Ribavirin 400 mg film-coated tablets

Summary of Product Characteristics Updated 21-Sep-2015 | Aurobindo Pharma - Milpharm Ltd.

1. Name of the medicinal product

Ribavirin 400 mg film-coated tablets

2. Qualitative and quantitative composition

Each film-coated tablet contains 400 mg of ribavirin.

For the full list of excipients, see section 6.1.

3. Pharmaceutical form

Film-coated tablet.

Reddish brown colored, oval shaped, beveled biconvex, film-coated tablets debossed with 'F' on one side and '11' on the other side. The size is 17.6 mm x 7.6 mm.

4. Clinical particulars

4.1 Therapeutic indications

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

The combination of Ribavirin with interferon alfa-2a is indicated in adult patients who are positive for serum HCV-RNA, including patients with compensated cirrhosis. (See section 4.4).

Please refer to the Summary of Product Characteristics (SPC) of interferon alfa-2a for prescribing information particular to either of these products.

4.2 Posology and method of administration

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

Method of Administration

Ribavirin film-coated tablets are administered orally in two divided doses with food (morning and evening). Due to the teratogenic potential of ribavirin, the tablets should not be broken or crushed. Ribavirin is available in a 200 mg tablet, there is no need for dividing or cutting the 400 mg tablet in half.

Posology

Ribavirin is used in combination with interferon alfa-2a. The exact dose and duration of treatment depend on the interferon product used.

Please refer to the SPC of interferon alfa-2a for further information on dosage and duration of treatment when Ribavirin is to be used in combination with either of these products.

Posology in combination with interferon alfa-2a:

Dose to be administered

The recommended dose of ribavirin in combination with interferon alfa-2a solution for injection depends on the patient's body weight (see Table 1).

Duration of treatment:

Patients should be treated with combination therapy with interferon alfa-2a for at least six months. Patients with HCV genotype 1 infections should receive 48 weeks of combination therapy. In patients infected with HCV of other genotypes, the decision to extend therapy to 48 weeks should be based on other prognostic factors (such as high viral load at baseline, male gender, age > 40 years and evidence of bridging fibrosis).

Table 1 Ribavirin Dosing Recommendations in Combination with Interferon alfa-2a

Patient weight (kg)	Daily Ribavirin dose	Duration of treatment	Number of 200 mg tablets
<75	1,000 mg	24 or 48 weeks	5 (2 morning, 3 evening)
≥75	1,200 mg	24 or 48 weeks	6 (3 morning, 3 evening)

Dosage modification for adverse reactions

Please refer to the SPC of interferon alfa-2a for further information on dose adjustment and discontinuation of treatment for either of these products.

If severe adverse reactions or laboratory abnormalities develop during therapy with ribavirin and interferon alfa-2a, modify the dosages of each product, until the adverse reactions abate. Guidelines were developed in clinical trials for dose modification (see Table 2).

If intolerance persists after dose adjustment, discontinuation of ribavirin or both ribavirin and interferon alfa-2a may be needed.

Table 2 Dosage Modification Guidelines for Management of Treatment-Emergent Anaemia		
Laboratory Values	Reduce only ribavirin dose to 600 mg/day* if:	Discontinue ribavirin if:**
Haemoglobin in Patients with No Cardiac Disease	<10 g/dl	<8.5 g/dl
Haemoglobin: Patients with History of Stable Cardiac Disease	≥ 2 g/dl decrease in haemoglobin during any 4 week period during treatment (permanent dose reduction)	<12 g/dl despite 4 weeks at reduced dose

*Patients whose dose of ribavirin is reduced to 600 mg daily receive one 200 mg tablet in the morning and two 200 mg tablets or one 400 mg tablet in the evening.

**If the abnormality is reversed, ribavirin may be restarted at 600 mg daily, and further increased to 800 mg daily at the discretion of the treating physician. However, a return to higher doses is not recommended.

