ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Ribavirin Mylan 200 mg hard capsules

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each hard capsule contains 200 mg of ribavirin.

Excipient with known effect: each hard capsule contains 15 mg of lactose monohydrate.
For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Hard capsule.

White opaque body imprinted "riba/200" in green and a white opaque cap imprinted "riba/200" in green.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Ribavirin Mylan is indicated for the treatment of chronic hepatitis C and must only be used as part of a combination regimen with interferon alfa-2b (adults, children (3 years of age and older) and adolescents). Ribavirin monotherapy must not be used.

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

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

Naïve patients
Adult Patients(18 years of age or older): Ribavirin Mylan is indicated, in combination with interferon alfa-2b, for the treatment of adult patients with all types of chronic hepatitis C except genotype 1, not previously treated, without liver decompensation, with elevated alanine aminotransferase (ALT), who are positive for serum HCV-RNA (see section 4.4).

Paediatric patients (children 3 years of age and older and adolescents): Ribavirin Mylan is indicated, in a combination regimen with interferon alfa-2b, for the treatment of children and adolescents 3 years of age and older, who have all types of chronic hepatitis C except genotype 1, not previously treated, without liver decompensation, and who are positive for serum HCV-RNA. When deciding not to defer treatment until adulthood, it is important to consider that the combination therapy can induce a growth inhibition that may be irreversible in some patients. The decision to treat should be made on a case by case basis (see section 4.4).

Previously treatment failure patients
Adult patients: Ribavirin Mylan is indicated, in combination with 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. (see section 5.1).

4.2 Posology and method of administration

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

Ribavirin Mylan must be used in combination with interferon alfa-2b.

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

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

Adult patients: Ribavirin Mylan must be used in combination with interferon alfa-2b (3 million international units [MIU] three times a week).

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).

Table 1 Ribavirin Mylan dose based on body weight

Patient weight (kg)	Daily Ribavirin Mylan 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

Ribavirin in combination with interferon alfa-2b:

Based on the results of clinical trials, it is recommended that patients be treated for at least six months. During those clinical trials in which patients were treated for one year, patients who failed to show a 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).

Duration of treatment – Naïve patients

- Genotypes Non-1: The decision to extend therapy to one year in patients with negative HCV-RNA after six months of treatment should be based on other prognostic factors (e.g., age >40 years, male gender, bridging fibrosis).

Duration of treatment – Retreatment

- Genotype 1: Treatment should be continued for another six month period (i.e., a total of one year) in patients who exhibit negative HCV-RNA after six months of treatment.

- Genotypes Non-1: The decision to extend therapy to one year in patients with negative HCVRNA after six months of treatment should be based on other prognostic factors (e.g., age > 40 years, male gender, bridging fibrosis).

Paediatric population:
Note: For patients who weigh <47 kg, or are unable to swallow capsules, ribavirin oral solution is available and should be used if appropriate.

Dosing for children and adolescent patients is determined by body weight for Ribavirin Mylan and by body surface area for interferon alfa-2b.

Dose to be administered for the combination therapy with interferon alfa-2b in paediatric patients:
In clinical studies performed in this population ribavirin and interferon alfa-2b were used in doses of 15 mg/kg/day and 3 million international units (MIU)/m^2 three times a week respectively (**Table 2**).

Table 2 Ribavirin Mylan paediatric dose based on body weight when used in combination with interferon alfa-2b in childen and adolescents

Patient weight (kg)	Daily Ribavirin dose	Number of 200 mg capsules
47 - 49	600 mg	3 capsules [a]
50 - 65	800 mg	4 capsules [b]
>65	Refer to adult dosing table (Table 1)	

[a] 1 morning, 2 evening
[b] 2 morning, 2 evening

Duration of treatment in children and adolescents

- Genotype 2 or 3: The recommended duration of treatment is 24 weeks.

Dose modification for all patients
If severe adverse reactions or laboratory abnormalities develop during therapy with Ribavirin Mylan and interferon alfa-2b, modify the dosages of each product if appropriate, until the adverse reactions abate. Guidelines were developed in clinical trials for dose modification (see Dosage modification guidelines, **Table 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 Ribavirin Mylan daily dose (see note 1) if:	Reduce only interferon alfa-2b dose (se note 2) if:	Discontinue combination therapy when the below test value is reported:**:
Haemoglobin	< 10 g/dl	-	< 8.5 g/dl
Adult: Haemoglobin in: patients with history of stable cardiac disease Paediatric: not applicable (see section 4.4)	≥ 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	-	Adult < 50 x 10^9/l Paediatric < 70 x 10^9/l	Adult < 25 x 10^9/l Paediatric < 50 x 10^9/l
Bilirubin – Direct	-	-	2.5 x ULN**
Bilirubin – Indirect	> 5 mg/dl	-	Adult > 4 mg/dl Paediatric > 5 mg/dl (for > 4 weeks)
Serum creatinine	-	-	> 2.0 mg/dl
Creatinine Clearance	-	-	Discontinue Ribavirin Mylan 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 interferon alfa-2b for dose modification and discontinuation

Note 1: In adult patients, 1st dose reduction of Ribavirin Mylan is by 200 mg/day (except in patients receiving the 1,400 mg, dose reduction should be by 400 mg/day). If needed, 2nd dose reduction of Ribavirin Mylan is by an additional 200 mg/day. Patients whose dose of Ribavirin Mylan is reduced to 600 mg daily receive one 200 mg capsule in the morning and two 200 mg capsules in the evening.
In children and adolescent patients treated with Ribavirin Mylan plus interferon alfa-2b, reduce Ribavirin Mylan dose to 7.5 mg/kg/day.

Note 2: In adult patients and children and adolescent patients treated with Ribavirin Mylan 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 Ribavirin Mylan. Patients with creatinine clearance < 50 ml/minute must not be treated with Ribavirin Mylan (see section 4.3). Subjects with impaired renal function should be more carefully monitored with respect to the development of anaemia. If serum creatinine rises to > 2 mg/dl **(Table 3)** Ribavirin Mylan and 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 Ribavirin Mylan 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 Ribavirin Mylan (see section 5.2).

Paediatric population (patients under the age of 18 years): Ribavirin Mylan may be used in combination with interferon alfa-2b in children (3 years of age and older) and adolescents. The selection of formulation is based on individual characteristics of the patient (see section 4.1). Safety

and effectiveness of Ribavirin Mylan with pegylated or other forms of interferon (i.e. not alfa-2b) in these patients have not been evaluated.
Patients co-infected with HCV/HIV: Patients taking NRTI treatment in association with ribavirin and interferon 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.

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). Ribavirin Mylan 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.

Children and adolescents:
- Existence of, or history of severe psychiatric conditions, particularly severe depression, suicidal ideation, or suicide attempt.

Because of co-administration with 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 Ribavirin combination therapy with peginterferon alfa-2b or interferon alfa-2b, and even after treatment discontinuation mainly during the 6-month follow-up period. Among children and adolescents, treated with Ribavirin in combination with interferon alfa-2b, suicidal ideation or attempts were reported more frequently compared to adult patients (2.4% versus 1%) during treatment and during the 6-month follow-up after treatment. As in adult patients, children and adolescents experienced other psychiatric adverse reactions (e.g., depression, emotional lability, and somnolence). 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 alpha interferons. Patients should be closely monitored for any signs or symptoms of psychiatric disorders. If such symptoms appear, the potential seriousness of these undesirable effects must be borne in mind by the prescribing physician and the need for adequate therapeutic management should be considered. If psychiatric symptoms persist or worsen, or suicidal ideation is identified, it is recommended that treatment with Ribavirin 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 Ribavirin 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.

- The use of Ribavirin and interferon alfa-2b or peginterferon alfa-2b in children and adolescents with existence of or history of severe psychiatric conditions is contraindicated (see section 4.3).

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

Paediatric population: Growth and development:
During the course of interferon (standard and pegylated)/ribavirin therapy lasting up to 48 weeks in patients ages 3 through 17 years, weight loss and growth inhibition were common. Long-term data available in children treated with the combination therapy of pegylated interferon/ribavirin are indicative of substantial growth retardation. Thirty two percent (30/94) of subjects demonstrated > 15 percentile decrease in height-for-age percentile 5 years after completion of therapy (see sections 4.8 and 5.1).
The longer term data available in children treated with the combination therapy with standard interferon/ribavirin are also indicative of substantial growth retardation (> 15 percentile decrease in height percentile as compared to baseline) in 21 % (n=20) of children despite being off treatment for more than 5 years. Final adult height was available for 14 of these children and show that 12 continued to have height deficits > 15 percentiles, 10 to 12 years after the end of treatment.

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

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

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

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

Haemolysis: A decrease in haemoglobin levels to < 10 g/dl was observed in up to 14% of adult patients and 7% of children and adolescents treated with Ribavirin in combination with peginterferon alfa-2b or interferon alfa-2b in clinical trials. Although ribavirin has no direct cardiovascular effects, anaemia associated with Ribavirin may result in deterioration of cardiac function, or exacerbation of the symptoms of coronary disease, or both. Thus, Ribavirin Mylan 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, Ribavirin Mylan 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 alpha 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 alpha 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 alpha interferons. Combination therapy with alpha 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).

