173) 51.7, 70.8
NR	28.6 (258/903)	57.0 (147/258) 49.0, 64.9	12.4 (59/476)	44.1 (26/59) 27.4, 60.7	13.6 (188/1,385) 11.2, 15.9
Genotype 1/4	23.0 (182/790)	51.6 (94/182) 42.1, 61.2	9.9 (44/446)	38.6 (17/44) 19.7, 57.5	9.9 (123/1,242) 7.7, 12.1
Genotype 2/3	67.9 (74/109)	70.3 (52/74) 56.6, 84.0	53.6 (15/28)	60.0 (9/15) 27.4, 92.6	46.0 (63/137) 35.0, 57.0
Genotype					
1	30.2 (343/1,135)	51.3 (176/343) 44.4, 58.3	23.0 (162/704)	42.6 (69/162) 32.6, 52.6	14.6 (270/1,846) 12.5, 16.7
2/3	77.1 (185/240)	73.0 (135/185) 64.6, 81.4	75.6 (96/127)	63.5 (61/96) 50.9, 76.2	55.3 (203/367) 48.6, 62.0
4	42.5 (17/40)	70.6 (12/17) 42.1, 99.1	44.4 (12/27)	50.0 (6/12) 12.8, 87.2	28.4 (19/67) 14.2, 42.5
METAVIR Fibrosis score					
F2	46.0 (193/420)	66.8 (129/193) 58.1, 75.6	33.6 (78/232)	57.7 (45/78) 43.3, 72.1	29.2 (191/653) 24.7, 33.8
F3	38.0 (163/429)	62.6 (102/163) 52.8, 72.3	32.4 (78/241)	51.3 (40/78) 36.7, 65.9	21.9 (147/672) 17.8, 26.0
F4	33.6 (192/572)	49.5 (95/192) 40.2, 58.8	29.7 (116/390)	44.8 (52/116) 32.9, 56.7	16.5 (159/966) 13.4, 19.5
Baseline Viral Load					
HVL (>600,000 IU/ml)	32.4 (280/864)	56.1 (157/280) 48.4, 63.7	26.5 (152/573)	41.4 (63/152) 31.2, 51.7	16.6 (239/1,441) 14.1, 19.1
LVL (≤600,000 IU/ml)	48.3 (269/557)	62.8 (169/269) 55.2, 70.4	41.0 (118/288)	61.0 (72/118) 49.5, 72.6	30.2 (256/848) 26.1, 34.2

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

Overall, approximately 36 % (821/2,286) of patients had undetectable plasma HCV-RNA levels at week 12 of therapy measured using a research-based test (limit of detection 125 IU/ml). In this subgroup, there was a 56 % (463/823) sustained virological response rate. For patients with prior failure on therapy with non-pegylated interferon or pegylated interferon and negative at week 12, the sustained response rates were 59 % and 50 %, respectively. Among 480 patients with > 2 log

viral reduction but detectable virus at week 12, altogether 188 patients continued therapy. In those patients the SVR was 12%.

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

- Retreatment of relapse patients with Rebetol and interferon alfa-2b combination treatment:
Two trials examined the use of Rebetol and interferon alfa-2b combination treatment in relapse patients (C95-144 and I95-145); 345 chronic hepatitis patients who had relapsed after previous interferon treatment were treated for six months with a six month follow-up. Combination therapy with Rebetol and interferon alfa-2b resulted in a sustained virological response that was ten-fold higher than that with interferon alfa-2b alone (49 % vs 5 %, $p < 0.0001$). This benefit was maintained irrespective of standard predictors of response to interferon alfa-2b such as virus level, HCV genotype and histological staging.