Special populations

Use in renal impairment: The recommended dose regimens (adjusted by the body weight cut-off of 75 kg) of ribavirin give rise to substantial increases in plasma concentrations of ribavirin in patients with renal impairment. There are insufficient data on the safety, efficacy and pharmacokinetics of ribavirin in patients with serum creatinine > 2 mg/dl or creatinine clearance < 50 ml/min, whether or not on haemodialysis, to support specific recommendations for dose adjustments (see section 5.2). Therefore, ribavirin should be used in such patients only when this is considered to be essential. Therapy should be initiated (or continued if renal impairment develops while on therapy) with extreme caution and intensive monitoring of haemoglobin concentrations, with corrective action as may be necessary, should be employed throughout the treatment period. (see section 4.4).

Use in hepatic impairment: Hepatic function does not affect the pharmacokinetics of ribavirin (see section 5.2). Therefore, no dose adjustment of Ribavirin is required in patients with hepatic impairment. The use of interferon alfa-2a is contraindicated in patients with decompensated cirrhosis and other forms of severe hepatic impairment.

Use in elderly patients over the age of 65: 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.

Use in patients under the age of 18 years: Treatment with ribavirin is not recommended for use in children and adolescents (<18 years) due to insufficient data on safety and efficacy in combination with interferon alfa-2a. Only limited safety and efficacy data are available in children and adolescents (6-18 years) in combination with peginterferon alfa-2a (see section 5.1).

4.3 Contraindications

See interferon alfa-2a prescribing information for contraindications related to either of these products.

- hypersensitivity to ribavirin or to any of the excipients listed in section 6.1.

- pregnant women (see section 4.4). Ribavirin must not be initiated until a report of a negative pregnancy test has been obtained immediately prior to initiation of therapy.

- women who are breast-feeding (see section 4.6).

- a history of severe pre-existing cardiac disease, including unstable or uncontrolled cardiac disease, in the previous six months.

- severe hepatic dysfunction or decompensated cirrhosis of the liver.

- haemoglobinopathies (e.g. thalassaemia, sickle-cell anaemia).

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-2a or interferon alfa-2a, and even after treatment discontinuation mainly during the 6-month follow-up period. Other CNS effects including aggressive behaviour (sometimes directed against others such as homicidal ideation), bipolar

disorders, mania, confusion and alterations of mental status have been observed with alpha interferons. Patients should be closely monitored for any signs or symptoms of psychiatric disorders. If such symptoms appear, the potential seriousness of these undesirable effects must be borne in mind by the prescribing physician and the need for adequate therapeutic management should be considered. If psychiatric symptoms persist or worsen, or suicidal ideation is identified, it is recommended that treatment with ribavirin and peginterferon alfa-2a or interferon alfa-2a 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-2a or interferon alfa-2a is judged necessary in patients with existence or history of severe psychiatric conditions, this should only be initiated after having ensured appropriate individualized diagnostic and therapeutic management of the psychiatric condition.

Patients with substance use/abuse:

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

Growth and development (children and adolescents): During the course of therapy lasting up to 48 weeks in patients aged 5 to 17 years, weight loss and growth inhibition were common (see sections 4.8 and 5.1).

At 2 years post-treatment with Pegasys, 16% of paediatric patients remained 15 percentiles or more below their baseline weight curve and 11% remained 15 percentiles or more below their baseline height curve.

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.

- 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. There are no data on long term effects on sexual maturation.

Please refer to the SPC of peginterferon alfa-2a or interferon alfa-2a for further information on special warnings and precautions for use related to either of these products.

All patients in the chronic hepatitis C studies had a liver biopsy before inclusion, but in certain cases (ie, patients with genotype 2 or 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.

In patients with normal ALT, progression of fibrosis occurs on average at a slower rate than in patients with elevated ALT. This should be considered in conjunction with other factors, such as HCV genotype, age, extrahepatic manifestations, risk of transmission, etc. which influence the decision to treat or not.

Teratogenic risk: See section 4.6

Prior to initiation of treatment with ribavirin the physician must comprehensively inform the patient of the teratogenic risk of ribavirin, the necessity of effective and continuous contraception, the possibility that contraceptive methods may fail and the possible consequences of pregnancy should it occur during treatment with ribavirin. For laboratory monitoring of pregnancy please refer to Laboratory tests.

Carcinogenicity: Ribavirin is mutagenic in some *in vivo* and *in vitro* genotoxicity assays. A potential carcinogenic effect of ribavirin cannot be excluded (see section 5.3).