Thyroid supplemental monitoring specific for children and adolescents: Approximately 12% to 21% of children treated with Ribavirin and interferon alfa-2b (pegylated and non-pegylated) developed increase in thyroid stimulating hormone (TSH). Another approximately 4% had a transient decrease below the lower limit of normal. Prior to initiation of interferon alfa-2b therapy, TSH levels must be evaluated and any thyroid abnormality detected at that time must be treated with conventional therapy. Interferon alfa-2b (pegylated and non-pegylated) therapy may be initiated if TSH levels can be maintained in the normal range by medication. Thyroid dysfunction during treatment with Ribavirin and interferon alfa-2b and during treatment with Ribavirin and peginterferon alfa-2b has been observed. If thyroid abnormalities are detected, the patient's thyroid status should be evaluated and treated as clinically appropriate. Children and adolescents should be monitored every 3 months for evidence of thyroid dysfunction (e.g. TSH).

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 Ribavirin Mylan and didanosine is not recommended due to the risk of mitochondrial toxicity (see section 4.5).
- co-administration of Ribavirin Mylan 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 Ribavirin 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 Ribavirin 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 Ribavirin 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 Ribavirin Mylan therapy:

- Haemoglobin — Adult: ≥ 12g/dl (females); ≥ 13g/dl (males)
  Children and adolescents: ≥ 11g/dl (females); ≥ 12g/dl (males)
- Platelets — ≥ 100,000/mm^3
- Neutrophil Count — ≥ 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 Ribavirin Mylan 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 Ribavirin Mylan hard capsule contains 15 mg of lactose monohydrate. Patients with rare hereditary problems of galactose intolerance, Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

4.5 Interaction with other medicinal products and other forms of interaction

Interaction studies have only been performed in adults.

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 alpha 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 Ribavirin and other medicinal products, except for peginterferon alfa-2b, interferon alfa-2b and antacids.

Interferon alfa-2b: No pharmacokinetic interactions were noted between Ribavirin 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 Ribavirin Mylan 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 Ribavirin Mylan 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: Ribavirin Mylan 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). Ribavirin Mylan 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 Ribavirin Mylan (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 Ribavirin Mylan 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.

Pregancy
The use of Ribavirin Mylan 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

Ribavirin Mylan have 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

Adult patients:
The safety of Ribavirin is evaluated from data from four clinical trials in patients with no previous exposure to interferon (interferon-naïve patients): two trials studied ribavirin capsules in combination with interferon alfa-2b, two trials studied ribavirin capsules 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 SPCs for adverse reactions that may be attributable to interferon 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 (cannot be estimated from the available data). 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 Ribavirin 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
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*
Gastrointestinal 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)*
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 > 4g/dl was observed in 30% of patients treated with Ribavirin and peginterferon alfa-2b and 37% of patients treated with Ribavirin + interferon alfa-2b. Haemoglobin levels dropped below 10 g/dl in up to 14% of adult patients and 7% of children and adolescents treated with Ribavirin in combination with either peginterferon alfa-2b or interferon alfa-2b.

Most cases of anaemia, neutropenia, and thrombocytopenia were mild (WHO grades 1 or 2). There were some cases of more severe neutropenia in patients treated with ribavirin capsules 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 Ribavirin 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 Ribavirin 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 Ribavirin in combination with peginterferon alfa-2b when compared to patients receiving Ribavirin 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 ribavirin capsules in combination with peginterferon alfa-2b. Anaemia (haemoglobin < 9.4 g/dl) was reported in 12% (23/194) of patients treated with Ribavirin in combination with peginterferon alfa-2b.

CD4 lymphocytes decrease:
Treatment with Ribavirin 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 Ribavirin 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 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 Ribavirin in combination with peginterferon alfa-2b.

Paediatric population:
In combination with peginterferon alfa-2b
In a clinical trial with 107 children and adolescent patients (3 to 17 years of age) treated with combination therapy of peginterferon alfa-2b and Ribavirin, dose modifications were required in 25 % of patients, most commonly for anaemia, neutropenia and weight loss. In general, the adverse reactions profile in children and adolescents was similar to that observed in adults, although there is a paediatric-specific concern regarding growth inhibition. During combination therapy for up to 48 weeks with pegylated interferon alfa-2b and Ribavirin, growth inhibition was observed that resulted in reduced height in some patients (see section 4.4). Weight loss and growth inhibition were very common during the treatment (at the end of treatment, mean decrease from baseline in weight and in height percentiles were of 15 percentiles and 8 percentiles, respectively) and growth velocity was inhibited (< 3rd percentile in 70 % of the patients).

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

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

In combination with interferon alfa-2b
In clinical trials of 118 children and adolescents 3 to 16 years of age treated with combination therapy of interferon alfa-2b and Ribavirin, 6% discontinued therapy due to adverse reactions. In general, the adverse reaction profile in the limited children and adolescent population studied was similar to that observed in adults, although there is a paediatric-specific concern regarding growth inhibition, as decrease in height percentile (mean percentile decrease of 9 percentile) and weight percentile (mean percentile decrease of 13 percentile were observed during treatment Within the 5 years follow-up post-treatment period, the children had a mean height of 44th percentile, which was below the median of the normative population and less than their mean baseline height (48th percentile). Twenty (21 %) of 97 children had a > 15 percentile decrease in height percentile, of whom 10 of the 20 children had a > 30 percentile decrease in their height percentile from the start of treatment to the end of long-term follow-up (up to 5 years). Final adult height was available for 14 of those children and demonstrated that 12 continued to show height deficits > 15 percentiles, 10 to 12 years after the end of treatment. During combination therapy for up to 48 weeks with interferon alfa-2b and Ribavirin, growth inhibition was observed that resulted in reduced final adult height in some patients. In particular, decrease in mean height percentile from baseline to the end of the long-term follow-up was most prominent in prepubertal age children (see section 4.4).

Furthermore, suicidal ideation or attempts were reported more frequently compared to adult patients (2.4% vs 1%) during treatment and during the 6 month follow-up after treatment. As in adult patients, children and adolescents also experienced other psychiatric adverse reactions (e.g., depression, emotional lability, and somnolence) (see section 4.4). In addition, injection site disorders, pyrexia, anorexia, vomiting, and emotional lability occurred more frequently in children and adolescents compared to adult patients. Dose modifications were required in 30% of patients, most commonly for anaemia and neutropenia.

Reported adverse reactions listed in **Table 5** are based on experience from the two multicentre children and adolescents clinical trials using Ribavirin with interferon alfa-2b or peginterferon alfa-2b. 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), and uncommon (≥ 1/1,000 to <1/100). Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

Table 5 Adverse reactions very commonly, commonly and uncommonly reported during clinical trials in children and adolescents with Ribavirin in combination with interferon alfa-2b or peginterferon alfa-2b

System Organ Class	Adverse Reactions
Infections and infestations	
Very common:	Viral infection, pharyngitis
Common:	Fungal infection, bacterial infection, pulmonary infection, nasopharyngitis, pharyngitis streptococcal, otitis media, sinusitis, tooth abscess, influenza, oral herpes, herpes simplex, urinary tract infection, vaginitis, gastroenteritis
Uncommon:	Pneumonia, ascariasis, enterobiasis, herpes zoster, cellulitis
Neoplasms benign, malignant and unspecified (including cysts and polyps)	
Common:	Neoplasm unspecified
Blood and lymphatic system disorders	
Very common:	Anaemia, neutropenia
Common:	Thrombocytopenia, lymphadenopathy
Endocrine disorders	
Very common:	Hypothyroidism
Common:	Hyperthyroidism, virilism
Metabolism and nutrition disorders	
Very common:	Anorexia, increased appetite, decreased appetite
Common:	Hypertriglyceridaemia, hyperuricemia
Psychiatric disorders	
Very common:	Depression, insomnia, emotional lability
Common:	Suicidal ideation, aggression, confusion, affect liability, behaviour disorder, agitation, somnambulism, anxiety, mood altered, restlessness, nervousness, sleep disorder, abnormal dreaming, apathy
Uncommon:	Abnormal behaviour, depressed mood, emotional disorder, fear, nightmare
Nervous system disorders	
Very common:	Headache, dizziness
Common:	Hyperkinesia, tremor, dysphonia, paresthaesia, hypoaesthesia, hyperaesthesia, concentration impaired, somnolence, disturbance in attention, poor quality of sleep
Uncommon:	Neuralgia, lethargy, psychomotor hyperactivity
Eye disorders	
Common:	Conjunctivitis, eye pain, abnormal vision, lacrimal gland disorder
Uncommon:	Conjunctival haemorrhage, eye pruritus, keratitis, vision blurred, photophobia
Ear and labyrinth disorders	
Common:	Vertigo
Cardiac disorders	
Common:	Tachycardia, palpitations