Long-term efficacy data- Adults
Two large long-term follow-up studies enrolled 1,071 patients and 567 patients after treatment in prior studies with non-pegylated interferon alfa-2b (with or without Rebetol) and pegylated interferon alfa-2b (with or without Rebetol), respectively. The purpose of the studies was to evaluate the durability of sustained virologic response (SVR) and assess the impact of continued viral negativity on clinical outcomes. At least 5 years of long-term follow-up was completed after treatment in 462 patients and 327 patients, respectively. 12 out of 492 sustained responders and only 3 out of 366 sustained responders relapsed, respectively, in the studies.
The Kaplan-Meier estimate for continued sustained response over 5 years is 97 % (95 % CI: 95-99 %) for patients receiving non-pegylated interferon alfa-2b (with or without Rebetol), and is 99 % (95 % CI: 98-100 %) for patients receiving pegylated interferon alfa-2b (with or without Rebetol).
SVR after treatment of chronic HCV with interferon alfa-2b (pegylated and non-pegylated, with or without Rebetol) results in long-term clearance of the virus providing resolution of the hepatic infection and clinical 'cure' from chronic HCV. However, this does not preclude the occurrence of hepatic events in patients with cirrhosis (including hepatocarcinoma).

5.2 Pharmacokinetic properties

Absorption
Ribavirin is absorbed rapidly following oral administration of a single dose (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. There is a linear relationship between dose and AUC_{tf} following single doses of 200-1,200 mg ribavirin. Volume of distribution is approximately 5,000 l. Ribavirin does not bind to plasma proteins.

Distribution
Ribavirin transport in non-plasma compartments has been most extensively studied in red cells, and has been identified to be primarily via an e_s-type equilibrative nucleoside transporter. This type of transporter is present on virtually all cell types and may account for the high volume of distribution of ribavirin. The ratio of whole blood:plasma ribavirin concentrations is approximately 60:1; the excess of ribavirin in whole blood exists as ribavirin nucleotides sequestered in erythrocytes.

Biotransformation
Ribavirin has two pathways of metabolism: 1) a reversible phosphorylation pathway; 2) a degradative pathway involving deribosylation and amide hydrolysis to yield a triazole carboxyacid metabolite. Both ribavirin and its triazole carboxamide and triazole carboxylic acid metabolites are also excreted renally.

Ribavirin has been shown to produce high inter- and intra-subject pharmacokinetic variability following single oral doses (intrasubject variability of approximately 30 % for both AUC and C_{max}), which may be due to extensive first pass metabolism and transfer within and beyond the blood compartment.

Elimination

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 four weeks, with mean steady state plasma concentrations approximately 2,200 ng/ml. Upon discontinuation of dosing the half-life was approximately 298 hours, which probably reflects slow elimination from non-plasma compartments.

Transfer into seminal fluid: Seminal transfer of ribavirin has been studied. Ribavirin concentration in seminal fluid is approximately two-fold higher compared to serum. However, ribavirin systemic exposure of a female partner after sexual intercourse with a treated patient has been estimated and remains extremely limited compared to therapeutic plasma concentration of ribavirin.

Food effect: The bioavailability of a single oral dose of ribavirin was increased by co-administration of a high fat meal (AUC_{tf} and C_{max} both increased by 70 %). It is possible that the increased bioavailability in this study was due to delayed transit of ribavirin or modified pH. The clinical relevance of results from this single dose study is unknown. In the pivotal clinical efficacy trial, patients were instructed to take ribavirin with food to achieve the maximal plasma concentration of ribavirin.

Renal function: Single-dose ribavirin pharmacokinetics were altered (increased AUC_{tf} and C_{max}) in patients with renal dysfunction compared with control subjects (creatinine clearance > 90 ml/minute). This appears to be due to reduction of apparent clearance in these patients. Ribavirin concentrations are essentially unchanged by haemodialysis.

Hepatic function: Single-dose pharmacokinetics of ribavirin in patients with mild, moderate or severe hepatic dysfunction (Child-Pugh Classification A, B or C) are similar to those of normal controls.

Elderly patients (≥ 65 years of age): Specific pharmacokinetic evaluations for elderly subjects have not been performed. However, in a population pharmacokinetic study, age was not a key factor in the kinetics of ribavirin; renal function is the determining factor.