Haemolysis and Cardiovascular system: A decrease in haemoglobin levels to <10 g/dl was observed in up to 15% of patients treated for 48 weeks with ribavirin 1000/1200 mg in combination with peginterferon alfa-2a and up to 19% of patients in combination with interferon alfa-2a. When ribavirin 800 mg was combined with peginterferon alfa-2a for 24 weeks, 3% of patients had a decrease in haemoglobin levels to <10 g/dl. The risk of developing anaemia is higher in the female population. 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 must be administered with caution to patients with pre-existing cardiac disease. Cardiac status must be assessed before start of therapy and monitored clinically during therapy; if any deterioration occurs, stop therapy (see section 4.2). 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.

Pancytopenia and bone marrow suppression have been reported in the literature to occur within 3 to 7 weeks after the administration of ribavirin and a peginterferon 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).

The use of ribavirin and peginterferon alfa-2a combination therapy in chronic hepatitis C patients who failed prior treatment has not been adequately studied in patients who discontinued prior therapy for haematological adverse events. Physicians considering treatment in these patients should carefully weigh the risks versus the benefits of re-treatment.

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

Liver function: In patients who develop evidence of hepatic decompensation during treatment, ribavirin in combination with peginterferon alfa-2a or interferon alfa-2a should be discontinued. When the increase in ALT levels is progressive and clinically significant, despite dose reduction, or is accompanied by increased direct bilirubin, therapy should be discontinued.

Renal impairment: The pharmacokinetics of ribavirin are altered in patients with renal dysfunction due to reduction of apparent clearance in these patients. Therefore, it is recommended that renal function be evaluated in all patients prior to initiation of ribavirin, preferably by estimating the patient's creatinine clearance. Substantial increases in ribavirin plasma concentrations are seen at the recommended dosing regimen in patients with serum creatinine >2 mg/dl or with creatinine clearance <50 ml/minute. There are insufficient data on the safety, efficacy and pharmacokinetics of ribavirin in such patients to support specific recommendations for dose adjustments (see section 5.2). ribavirin therapy should not be initiated (or continued if renal impairment occurs while on treatment) in such patients, whether or not on haemodialysis, unless it is considered to be essential. Extreme caution is required. Haemoglobin concentrations should be monitored intensively during treatment and corrective action taken as necessary (see section 4.2).

Ocular changes: Ribavirin is used in combination therapy with alpha interferons. Retinopathy including retinal haemorrhages, cotton wool spots, papilloedema, optic neuropathy and retinal artery or vein obstruction 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 pre-existing ophthalmologic disorders (eg, 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.

Transplantation: The safety and efficacy of peginterferon-alfa-2a and ribavirin treatment have not been established in patients with liver and other transplantations. Liver and renal graft rejections have been reported with peginterferon-alfa-2a, alone or in combination with ribavirin.

HIV/HCV Co-infection: 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 peginterferon alfa-2a with or without ribavirin. In study NR15961, patients concurrently treated with stavudine and interferon therapy with or without ribavirin, the incidence of pancreatitis and/or lactic acidosis was 3% (12/398).

Chronic hepatitis C patients co-infected with HIV and receiving Highly Active Anti-Retroviral Therapy (HAART) may be at increased risk of serious adverse effects (e.g. lactic acidosis; peripheral neuropathy; pancreatitis).

Co-infected patients with advanced cirrhosis receiving HAART may also be at increased risk of hepatic decompensation and possibly death if treated with ribavirin in combination with interferons. Baseline variables in co-infected cirrhotic patients that may be associated with hepatic decompensation include: increased serum bilirubin, decreased haemoglobin, increased alkaline phosphatase or decreased platelet count, and treatment with didanosine (ddI). Caution should therefore be exercised when adding peginterferon alfa-2a and ribavirin to HAART (see section 4.5).

The concomitant use of ribavirin with zidovudine is not recommended due to an increased risk of anaemia (see section 4.5).

During treatment co-infected patients should be closely monitored, for signs and symptoms of hepatic decompensation (including ascites, encephalopathy, variceal bleeding, impaired hepatic synthetic function e.g. Child-Pugh score of 7 or greater). The Child-Pugh scoring may be affected by factors related to treatment (i.e. indirect hyperbilirubinemia, decreased albumin) and not necessarily attributable to hepatic decompensation. Treatment with ribavirin in combination with peginterferon alfa-2a or interferon alfa-2a should be discontinued immediately in patients with hepatic decompensation.