Vascular disorders	
Common:	Pallor, flushing,
Uncommon:	Hypotension
Respiratory, thoracic and mediastinal disorders	
Common:	Dyspnoea, tachypnea, epistaxis, coughing, nasal congestion, nasal irritation, rhinorrhoea, sneezing, pharyngolaryngeal pain
Uncommon:	Wheezing, nasal discomfort
Gastrointestinal disorders	
Very common:	Abdominal pain, abdominal pain upper, vomiting, diarrhoea, nausea
Common:	Mouth ulceration, stomatitis ulcerative, stomatitis, aphthous stomatitis, dyspepsia, cheilosis, glossitis, gastroesophoageal reflux, rectal disorder, gastrointestinal disorder, constipation, loose stools, toothache, tooth disorder, stomach discomfort, oral pain
Uncommon:	Gingivitis
Hepatobiliary disorders	
Common:	Hepatic function abnormal
Uncommon:	Hepatomegaly
Skin and subcutaneous tissue disorders	
Very common:	Alopecia, rash
Common:	Pruritus, photosensitivity reaction, maculopapular rash, eczema, hyperhidrosis, acne, skin disorder, nail disorder, skin discolouration, dry skin, erythema, bruise
Uncommon:	Pigmentation disorder, dermatitis atopic, skin exfoliation
Musculoskeletal and connective tissue disorders	
Very common:	Arthralgia, myalgia, musculoskeletal pain
Common:	Pain in extremity, back pain, muscle contracture
Renal and urinary disorders	
Common:	Enuresis, micturition disorder, urinary incontinence, proteinuria
Reproductive system and breast disorders	
Common:	Female: amenorrhea, menorrhagia, menstrual disorder, vaginal disorder, Male: testicular pain
Uncommon:	Female: dysmenorrhoea
General disorders and administration site conditions	
Very common:	Injection site inflammation, injection site reaction, injection site erythema, injection site pain, fatigue, rigors, pyrexia, influenza-like illness, asthenia, malaise, irritability
Common:	Chest pain, oedema, pain, injection site pruritus, injection site rash, injection site dryness, feeling cold
Uncommon:	Chest discomfort, facial pain, injection site induration
Investigations	
Very common:	Growth rate decrease (height and/or weight decrease for age)
Common:	Blood thyroid stimulating hormone increased, thyroglobulin increased
Uncommon:	Anti-thyroid antibody positive
Injury, poisoning and procedural complications	
Common:	Skin laceration
Uncommon:	Contusion

Most of the changes in laboratory values in the ribavirin /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 ribavirin 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.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V*.

4.9 Overdose

In clinical trials with Ribavirin used in combination with peginterferon alfa-2b or interferon alfa-2b, the maximum overdose reported was a total dose of 10 g of Ribavirin (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: J05AB04.

Mechanism of action
Ribavirin (Ribavirin Mylan) is a synthetic nucleoside analogue which has shown *in vitro* activity against some RNA and DNA viruses. The mechanism by which Ribavirin in combination with peginterferon alfa-2b or interferon alfa-2b exerts its effects against HCV is unknown.

Pharmacodynamic effects
Oral formulations of Ribavirin monotherapy have been investigated as therapy for chronic hepatitis C in several clinical trials. Results of these investigations showed that Ribavirin 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 efficacy and safety

Adult Population
The use of Ribavirin 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 Ribavirin + interferon alfa-2b (C95-132 and I95-143) and one with Ribavirin + 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 ribavirin capsules to interferon alfa-2b (41% vs 16%, $p < 0.001$).

In clinical trials C95-132 and I95-143, Ribavirin + 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:

- Ribavirin (800 mg/day) + peginterferon alfa-2b (1.5 micrograms/kg/week) (n=511).
- Ribavirin (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).
- Ribavirin (1,000/1,200 mg/day) + interferon alfa-2b (3 MIU three times a week) (n=505).

In this trial, the combination of Ribavirin and peginterferon alfa-2b (1.5 micrograms/kg/week) was significantly more effective than the combination of Ribavirin 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 Ribavirin administered in combination with peginterferon alfa-2b or interferon alfa-2b. In those patients that received >10.6 mg/kg Ribavirin (800 mg dose in typical 75 kg patient), regardless of genotype or viral load, response rates were significantly higher than in those patients that received ≤ 10.6 mg/kg Ribavirin (**Table 6**), while response rates in patients that received > 13.2 mg/kg ribavirin were even higher.

Table 6 Sustained response rates with Ribavirin + peginterferon alfa-2b (By Ribavirin [mg/kg], genotype and viral load)

HCV Genotype	Ribavirin Dose (mg/kg)	P 1.5/R	P 0.5/R	I/R
All Genotypes	All	54 %	47 %	47 %
	≤ 10.6	50 %	41 %	27 %
	> 10.6	61 %	48 %	47 %
Genotype 1	**All**	**46 %**	**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 Ribavirin (800 mg) + peginterferon alfa-2b (1.5 micrograms/kg)
P0.5/R Ribavirin (1,000/1,200 mg) + peginterferon alfa-2b (1.5 to 0.5 microgram/kg)
I/R Ribavirin (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 7**). Twenty-four % had bridging fibrosis or cirrhosis (Knodell 3/4).

Table 7 Virologic Response at End of Treatment, Sustained Virologic Response and Relapse by HCV Genotype and Viral Load*

	Ribavirin 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 Ribavirin. The overall sustained response rate after a 24 week treatment duration was 50%. Forty-one percent of subjects (97/235) had nondetectable plasma HCV-RNA levels at week 4 and week 24 of therapy. In this subgroup, there was a 92 % (89/97) sustained virological response rate. The high sustained response rate in this subgroup of patients was identified in an interim analysis (n=49) and prospectively confirmed (n=48).
Limited historical data indicate that treatment for 48 weeks might be associated with a higher sustained response rate (11/11) and with a lower risk of relapse (0/11 as compared to 7/96 following 24 weeks of treatment).

A large randomized trial compared the safety and efficacy of treatment for 48 weeks with two peginterferon alfa-2b/ Ribavirin regimens [peginterferon alfa-2b 1.5 µg/kg and 1 µg/kg subcutaneously once weekly both in combination with Ribavirin 800 to 1,400 mg p.o. daily (in two divided doses)] and peginterferon alfa-2a 180 µg subcutaneously once weekly with ribavirin 1,000 to 1,200 mg p.o. daily (in two divided doses) in 3,070 treatment-naïve adults with chronic hepatitis C genotype 1. Response to the treatment was measured by Sustained Virologic Response (SVR) which is defined as undetectable HCV-RNA at 24 weeks post-treatment (see **Table 8**).

Table 8 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 + Ribavirin	peginterferon alfa-2b 1 µg/kg + Ribavirin	peginterferon alfa-2a 180 µg + ribavirin
Undetectable HCV-RNA at treatment week 12	40 (407/1,019)	36 (366/1,016)	45 (466/1,035)
End of treatment response*	53 (542/1,019)	49 (500/1,016)	64 (667/1,035)
Relapse*	24 (123/523)	20 (95/475)	32 (193/612)
SVR*	40 (406/1,019)	38 (386/1,016)	41 (423/1,035)
SVR in patients with undetectable HCV-RNA at treatment week 12	81 (328/407)	83 (303/366)	74 (344/466)

*HCV-RNA PCR assay, with a lower limit of quantitation of 27 IU/ml

Lack of early virologic response by treatment week 12 (detectable HCV-RNA with a < 2 $\log_{10}$ reduction from baseline) was a criterion for discontinuation of treatment.

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

Predictability of sustained virological response in naïve patients
Virological response by week 12 is defined as at least 2-log viral load decrease or undetectable levels of HCV-RNA.Virological response by week 4 is defined as at least 1-log viral load decrease or undetectable levels of HCV-RNA. These time points (treatment week 4 and treatment week 12) have been shown to be predictive for sustained response (**Table 9**).

Table 9 Predictive Value of In-Treatment Virologic Response while on peginterferon alfa-2b 1.5 µg/kg/ Ribavirin 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		**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 10**. 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 Ribavirin (800 mg/day) plus peginterferon alfa-2b (1.5 µg/kg/week) or Ribavirin (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 Ribavirin (800-1,200 mg/day based on weight) plus peginterferon alfa-2b (100 or 150 µg/week based on weight) or Ribavirin (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 10 Sustained virological response based on genotype after Ribavirin in combination with peginterferon alfa-2b in HCV/HIV co-infected patients

	Study 1[1]			**Study 2[2]**		
	Ribavirin (800 mg/day) + peginterferon alfa-2b (1.5 µg /kg/ week)	Ribavirin (800 mg/day) + interferon alfa-2b (3 MIU TIW)	p Value[a]	Ribavirin (800-1,200 mg/day)[d] + peginterferon alfa-2b (100 or 150[c] µg/week)	Ribavirin (800-1,200 mg/day)[d] + interferon alfa-2b (3 MIU TIW)	p value[b]
All	27% (56/205)	20% (41/205)	0.047	44% (23/52)	21% (9/43)	0.017
Genotype 1, 4	17% (21/125)	6% (8/129)	0.006	38% (12/32)	7% (2/27)	0.007
Genotype 2, 3	44% (35/80)	43% (33/76)	0.88	53% (10/19)	47% (7/15)	0.730

MIU = million international units; TIW = three times a week.
a: p value based on Cochran-Mantel Haenszel Chi square test.
b: p value based on chi-square test.
c: subjects < 75 kg received 100 µg/week peginterferon alfa-2b and subjects ≥ 75 kg received 150 µg/week peginterferon alfa-2b .
d: Ribavirin dosing was 800mg 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): 1737-1736.