Population pharmacokinetic analysis was performed using sparsely sampled serum concentration values from four controlled clinical trials. The clearance model developed showed that body weight, gender, age, and serum creatinine were the main covariates. For males, clearance was approximately 20 % higher than for females. Clearance increased as a function of body weight and was reduced at ages greater than 40 years. Effects of these covariates on ribavirin clearance appear to be of limited clinical significance due to the substantial residual variability not accounted for by the model.

5.3 Preclinical safety data

Ribavirin: Ribavirin is embryotoxic or teratogenic, or both, at doses well below the recommended human dose in all animal species in which studies have been conducted. Malformations of the skull, palate, eye, jaw, limbs, skeleton and gastrointestinal tract were noted. The incidence and severity of teratogenic effects increased with escalation of the dose. Survival of foetuses and offspring was reduced.

In a juvenile rat toxicity study, pups dosed from postnatal day 7 to 63 with 10, 25 and 50 mg/kg of ribavirin demonstrated a dose-related decrease in overall growth, which was subsequently manifested as slight decreases in body weight, crown-rump length and bone length. At the end of the recovery period, tibial and femoral changes were minimal although generally statistically significant compared to controls in males at all dose levels and in females dosed with the two highest doses compared to controls. No histopathological effects on bone were observed. No ribavirin effects were observed regarding neurobehavioural or reproductive development. Plasma concentrations achieved in rat pups were below human plasma concentrations at the therapeutic dose.

Erythrocytes are a primary target of toxicity for ribavirin in animal studies. Anaemia occurs shortly after initiation of dosing, but is rapidly reversible upon cessation of treatment.

In 3- and 6-month studies in mice to investigate ribavirin-induced testicular and sperm effects, abnormalities in sperm, occurred at doses of 15 mg/kg and above. These doses in animals produce systemic exposures well below those achieved in humans at therapeutic doses. Upon cessation of

treatment, essentially total recovery from ribavirin-induced testicular toxicity occurred within one or two spermatogenic cycles (see section **4.6**).

Genotoxicity studies have demonstrated that ribavirin does exert some genotoxic activity. Ribavirin was active in the Balb/3T3 *in vitro* Transformation Assay. Genotoxic activity was observed in the mouse lymphoma assay, and at doses of 20-200 mg/kg in a mouse micronucleus assay. A dominant lethal assay in rats was negative, indicating that if mutations occurred in rats they were not transmitted through male gametes.

Conventional carcinogenicity rodent studies with low exposures compared to human exposure under therapeutic conditions (factor 0.1 in rats and 1 in mice) did not reveal tumorigenicity of ribavirin. In addition, in a 26 week carcinogenicity study using the heterozygous p53(+/-) mouse model, ribavirin did not produce tumours at the maximally tolerated dose of 300 mg/kg (plasma exposure factor approximately 2.5 compared to human exposure). These studies suggest that a carcinogenic potential of ribavirin in humans is unlikely.

Ribavirin plus interferon : When used in combination with peginterferon alfa-2b or interferon alfa-2b, ribavirin did not cause any effects not previously seen with either active substance alone. The major treatment-related change was a reversible mild to moderate anaemia, the severity of which was greater than that produced by either active substance alone.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Capsule contents:
- Microcrystalline cellulose,
- Lactose monohydrate,
- Croscarmellose sodium,
- Magnesium stearate.

Capsule shell:
- Gelatine,
- Titanium dioxide,
- Sodium lauryl sulfate (used as a manufacturing aid, at very low levels).

Capsule imprint:
- Shellac,
- Dehydrated Alcohol,
- Isopropyl Alcohol,
- Butyl Alcohol,
- Propylene glycol,
- Strong Ammonia Solution,
- Colouring agent (FD&C Blue # 2 Aluminum Lake).

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

24 months

6.4 Special precautions for storage

Store below 25°C.

6.5 Nature and contents of container

Ribavirin capsules are packaged in blisters consisting of polyvinyl chloride (PVC)/polyethylene (PE)/polyvinylidene chloride (PVdC).

Packs of 70, 84, 140, 168 capsules**.**
Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements.

7. MANUFACTURER

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

8. LICENSE HOLDER

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

9. LICENSE No.

116-93-29850-01

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