Co-administration of ribavirin and didanosine is not recommended due to the risk of mitochondrial toxicity (see Section 4.5). Moreover, co-administration of ribavirin and stavudine should be avoided to limit the risk of overlapping mitochondrial toxicity.

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 in combination with peginterferon alfa-2a or interferon alfa-2a:

Haemoglobin	≥12 g/dl (females); ≥13 g/dl (males)

Platelets	≥90,000/mm^3
Neutrophil Count	≥1,500/mm^3

In patients co-infected with HIV-HCV, limited efficacy and safety data 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.

Laboratory evaluations are to be conducted at weeks 2 and 4 of therapy, and periodically thereafter as clinically appropriate.

For women of childbearing potential: Female patients must have a routine pregnancy test performed monthly during treatment and for 4 months thereafter. Female partners of male patients must have a routine pregnancy test performed monthly during treatment and for 7 months thereafter.

Uric acid may increase with ribavirin due to haemolysis and therefore predisposed patients should be carefully monitored for development of gout.

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-2a 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-2a. 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.

4.5 Interaction with other medicinal products and other forms of interaction

Interaction studies have been conducted with ribavirin in combination with peginterferon alfa-2a, interferon alfa-2b and antacids. Ribavirin concentrations are similar when given alone or concomitantly with interferon alfa-2b or peginterferon alfa-2a.

Any potential for interactions may persist for up to 2 months (5 half lives for ribavirin) after cessation of ribavirin therapy due to the long half-life.

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.

Antacid: The bioavailability of ribavirin 600 mg was decreased by co-administration with an antacid containing magnesium, aluminium and methicone; 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 analogues: Ribavirin was shown *in vitro* to inhibit phosphorylation of zidovudine and stavudine. The clinical significance of these findings is unknown. However, these *in vitro* findings raise the possibility that concurrent use of ribavirin with either zidovudine or stavudine might lead to increased HIV plasma viraemia. Therefore, it is recommended that plasma HIV RNA levels be closely monitored in patients treated with ribavirin concurrently with either of these two agents. If HIV RNA levels increase, the use of ribavirin concomitantly with reverse transcriptase inhibitors must be reviewed.

Didanosine (ddI): Co-administration of ribavirin and didanosine is not recommended. Exposure to didanosine or its active metabolite (dideoxyadenosine 5'-triphosphate) is increased *in vitro* when didanosine is co-administered with ribavirin. Reports of fatal hepatic failure as well as peripheral neuropathy, pancreatitis, and symptomatic hyperlactataemia/lactic acidosis have been reported with use of ribavirin.

Azathioprine: 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 ribavirin and peginterferon alfa-2a 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 haematologic monitoring be done during concomitant azathioprine use to identify signs of myelotoxicity, at which time treatment with these drugs should be stopped (see section 4.4).

HIV-HCV co-infected patients

No apparent evidence of drug interaction was observed in 47 HIV-HCV co-infected patients who completed a 12 week pharmacokinetic substudy to examine the effect of ribavirin on the intracellular phosphorylation of some nucleoside reverse transcriptase inhibitors (lamivudine and zidovudine or stavudine). However, due to high variability, the confidence intervals were quite wide. Plasma exposure of ribavirin did not appear to be affected by concomitant administration of nucleoside reverse transcriptase inhibitors (NRTIs).

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 ART regimen if this is already established. This would be particularly important in patients with a known history of zidovudine induced anaemia.

4.6 Fertility, pregnancy and lactation

Preclinical data: 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 well below the recommended human dose. 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 ribavirin dose. Survival of foetuses and offspring was reduced.