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

Patients who were HCV-RNA negative at Treatment week 12 continued treatment for 48 weeks and were followed for 24 weeks post-treatment. Response week 12 was defined as undetectable HCV-RNA after 12 weeks of treatment. Sustained Virologic Response (SVR) is defined as undetectable HCV-RNA at 24 weeks post-treatment (**Table 11**).

Table 11 Rates of Response to retreatment in prior treatment failures

	Patients with undetectable HCV-RNA at treatment week 12 and SVR upon retreatment	Overall Population*

	interferon alfa/ribavirin		peginterferon alfa/ribavirin		
	Response week 12 % (n/N)	SVR% (n/N) 99% CI	Response week 12 % (n/N)	SVR% (n/N) 99% CI	SVR% (n/N) 99% CI
Overall	38.6(549/1,423)	59.4 (326/549) 54.0, 64.8	31.5(272/863)	50.4 (137/272) 42.6, 58.2	21.7 (497-2,293) 19.5, 23.9
Prior Response					
Relapse	67.7 (203/300)	59.6 (121/203) 50.7, 68.5	58.1 (200/344)	52.5 (105/200) 43.4, 61.6	37.7 (243/645) 32.8, 42.6
Genotype 1/4	59.7 (129/216)	51.2 (66/129) 39.8, 62.5	48.6 (122/251)	44.3 (54/122) 32.7, 55.8	28.6 (134/468) 23.3, 34.0
Genotype 2/3	88.9 (72/81)	73.6 (53/72) (60.2, 87.0)	83.7 (77/92)	64.9 (50/77) 50.9, 78.9	61.3 (106/173) 51.7, 70.8
NR	28.6 (258/903)	57.0 (147/258) 49.0, 64.9	12.4 (59/476)	44.1 (26/59) 27.4, 60.7	13.6 (188/1,385) 11.2, 16.9
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 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 alpha/ribavirin were less likely to achieve a week 12 response to retreatment than non-responders to non-pegylated interferon alpha/ribavirin (12.4% vs. 28.6%). However, if a week 12 response was achieved, there was little difference in SVR regardless of prior treatment or prior response.

- Retreatment of relapse patients with Ribavirin and interferon alfa-2b combination treatment
Two trials examined the use of Ribavirin 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 Ribavirin 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 Ribavirin) and pegylated interferon alfa-2b (with or without Ribavirin), 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. Twelve 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 Ribavirin), and is 99 % (95 % CI: 98-100 %) for patients receiving pegylated interferon alfa-2b (with or without Ribavirin).
SVR after treatment of chronic HCV with interferon alfa-2b (pegylated and non-pegylated, with or without Ribavirin) results in long-term clearance of the virus providing resolution of the hepatic infection and clinical 'cure' from chronic HCV. However, this does not preclude the occurrence of hepatic events in patients with cirrhosis (including hepatocarcinoma).

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

Table 12 Sustained virological response rates (n[a,b] (%)) in previously untreated children and adolescents by genotype and treatment duration – All subjects
n = 107

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

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

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

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

Ribavirin in combination with interferon alfa-2b

Children and adolescents 3 to 16 years of age with compensated chronic hepatitis C and detectable HCV-RNA (assessed by a central laboratory using a research-based RT-PCR assay) were enrolled in two multicentre trials and received Ribavirin 15 mg/kg per day plus interferon alfa-2b 3 MIU/m^2 3 times a week for 1 year followed by 6 months follow-up after treatment. A total of 118 patients were enrolled: 57 % male, 80 % Caucasian, and 78 % genotype 1, 64 % ≤ 12 years of age. The population enrolled mainly consisted in children with mild to moderate hepatitis C. In the two multicentre trials, sustained virological response rates in children and adolescents were similar to those in adults. Due to the lack of data in these two multicentre trials for children with severe progression of the disease, and the potential for undesirable effects, the benefit/risk of the combination of ribavirin and interferon alfa-2b needs to be carefully considered in this population (see sections 4.1, 4.4 and 4.8). The study results are summarized in **Table 13**.

Table 13 Sustained virological response in previously untreated children and adolescents

	Ribavirin 15 mg/kg/day **interferon alfa-2b 3 MIU/m^2** 3 times a week
Overall Response[a] (n = 118)	54 (46 %)*
Genotype 1 (n = 92)	33 (36 %)*
Genotype 2/3/4 (n = 26)	21 (81 %)*

* Number (%) of patients

a. Defined as HCV-RNA below limit of detection using a research based RT-PCR assay at end of treatment and during follow-up period.

Long-term efficacy data– Paediatric population

Ribavirin in combination with peginterferon alfa-2b

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

Ribavirin in combination with interferon alfa-2b

A five-year long-term, observational, follow-up study enrolled 97 paediatric chronic hepatitis C patients after treatment in two previously mentioned multicentre trials. Seventy percent (68/97) of all enrolled subjects completed this study of which 75 % (42/56) were sustained responders. The purpose of the study was to annually evaluate the durability of sustained virologic response (SVR) and assess the impact of continued viral negativity on clinical outcomes for patients who were sustained responders 24 weeks post-treatment of the 48-week interferon alfa-2b and ribavirin treatment. All but one of the paediatric subjects remained sustained virologic responders during long-term follow-up after completion of treatment with interferon alfa-2b plus ribavirin. The Kaplan-Meier estimate for continued sustained response over 5 years is 98 % [95 % CI: 95 %, 100 %] for paediatric patients

treated with interferon alfa-2b and ribavirin. Additionally, 98 % (51/52) with normal ALT levels at follow-up week 24 maintained normal ALT levels at their last visit.

SVR after treatment of chronic HCV with non-pegylated interferon alfa-2b with Ribavirin results in long-term clearance of the virus providing resolution of the hepatic infection and clinical 'cure' from chronic HCV. However, this does not preclude the occurrence of hepatic events in patients with cirrhosis (including hepatocarcinoma).

5.2 Pharmacokinetic properties

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 (intra-subject 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.

Paediatric population:
Ribavirin in combination with peginterferon alfa-2b
Multiple-dose pharmacokinetic properties for Ribavirin and peginterferon alfa-2b in children and adolescent patients with chronic hepatitis C have been evaluated during a clinical study. In children and adolescent patients receiving body surface area-adjusted dosing of peginterferon alfa-2b at 60 µg/m^2/week, the log transformed ratio estimate of exposure during the dosing interval is predicted to be 58 % (90 % CI: 141-177 %) higher than observed in adults receiving 1.5 µg/kg/week. The pharmacokinetics of Ribavirin (dose-normalized) in this trial were similar to those reported in a prior study of Ribavirin in combination with interferon alfa-2b in children and adolescent patients and in adult patients.

Ribavirin in combination with interferon alfa-2b
Multiple-dose pharmacokinetic properties for Ribavirin and interferon alfa-2b in children and adolescents with chronic hepatitis C between 5 and 16 years of age are summarized in **Table 14.** The pharmacokinetics of Ribavirin and interferon alfa-2b (dose-normalized) are similar in adults and children or adolescents.

Table 14 Mean (% CV) multiple-dose pharmacokinetic parameters for interferon alfa-2b and Ribavirin when administered to children or adolescents with chronic hepatitis C

Parameter	**Ribavirin** 15 mg/kg/day as 2 divided doses (n = 17)	**Interferon alfa-2b** 3 MIU/m^2 3 times a week (n = 54)
Parameter	**Ribavirin** 15 mg/kg/day as 2 divided doses (n = 17)	**Interferon alfa-2b** 3 MIU/m^2 3 times a week (n = 54)
T_{max} (hr)	1.9 (83)	5.9 (36)
C_{max} (ng/ml)	3,275 (25)	51 (48)
AUC*	29,774 (26)	622 (48)
Apparent clearance l/hr/kg	0.27 (27)	**Not done**

*AUC_{12} (ng.hr/ml) for Ribavirin; AUC_{0-24} (IU.hr/ml) for interferon alfa-2b

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,
- Povidone.

Capsule shell:
- Gelatin,
- Titanium dioxide (E171).

Capsule imprint:

Shellac,
Propylene glycol,
Ammonia solution, concentrated,
Yellow iron oxide (E172),
Indigotine (E132),
Titanium dioxide (E171).

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

Bottles: 36 months
Blisters: 36 months

6.4 Special precautions for storage

Bottles: Do not store above 30°C.
Blisters: No special storage conditions.

6.5 Nature and contents of container

Ribavirin Mylan capsules are packaged in:

High-density polyethylene (HDPE) bottle, closed with a child resistant (CR) polypropylene (PP) screw cap.

Pack sizes of 84, 112, 140 and 168 capsules.

Blisters:
Cardboard box containing 56 or 168 hard capsules in PVC/Aclar – Aluminium foil blisters

Unit Dose Blisters:
Cardboard box containing 56x1, 84x1, 112x1, 140x1, 168x1 hard capsules in PVC/Aclar – Aluminium foil perforated unit dose blisters

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements for disposal.

7. MARKETING AUTHORISATION HOLDER

Generics [UK] Limited,
Station Close,
Potters Bar,
Hertfordshire,
EN6 1TL,
United Kingdom.

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/10/634/001
EU/1/10/634/002
EU/1/10/634/003
EU/1/10/634/004
EU/1/10/634/005
EU/1/10/634/006
EU/1/10/634/007
EU/1/10/634/008
EU/1/10/634/009
EU/1/10/634/010
EU/1/10/634/011

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 10 June 2010

10. DATE OF REVISION OF THE TEXT

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

ANNEX II

A. MANUFACTURER(S) RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

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

A. MANUFACTURER(S) RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer responsible for batch release

Penn Pharmaceutical Services Ltd.
23-24 Tafarnaubach Industrial Estate
Tredegar, Gwent NP2 3AA
United Kingdom

McDermott Laboratories Ltd t/a Gerard Laboratories
35/36 Baldoyle Industrial Estate,
Grange Road, Dublin 13
Ireland

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

- **Conditions or restrictions regarding supply and use imposed on the marketing authorisation holder**

Medicinal product subject to restricted medical prescription (See Annex I: Summary of Product Characteristics, Section 4.2)

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

Pharmacovigilance system

The MAH must ensure that the system of pharmacovigilance, presented in Module 1.8.1 of the Marketing Authorisation, is in place and functioning before and whilst the product is on the market.

PSURs

The marketing authorisation holder shall submit periodic safety update reports for this product in accordance with the requirements set out in the list of Union reference dates (EURD list)) provided for under Article 107c(7) of Directive 2001/83/EC and published on the European medicines web-portal.

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

Not applicable.

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

Carton

1. NAME OF THE MEDICINAL PRODUCT

Ribavirin Mylan 200 mg hard capsules
Ribavirin

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each hard capsule contains 200 mg ribavirin.

3. LIST OF EXCIPIENTS

Contains lactose.
See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

56x1 hard capsules
84x1 hard capsules
112x1 hard capsules
140x1 hard capsules
168x1 hard capsules56 hard capsules
84 hard capsules
112 hard capsules
140 hard capsules
168 hard capsules

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Oral use.
Read the package leaflet before use.

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

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Bottles - Do not store above 30°C.
Blisters - No special storage conditions.

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

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Generics [UK] Limited,
Station Close,
Potters Bar,
Hertfordshire,
EN6 1TL
United Kingdom.

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/10/634/001
EU/1/10/634/002
EU/1/10/634/003
EU/1/10/634/004
EU/1/10/634/005
EU/1/10/634/006
EU/1/10/634/007
EU/1/10/634/008
EU/1/10/634/009
EU/1/10/634/010
EU/1/10/634/011

13. BATCH NUMBER

Batch

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Ribavirin Mylan hard capsules

PARTICULARS TO APPEAR ON THE IMMEDIATE PACKAGING

Bottle

1. NAME OF THE MEDICINAL PRODUCT

Ribavirin Mylan 200 mg hard capsules
Ribavirin

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each capsule contains 200 mg ribavirin.

3. LIST OF EXCIPIENTS

Contains lactose.
See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

84 hard capsules
112 hard capsules
140 hard capsules
168 hard capsules

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Oral use
Read the package leaflet before use.

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

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Do not store above 30°C.

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

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Generics [UK] Limited,
Station Close,
Potters Bar,
Hertfordshire,
EN6 1TL,
United Kingdom.

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/10/634/001
EU/1/10/634/002
EU/1/10/634/003
EU/1/10/634/004

13. BATCH NUMBER

Batch

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

MINIMUM PARTICULARS TO APPEAR ON UNIT DOSE BLISTERS

PVC/Aclar® - Aluminium

1. NAME OF THE MEDICINAL PRODUCT

Ribavirin Mylan 200 mg hard capsules
Ribavirin

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Generics [UK] Limited

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Batch

5. OTHER

B. PACKAGE LEAFLET

Package leaflet: Information for the user

Ribavirin Mylan 200 mg hard capsules
ribavirin

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

What is in this leaflet:

1. What Ribavirin Mylan is and what it is used for

Ribavirin Mylan contain the active substance ribavirin. Ribavirin Mylan stops the multiplication of many types of viruses, including hepatitis C virus. Ribavirin Mylan must not be used without interferon alfa-2b, i.e. Ribavirin Mylan must not be used alone.

Previously untreated patients:
The combination of Ribavirin Mylan with interferon alfa-2b is used to treat patients 3 years of age and older who have chronic hepatitis C (HCV) infection. For children and adolescents weighing less than 47 kg a solution formulation is available.

Previously treated adult patients:
The combination of Ribavirin Mylan with interferon alfa-2b is used to treat adult patients with chronic hepatitis C, who have previously responded to treatment with an alpha interferon alone, but whose condition has recurred.

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

2. What you need to know before you take Ribavirin Mylan

Do not take Ribavirin Mylan:
If any of the following apply to you or the child you are caring for, **do not take** Ribavirin Mylan, and **tell your doctor** if you:

- are **allergic** (hypersensitive) to ribavirin or any of the other ingredients of this medicine (listed in section 6).
- are **pregnant or planning to become pregnant**. (see section "Pregnancy, breast-feeding and fertility")
- are **breast-feeding**.
- had a problem with your **heart** during the past 6 months.

- have severe medical conditions that leave you very weak.
- have severe **kidney** disease and/or are on haemodialysis.
- have a serious problem with your **liver** other than chronic hepatitis C.
- have any **blood disorders**, such as anaemia (low blood count), thalassemia, sickle-cell anaemia.
- have autoimmune hepatitis or any other problem with your **immune system**.
- are taking medicine that suppresses your immune system (that protects you against infection and some diseases).

Children and adolescents must not take combination therapy with Ribavirin Mylan and alpha interferon when there is existence or history of serious nervous or mental problems, such as severe depression, thoughts of suicide or attempted suicide.

Reminder: Please read the "Do not take" section of the Package Leaflet for interferon alfa-2b before you begin combination treatment with this medicine.

Warnings and precautions

Talk to your doctor or pharmacist before taking Ribavirin Mylan.

Seek medical help **immediately** if you develop symptoms of a severe allergic reaction (such as difficulty in breathing, wheezing or hives) while taking this treatment.

Children and adolescents weighing less than 47 kg:
The use of Ribavirin Mylan hard capsules is not recommended. An oral solution of ribavirin may be available for children 3 years of age and older and adolescents weighing less than 47 kg.

You should **tell your doctor** if you or the child you are caring for:
- are an adult who has or had a severe **nervous or mental disorder**, confusion, unconsciousness, or have had **thoughts of suicide** or **have attempted suicide, or have a history of substance abuse (e.g., alcohol or drugs)**.
- have ever had **depression** or develop symptoms associated with depression (e.g. feeling of sadness, dejection, etc.) while on treatment with this medicine (see section 4. "Possible side effects").
- are a woman of **childbearing** age (see section "Pregnancy, breast-feeding and fertility").
- are a **male** and your female partner is of childbearing age (see section "Pregnancy, breast-feeding and fertility").
- had a previous serious **heart** condition or have cardiac disease. are older than **65 years** or if you have problems with your **kidneys.**
- have or have had any **serious illness.**
- have **thyroid** problems.

During treatment with Ribavirin Mylan in combination therapy with an alfa interferon, **dental and gum disorders**, which may lead to loss of teeth, have been reported. In addition, **dry mouth** that could have a damaging effect on teeth and membranes of the mouth has been reported during long-term treatment with Ribavirin Mylan in combination therapy with an alpha interferon. You should brush your teeth thoroughly twice daily and have regular dental examinations. In addition some patients may experience **vomiting**. If you have this reaction, be sure to rinse your mouth thoroughly afterwards.

During treatment with Ribavirin Mylan in combination therapy with an alpha interferon, patients may experience **eye problems,** or loss of vision in rare instances. If you receive ribavirin in combination with an alpha interferon, you 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 pre-existing eye disorders (e.g. diabetic or hypertensive retinopathy) should receive periodic eye exams during combination therapy with ribavirin and an alpha interferon. Combination therapy with

ribavirin and an alpha interferon should be discontinued in patients who develop new or worsening eye disorders.