Female patients: Ribavirin must not be used by women who are pregnant (see section 4.3 and section 4.4). Extreme care must be taken to avoid pregnancy in female patients. Ribavirin therapy must not be initiated until a report of a negative pregnancy test has been obtained immediately prior to initiation of therapy. Any birth control method can fail. Therefore, it is critically important that women of childbearing potential must use a form of effective contraception, during treatment and for 4 months after treatment has been concluded; routine monthly pregnancy tests must be performed during this time. If pregnancy does occur during treatment or within 4 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. Ribavirin accumulates intracellularly and is cleared from the body very slowly. In animal studies, ribavirin produced changes in sperm at doses below the clinical dose. It is unknown whether the ribavirin that is contained in sperm will exert its known teratogenic effects upon fertilisation of the ova. Either male patients or their female partners of childbearing age must, therefore, be counselled to use a form of effective contraception during treatment with ribavirin and for 7 months after treatment has been concluded. A pregnancy test must be performed before therapy is started. Men whose partners are pregnant must be instructed to use a condom to minimise delivery of ribavirin to the partner.

Lactation: It is not known whether ribavirin is excreted in human milk. Because of the potential for adverse reactions in nursing infants, nursing must be discontinued prior to initiation of treatment.

4.7 Effects on ability to drive and use machines

Ribavirin has no or negligible influence on the ability to drive and use machines. However, peginterferon alfa-2a or interferon alfa-2a used in combination with ribavirin may have an effect. Please refer to the SPC of peginterferon alfa-2a or interferon alfa-2a for further information.

4.8 Undesirable effects

See peginterferon alfa-2a or interferon alfa-2a prescribing information for additional undesirable effects for either of these products.

Adverse events reported in patients receiving ribavirin in combination with interferon alfa-2a are essentially the same as for those reported for ribavirin in combination with peginterferon alfa-2a.

Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

Chronic Hepatitis C

The most frequently reported adverse events with ribavirin in combination with peginterferon alfa-2a 180 micrograms were mostly mild to moderate in severity and were manageable without the need for modification of doses or discontinuation of therapy.

Chronic hepatitis C in prior non-responder patients

Overall, the safety profile for ribavirin in combination with peginterferon alfa-2a in prior non-responder patients was similar to that in naive patients. In a clinical trial of non-responder patients to prior pegylated interferon alfa-2b/ribavirin, which exposed patients to either 48 or 72 weeks of treatment, the frequency of withdrawal for adverse events or laboratory abnormalities from peginterferon alfa-2a treatment and ribavirin treatment was 6% and 7%, respectively, in the 48 week arms and 12% and 13%, respectively, in the 72 week arms. Similarly, for patients with cirrhosis or transition to cirrhosis, the frequencies of withdrawal from peginterferon alfa-2a treatment and ribavirin treatment were higher in the 72-week treatment arms (13% and 15%) than in the 48-week arms (6% and 6%). Patients who withdrew from previous therapy with pegylated interferon alfa-2b/ribavirin because of haematological toxicity were excluded from enrolling in this trial.

In another clinical trial, non-responder patients with advanced fibrosisis or cirrhosis (Ishak score of 3 to 6) and baseline platelet counts as low as 50,000/mm3 were treated for 48 weeks. Haematologic laboratory abnormalities observed during the first 20 weeks of the trial included anaemia (26% of patients experienced a haemoglobin level of <10 g/dl), neutropenia (30% experienced an ANC <750/mm3), and thrombocytopenia (13% experienced a platelet count <50,000/mm3) (see section 4.4).

Chronic Hepatitis C and Human Immunodeficiency Virus Co-infection

In HIV-HCV co-infected patients, the clinical adverse event profiles reported for peginterferon alfa-2a, alone or in combination with ribavirin, were similar to those observed in HCV mono-infected patients. For HIV-HCV patients receiving Ribavirin and peginterferon alfa-2a combination therapy other undesirable effects have been reported in ≥1% to ≤2% of patients: hyperlactacidaemia/lactic acidosis, influenza, pneumonia, affect lability, apathy, tinnitus,

pharyngolaryngeal pain, cheilitis, acquired lipodystrophy and chromaturia. Peginterferon alfa-2a treatment 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 peginterferon alfa-2a had no observable negative impact on the control of HIV viraemia during therapy or follow-up. Limited safety data (N= 51) are available in co-infected patients with CD4+ cell counts ≤ 200/µl. (see peginterferon alfa-2a SPC).

Table 3 shows the undesirable effects reported in patients who have received ribavirin and peginterferon alfa-2a or interferon alfa-2a therapy.