Children and adolescents:
The use of Ribavirin Mylan is not recommended for use in patients under the age of 3 years. An oral solution of ribavirin is available for children 3 years of age and older and adolescents weighing less than 47 kg.

Reminder: Please read the "Warnings and precautions" section of the Package Leaflet for interferon alfa-2b before you begin combination treatment.

Other medicines and Ribavirin Mylan

Tell your doctor or pharmacist if you or the child you are caring for are taking, have recently taken or might take any other medicines and/or:
-
- are receiving azathioprine in combination with ribavirin and pegylated alpha interferons and, therefore may be at an increased risk of developing severe blood disorders.
- are infected with both **Human Immunodeficiency Virus** (HIV-positive) and **Hepatitis C Virus** (HCV) and are being treated with an anti-HIV medicinal product(s) – [nucleoside reverse transcriptase inhibitor (**NRTI**), and/or highly active anti-retroviral therapy (**HAART**)]:
  - Taking Ribavirin Mylan in combination with an alpha interferon and an anti-HIV medicinal product(s) may increase the risk of lactic acidosis, liver failure, and blood abnormalities development (reduction in number of red blood cells which carry oxygen, certain white blood cells that fight infection, and blood clotting cells called platelets).
  - With **zidovudine** or **stavudine**, it is not certain if Ribavirin Mylan will change the way these medicines work. Therefore, your blood will be checked regularly to be sure that the HIV infection is not getting worse. If it gets worse, your doctor will decide whether or not your Ribavirin Mylan treatment needs to be changed. Additionally, patients receiving **zidovudine** with **ribavirin** in combination **with alpha interferons** could be at increased risk of developing anaemia (low number of red blood cells). Therefore the use of zidovudine and ribavirin in combination with alpha interferons is not recommended.
  - Due to the risk of lactic acidosis (a build-up of lactic acid in the body) and pancreatitis, the use of **ribavirin and didanosine** is not recommended and the use of **ribavirin and stavudine** should be avoided.
  - Co-infected patients with advanced liver disease receiving (HAART) may be at increased risk of worsening liver function. Adding treatment with alfa interferons alone or in combination with ribavirin may increase the risk in this patient subset.

Reminder: Please read the "Other medicines" section of the Package Leaflet for interferon alfa-2b before you begin combination treatment.

Ribavirin Mylan with food and drink
Ribavirin Mylan must be taken with food. See section 3

Pregnancy, breast-feeding and fertility

Pregnancy
If you are **pregnant** you must not take Ribavirin Mylan. Ribavirin Mylan can be very damaging to your unborn baby (embryo).

Both female and male patients must take **special precautions** in their sexual activity if there is any possibility for pregnancy to occur:

- **Girl** or **woman** of childbearing age:

You must have a negative pregnancy test before treatment, each month during treatment, and for the 4 months after treatment is stopped. This should be discussed with your doctor.

- **Men**
  Do not have sex with a pregnant woman unless you **use a condom**. This will lessen the possibility for ribavirin to be left in the woman's body.
  If your female partner is not pregnant now but is of childbearing age, she must be tested for pregnancy each month during treatment and for the 7 months after treatment has stopped. You or your female partner must use an effective contraceptive during the time you are taking ribavirin and for 7 months after stopping treatment. This should be discussed with your doctor (see "Do not take Ribavirin Mylan").

Breast-feeding
If you are a woman who is **breast-feeding**, you must not take Ribavirin Mylan. Discontinue breast-feeding before starting to take Ribavirin Mylan.

Driving and using machines
Ribavirin Mylan does not affect your ability to drive or use machines; however, interferon alfa-2b may affect your ability to drive or use machines. Therefore, do not drive or use machines if you become tired, sleepy, or confused from this treatment.

Ribavirin Mylan contains lactose
Each Ribavirin Mylan hard capsule contains a small amount of **lactose**. If you have been told by your doctor that you have **an intolerance to some sugars**, discuss with your doctor before taking this medicinal product.

3. How to take Ribavirin Mylan

General information about taking Ribavirin Mylan
If the child you are caring for is **under the age of 3 years**, do not administer.

Always take this medicine exactly as your doctor or pharmacist has told you. Check with your doctor or pharmacist if you are not sure.
Do not take more than the recommended dosage and take the medicine for as long as prescribed.
Your doctor has determined the correct dose of Ribavirin Mylan based on how much you or the child you are caring for weighs.

Standard blood tests will be taken to check your blood, kidney and liver function.
- Blood tests will be done regularly to help your doctor to know if this treatment is working.
- Depending upon the results of these tests, your doctor may change/adjust the number of hard capsules you or the child you are caring for take, prescribe a different pack size of Ribavirin Mylan, and/or change the length of time to take this treatment.
- If you have or develop severe kidney or liver problems, this treatment will be stopped.

The recommended dose, according to how much the patient weighs, is shown in the table below:
1. Look for the line that shows how much the adult or child/adolescent weighs.
   Reminder: If the child is under the age of 3 years, do not administer.
2. Read across on the same line to see how many hard capsules to take.
   Reminder: If your doctor's instructions are different from the amounts in the below table, follow your doctor's instructions.
3. If you have any questions about the dose, ask your doctor.

Ribavirin Mylan for oral use - dose based on body weight		
If the **adult** weighs	Usual daily Ribavirin	Number of 200 mg capsules

(kg)	Mylan dose	
< 65	800 mg	2 capsules in the morning and 2 capsules in the evening
65 – 80	1,000 mg	2 capsules in the morning and 3 capsules in the evening
81 - 105	1,200 mg	3 capsules in the morning and 3 capsules in the evening
> 105	1,400 mg	3 capsules in the morning and 4 capsules in the evening
If the **child/adolescent** weighs (kg)	Usual daily Ribavirin Mylan dose	Number of 200 mg capsules
47 – 49	600 mg	1 capsule in the morning and 2 capsules in the evening
50 – 65	800 mg	2 capsules in the morning and 2 capsules in the evening
> 65	see adult dose and corresponding number of hard capsules	

Take your prescribed dose by mouth with water and during your meal. Do not chew the hard capsules. For children or adolescents who cannot swallow a hard capsule, an oral solution of ribavirin is available.

Reminder: Ribavirin Mylan is only to be used in combination with interferon alfa-2b for hepatitis C virus infection. For complete information be sure to read the "How to take" section of the Package Leaflet for interferon alfa-2b.

Interferon medicine that is used in combination with Ribavirin Mylan may cause unusual tiredness; if you are injecting this medicine yourself or giving it to a child, use it at bedtime.

If you take more Ribavirin Mylan than you should
Tell your doctor or pharmacist as soon as possible.

If you forget to take Ribavirin Mylan
If you are self-administering treatment, or if you are the caregiver of a child taking Ribavirin Mylan in combination with interferon alfa-2b, take/administer the missed dose as soon as possible during the same day. If an entire day has gone by, check with your doctor. Do not take a double dose to make up for a forgotten dose.

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

4. Possible side effects

Please read the "Possible side effects" section of the Package Leaflet for interferon alfa-2b.

Like all medicines, this medicine used in combination with an alpha interferon product can cause side effects, although not everybody gets them. Although not all of these unwanted effects may occur, they may need medical attention if they do occur.

Psychiatric and Central Nervous System:
Some people get depressed when taking Ribavirin in combination treatment with an interferon, and in some cases people had thoughts about threatening the life of others, suicidal thoughts or aggressive behaviour (sometimes directed against others). Some patients have actually committed suicide. Be sure to seek emergency care if you notice that you are becoming depressed or have suicidal thoughts or change in your behaviour. You may want to consider asking a family member or close friend to help you stay alert to signs of depression or changes in your behaviour.

Children and adolescents are particularly prone to develop depression when being treated with ribavirin and interferon alpha. Immediately contact the doctor or seek emergency treatment if they

display any unusual behavioural symptoms, feel depressed, or feel they want to harm themselves or others.

Growth and development (children and adolescents):
During the one year of treatment with Ribavirin in combination with interferon alfa-2b, some children and adolescents did not grow or gain weight as much as expected. Some children did not reach their projected height within 1-12 years after completing treatment.

Contact your doctor immediately if you notice any of the following side effects occuring during combination treatment with an alpha interferon product:

- chest pain or persistent cough; changes in the way your heart beats, fainting,
- confusion, feeling depressed; suicidal thoughts or aggressive behaviour, attempt suicide, thoughts about threatening the life of others,
- feelings of numbness or tingling,
- trouble sleeping, thinking or concentrating,
- severe stomach pain; black or tar-like stools; blood in stool or urine, lower back or side pain,
- painful or difficult urination,
- severe bleeding from your nose,
- fever or chills beginning after a few weeks of treatment,
- problems with your eyesight or hearing**,**
- severe skin rash or redness.

The following side effects have been reported with the combination of Ribavirin Mylan and an alpha interferon product **in adults**:

Very common: may affect more than 1 in 10 people

- decreases in the number of red blood cells (that may cause fatigue, shortness of breath, dizziness), decrease in neutrophils (that make you more susceptible to different infections).
- difficulty concentrating, feeling anxious or nervous, mood swings, feeling depressed or irritable, tired feeling, trouble falling asleep or staying asleep,
- cough, dry mouth, pharyngitis (sore throat),
- diarrhoea, dizziness, fever, flu-like symptoms, headache, nausea, shaking chills, virus infection, vomiting, weakness,
- loss of appetite, loss of weight, stomach pain,
- dry skin, irritation, pain or redness at the site of injection, hair loss, itching, muscle pain, muscle aches, pain in joints and muscles, rash.

Common: may affect up to 1 in 10 people

- decrease in blood clotting cells called platelets that may result in easy bruising and spontaneous bleeding, decrease in certain white blood cells called lymphocytes that help fight infection, decrease in thyroid gland activity (which may make you feel tired, depressed, increase your sensitivity to cold and other symptoms) excess of sugar or uric acid (as in gout) in the blood, low calcium level in the blood, severe anaemia,
  fungal or bacterial infections, crying, agitation, amnesia, memory impaired, nervousness, abnormal behaviour, aggressive behaviour, anger, feeling confused, lack of interest, mental disorder, mood changes, unusual dreams, wanting to harm yourself, feeling sleepy, trouble sleeping, lack of interest in sex or inability to perform, vertigo (spinning feeling),
- blurred or abnormal vision, eye irritation or pain or infection, dry or teary eyes, changes in your hearing or voice, ringing in ears, ear infection, earache, cold sores (herpes simplex), change in taste, taste loss, bleeding gums or sores in mouth, burning sensation on tongue, sore tongue, inflamed gums, tooth problem, migraine, respiratory infections, sinusitis, nose bleed, nonproductive cough, rapid or difficult breathing, stuffy or runny nose, thirst, tooth disorder,

- cardiac murmur (abnormal heart beat sounds), chest pain or discomfort, feeling faint, feeling unwell, flushing, increased sweating, heat intolerance and excessive sweating, low or high blood pressure, palpitations (pounding heart beat), rapid heart rate.
- bloating, constipation, indigestion intestinal gas (flatus), increased appetite, irritated colon, irritation of prostate gland, jaundice (yellow skin), loose stools, pain on the right side around your ribs, enlarged liver, stomach upset, frequent need to urinate, passing more urine than usual, urinary tract infection, abnormal urine,
- difficult, irregular, or no menstrual period, abnormally heavy and prolonged menstrual periods, painful menstruation, disorder of ovary or vagina, breast pain, erectile problem,
- abnormal hair texture, acne, arthritis, bruising, eczema (inflamed, red, itchy and dryness of the skin with possible oozing lesions), hives, increased or decreased sensitivity to touch, nail disorder, muscle spasms, numbness or tingling feeling, limb pain, pain at the site of injection, pain in joints, shaky hands, psoriasis, puffy or swollen hands and ankles, sensitivity to sunlight, rash with raised spotted lesions, , redness of skin or skin disorder, swollen face, swollen glands (swollen lymph nodes), tense muscles, tumour (unspecified), unsteady when walking, water impairment.

Uncommon: may affect up to 1 in 100 people
- hearing or seeing images that are not present,
- heart attack, panic attack,
- hypersensitivity reaction to the medication,
- inflammation of pancreas, pain in bone, diabetes mellitus,
- muscle weakness.

Rare: may affect up to 1 in 1,000 people
- seizure (convulsions),
- pneumonia,
- rheumatoid arthritis, kidney problems,
- dark or bloody stools, intense abdominal pain,
- sarcoidosis (a disease characterised by persistent fever, weight loss, joint pain and swelling, skin lesions and swollen glands),
- vasculitis.

Very rare: may affect up to 1 in 10,000 people
- suicide.
- stroke (cerebrovascular events).

Not known: frequency cannot be estimated from the available data
- thoughts about threatening the life of others,
- mania (excessive or unreasonable enthusiasm),
- pericarditis (inflammation of the lining of the heart), pericardial effusion [a fluid collection that develops between the pericardium (the lining of the heart) and the heart itself.
- change in colour of the tongue.

Additional side effects in children and adolescents

The following side effects have been reported with the combination of Ribavirin Mylan and interferon alfa-2b product **in children and adolescents:**

Very common: may affect more than 1 in 10 people
- decreases in the number of red blood cells (that may cause fatigue, shortness of breath, dizziness) decrease in neutrophils (that make you more susceptible to different infections),

- decrease in thyroid gland activity (which may make you feel tired, depressed, increase your sensitivity to cold and other symptoms),
- feeling depressed or irritable, feeling sick to stomach, feeling unwell, mood swings, tired feeling, trouble falling asleep or staying asleep, virus infection, weakness,
- diarrhoea, dizziness, fever, flu-like symptoms, headache, loss of or increase in appetite, loss of weight, decrease in the rate of growth (height and weight), pain on right side of ribs, pharyngitis (sore throat), shaking chills, stomach pain, vomiting,
- dry skin, hair loss, irritation, pain or redness at the site of injection, itching, muscle pain, muscle aches, pain in joints and muscles, rash.

Common: may affect up to 1 in 10 people

- decrease in blood clotting cells called platelets (that may result in easy bruising and spontaneous bleeding),
- excess of triglycerides in the blood, excess of uric acid (as in gout) in the blood, increase in thyroid gland activity (which may cause nervousness, heat intolerance and excessive sweating, weight loss, palpitation, tremors),
- agitation, anger, aggressive behaviour, behaviour disorder, difficulty concentrating, emotional instability, fainting, feeling anxious or nervous, feeling cold, feeling confused, feeling of restlessness, feeling sleepy, lack of interest or attention, mood changes, pain, poor quality sleep, sleepwalking, suicide attempt, trouble sleeping, unusual dreams, wanting to harm yourself,
- bacterial infections, common cold, fungal infections, abnormal vision, dry or teary eyes, ear infection, eye irritation or pain or infection, change in taste, changes in your voice, cold sores, coughing, inflamed gums, nose bleed, nose irritation, oral pain, pharyngitis (sore throat), rapid breathing, respiratory infections, scaling lips and clefts in the corner of the mouth, shortness of breath, sinusitis, sneezing, sores in mouth, sore tongue, stuffy or runny nose, throat pain, toothache, tooth abscess, tooth disorder, vertigo (spinning feeling), weakness
- chest pain, flushing, palpitations (pounding heart beat), rapid heart rate,
- abnormal liver function,
- acid reflux, back pain, bedwetting, constipation, gastroesophageal or rectal disorder, incontinence, increased appetite, inflammation of the membrane of the stomach and intestine, stomach upset, loose stools,
- urination disorders, urinary tract infection,
- difficult, irregular or no menstrual period, abnormally heavy and prolonged menstrual periods, disorder of vagina, inflammation of the vagina, testis pain, development of male body traits,
- acne, bruising, eczema (inflamed, red, itchy and dryness of the skin with possible oozing lesions), increased or decreased sensitivity to touch, increased sweating, increase in muscle movement, tense muscle, irritation or itching at the site of injection, limb pain, nail disorder, numbness or tingling feeling, pale skin, rash with raised spotted lesions, shaky hands, redness of skin or skin disorder, skin discolouration, skin sensitive to sunlight, skin wound, swelling due to a build-up of excess water, swollen glands (swollen lymph nodes), tremor, tumour (unspecified).

Uncommon: may affect up to 1 in 100 people

- abnormal behaviour, emotional disorder, fear, nightmare,
- bleeding of the mucous membrane that lines the inner surface of the eyelids, blurred vision, drowsiness, intolerance to light, itchy eyes, facial pain, inflamed gums,
- chest discomfort, difficult breathing, lung infection, nasal discomfort, pneumonia, wheezing,
- low blood pressure,
- enlarged liver,
- painful menstruation,
- itchy anal area (pinworms or ascarids), blistering rash (shingles), decreased sensitivity to touch, muscle twitching, pain in skin, paleness, peeling of skin, redness, swelling.

The attempt to harm yourself has also been reported in adults, children, and adolescents.

Ribavirin Mylan in combination with an alpha interferon product may also cause:
- aplastic anaemia, pure red cell aplasia (a condition where the body stopped or reduced the production of red blood cells); this causes severe anaemia, symptoms of which would include unusual tiredness and a lack of energy,
- delusions,
- upper and lower respiratory tract infection,
- inflammation of the pancreas,
- severe rashes which may be associated with blisters in the mouth, nose, eyes and other mucosal membranes (erythema multiforme, Stevens Johnson syndrome), toxic epidermal necrolysis (blistering and peeling of the top layer of skin),

The following other side effects have also been reported with the combination of Ribavirin Mylan and an alpha interferon product:
- abnormal thoughts, hearing or seeing images that are not present, altered mental status, disorientation,
- angioedema (swelling of the hands, feet, ankles, face, lips, mouth, or throat which may cause difficulty in swallowing or breathing),
- Vogt-Koyanagi-Harada syndrome (an autoimmune inflammatory disorder affecting the eyes, skin and the membranes of the ears, brain and spinal cord),
- bronchoconstriction and anaphylaxis (a severe, whole-body allergic reaction), constant cough,
- eye problems including damage to the retina, obstruction of the retinal artery, inflammation of the optic nerve, swelling of the eye and cotton wool spots (white deposits on the retina),
- enlarged abdominal area, heartburn, trouble having bowel movement or painful bowel movement,
- acute hypersensitivity reactions including urticaria (hives), bruises, intense pain in a limb, leg or thigh pain, loss of range of motion, stiffness, sarcoidosis, (a disease characterised by persistent fever, weight loss, joint pain and swelling, skin lesions and swollen glands).

Ribavirin Mylan in combination with interferon alfa-2b may also cause:
- dark, cloudy or abnormally coloured urine,
- difficulty breathing, changes in the way your heart beats, chest pain, pain down left arm, jaw pain,
- loss of consciousness,
- loss of use, drooping or loss of power of facial muscles, loss of feeling sensation,
- loss of vision.

You or your caregiver should call your doctor immediately if you have any of these symptoms.

For HCV/HIV co-infected patients receiving Ribavirin Mylan in combination with peginterferon alfa-2b, there is an increased risk of lactic acidosis, liver failure and blood abnormalities (reduction in red or white blood cells that fight infection, and blood clotting cells called platelets).

The following additional side effects have occurred in HCV/HIV co-infected patients receiving Ribavirin in combination with peginterferon alfa-2b: oral thrush, changes in the amount and distribution of body fat, reduction in the amount of white blood cells, decreased appetite, increase in gamma-glutamyltransferase (an enzyme produced by the liver, associated with early liver cell damage), back pain, increase amounts of amylase (an enzyme present in the blood) and lactic acid, hepatitis, increased lipase (the enzyme necessary for the absorption and digestion of nutrients in the intestines) and limb pain.

Reporting of side effects
If you get any of the side effects talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting

system listed in Appendix V*. By reporting side effects, you can help provide more information on the safety of this medicine.

5. How to store Ribavirin Mylan

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

Do not use this medicine after the expiry date which is stated on the bottle or blister after EXP. The expiry date refers to the last date of that month.

Do not store the bottles above 30°C.

There are no special storage conditions for capsules packed in blisters.

Do not use this medicine if you notice any change in the appearance of the capsules.

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

6. Contents of the pack and other information

What Ribavirin Mylan contains

- The active substance is ribavirin. Each hard capsule contains 200 mg ribavirin.
- The other ingredients are croscarmellose sodium, lactose monohydrate, microcrystalline cellulose, povidone. The capsule shell contains gelatine and titanium dioxide (E171). The capsule shell imprint contains shellac, propylene glycol, strong ammonia solution, colouring agents (E172, E132, E171).

What Ribavirin Mylan looks like and contents of the pack

The Ribavirin Mylan hard capsule is a white, opaque, hard capsule imprinted with green ink.

The Ribavirin Mylan hard capsule is available in different pack sizes:

High-density polyethylene (HDPE) bottle, closed with a child-resistant (CR) polypropylene (PP) screw cap. Pack sizes of 84, 112, 140 and 168 capsules.

Blisters:
Cardboard box containing 56 or 168 hard capsules in PVC/Aclar – Aluminium foil blisters

Unit Dose Blisters:
Cardboard box containing 56x1, 84x1, 112x1, 140x1, 168x1 hard capsules in PVC/Aclar – Aluminium foil perforated unit dose blisters

Not all pack sizes may be marketed.

Your physician will prescribe the pack size which is best for you.

Marketing Authorisation Holder

Generics [UK] Limited,
Station Close,
Potters Bar,

Hertfordshire,
EN6 1TL
United Kingdom.

Manufacturer

Penn Pharmaceutical Services Ltd
23-24 Tafarnaubach Industrial Estate,
Tredegar,
Gwent, NP22 3AA
United Kingom

McDermott Laboratories Ltd t/a Gerard Laboratories
35/36 Baldoyle Industrial Estate,
Grange Road, Dublin 13
Ireland

For any information about this medicine, please contact the local representative of the Marketing Authorisation Holder:

België/Belgique/Belgien
Mylan bvba/sprl
Tél/Tel: + 0032 02 658 61 00

България
Generics [UK] Ltd
Тел.: +44 1707 853000
(United Kingdom)

Ceská republika
Mylan Pharmaceuticals s.r.o.
Tel: +420 274 770 201

Danmark
Mylan AB
Tlf: + 46 8-555 227 50
(Sweden)

Deutschland
Mylan dura GmbH
Tel: + 49-(0) 6131 9512 0

Eesti
Generics [UK] Ltd
Tel: +44 1707 853000
(United Kingdom)

Ελλάδα
Generics Pharma Hellas ΕΠΕ
Τηλ: +30 210 9936410

España
Mylan Pharmaceuticals, S.L.
tel: +34 93 378 6400

France
Mylan SAS
Tel: +33 4 37 25 75 00

Hrvatska Generics [UK] Ltd
Tel: +44 1707 853000
(United Kingdom)

Lietuva
Generics [UK] Ltd
Tel: +44 1707 853000
(United Kingdom)

Luxembourg/Luxemburg
Generics [UK] Ltd
Tél/Tel: +44 1707 853000
(United Kingdom)

Magyarország
Generics [UK] Ltd
Tel: +44 1707 853000
(United Kingdom)

Malta
George Borg Barthet Ltd
Tel: +356 21244205

Nederland
Mylan B.V
Tel: + +31 (0)33 2997080

Norge
Mylan AB
Tlf: + 46 8-555 227 50
(Sweden)

Österreich
Arcana Arzneimittel GmbH
Tel: ++43 1 416 24 18

Polska
Mylan Sp. z o.o.
Tel: +48 22 5466400

Portugal
Mylan Lda.
Tel: + 351 21 412 72 00

România
Generics [UK]Limited
Tel: + 44 1707 853000

Ireland
Mc Dermott Laboratories Ltd t/a Gerard Laboratories
Tel: 1800 272 272
or +353 (0)1 832 2250

Ísland
Mylan AB
Sími: + 46 8-555 227 50
(Sweden)

Italia
Mylan S.p.A
Tel: + +39/02-61246921

Κύπρος
Pharmaceutical Trading Co Ltd
Τηλ: +357 24656165

Latvija
Generics [UK] Ltd
Tel: +44 1707 853000
(United Kingdom)

This Leaflet was Last Approved In.

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

(United Kingdom)

Slovenija
Generics [UK] Ltd
Tél: +44 1707 853000
(United Kingdom)

Slovenská republika
Mylan s r. o
Tel: + 421 2 32 604 901

Suomi/Finland
Mylan OY
Puh/Tel: + 358 9-46 60 03

Sverige
Mylan AB
Tel: + 46 8-555 227 50

United Kingdom
Generics [UK] Ltd
Tel: +44 1707 853000

Annex IV
Scientific conclusions and grounds for variation to the terms of the marketing authorisations

Scientific conclusions

Taking into account the PRAC Assessment Report on the PSURs for Ribavirin containing medicinal products, the scientific conclusions are as follows:

This PSUSA covers a yearly period with a Data lock point up to 24 July 2013.

The MAH submitted an evaluation of a signal on tongue hyperpigmentation, as requested in the previous PSUR of Ribavirin. The number of cases of tongue pigmentation reported to date with ribavirin and/or peginterferon alfa 2b, even though some of them are insufficiently documented, is significant. In literature case reports, a positive dechallenge (with slowly resolution of symptoms) was generally reported after stopping antiviral therapy which is in favour of drug causality. This evaluation led to the conclusion that bitherapy with ribavirin and peginterferon can induce tongue pigmentation. PRAC therefore recommends the inclusion of this adverse reaction in section 4.8 of the SmPC of the oral formulations of ribavirin containing products. The package leaflet should be updated accordingly.

Furthermore, it was noted that the following adverse drug reactions should be included across the product information of all the ribavirin containing products: tinnitus, hypotension, vasculitis and cerebrovascular ischaemia. As such PRAC recommended that these adverse drug reactions be added to the product information of those products that do not contain them.

The CHMP agrees with the scientific conclusions made by the PRAC.

Grounds recommending the variation to the terms of the Marketing Authorisations

On the basis of the scientific conclusions for Ribavirin containing medicinal products the CHMP is of the opinion that the benefit-risk balance of the medicinal products containing the active substance Ribavirin is favourable subject to the proposed changes to the product information.

The CHMP recommends that the terms of the Marketing Authorisations should be varied.