Table 3 Undesirable Effects Reported with Ribavirin in combination with Peginterferon alfa-2a for HCV Patients

Body system	Very Common ≥1 /10	Common ≥1 /100 to < 1 /10	Uncommon ≥1 /1000 to < 1 /100	Rare ≥1 /10,000 to < 1 /1000	Very rare <1/10,000	Frequency not known*
Infections and infestations		Upper respiratory infection, bronchitis, oral candidiasis, herpes simplex	Lower respiratory tract infection, pneumonia, urinary tract infection, skin infection	Endocarditis, Otitis externa		
Neoplasms benign and malignant			Malignant hepatic neoplasm			
Blood and lymphatic system disorders	Anaemia	Thrombocytopenia, lymphadenopathy		Pancytopenia	Aplastic anaemia	Pure red cell aplasia
Immune system disorders			Sarcoidosis, thyroiditis	Anaphylaxis, systemic lupus erythematosus, rheumatoid arthritis	idiopathic or thrombotic thrombocytopenic purpura	Liver and renal graft rejection, Vogt-Koyanagi-Harada disease
Endocrine disorders		Hypothyroidism, hyperthyroidism	Diabetes			
Metabolism and Nutrition Disorders	Anorexia		Dehydration			
Psychiatric disorders	Depression, insomnia	Mood alteration, emotional disorders, anxiety, aggression, nervousness, libido decreased	Suicidal ideation, hallucinations, anger	Suicide, psychotic disorder		Mania, bipolar disorders, homicidal ideation
Nervous system disorders	Headache, dizziness, concentration impaired	Memory impairment, syncope, weakness, migraine, hypoaesthesia, hyperaesthesia, paraesthesia, tremor, taste disturbance, nightmares, somnolence	Peripheral neuropathy	Coma, convulsions, facial palsy		
Eye disorders		Vision blurred, eye pain, eye inflammation, xerophthalmia	Retinal haemorrhage	Optic neuropathy, papilloedema, retinal vascular disorder,	Vision loss	Serious retinal detachment

				retinopathy, corneal ulcer		
Ear and labyrinth disorders		Vertigo, earache	Hearing loss			
Cardiac disorders		Tachycardia, palpitations, oedema peripheral		Myocardial infarction, congestive heart failure, angina, Supraventricular tachycardia arrhythmia, atrial fibrillation, pericarditis		
Vascular disorders		Flushing	Hypertension	Cerebral haemorrhage		
Respiratory, thoracic and mediastinal disorders	Dyspnoea, cough	Dyspnoea exertional, epistaxis, nasopharyngitis, sinus congestion, nasal congestion, rhinitis, sore throat	Wheezing	Interstitial pneumonitis with fatal outcome, pulmonary embolism		
Gastrointestinal disorders	Diarrhoea, nausea, abdominal pain	Vomiting, dyspepsia, dysphagia, mouth ulceration, gingival bleeding, glossitis, stomatitis, flatulence, constipation, dry mouth	Gastrointestinal bleeding, cheilitis, gingivitis	Peptic ulcer, pancreatitis		
Hepato-biliary disorders			Hepatic dysfunction	Hepatic failure, cholangitis, fatty liver		
Skin and subcutaneous tissue disorders	Alopecia, dermatitis, pruritis, dry skin	Rash, sweating increased, psoriasis, urticaria, eczema, skin disorder, photo-sensitivity reaction, night sweats			Toxic epidermal necrolysis, Stevens-Johnson syndrome, angioedema, erythema multiforme	
Musculoskeletal and connective tissue disorders	Myalgia, arthralgia	Back pain, arthritis, muscle weakness, bone pain, neck pain, musculoskeletal pain, muscle cramps		Myositis		Rhabdomyolysis
Renal and Urinary disorders						Renal failure, nephrotic syndrome
Reproductive system and breast disorders		Impotence				
General disorders and administration site conditions	Pyrexia, rigors, pain, asthenia, fatigue,	Chest pain, influenza like illness, malaise,				

	injection site reaction, irritability	lethargy, hot flushes, thirst				
Investigations		Weight decreased				
Injury and poisoning				Substance overdose		

*** Identified in postmarketing experience**

Laboratory values: In clinical trials of ribavirin in combination with peginterferon alfa-2a or interferon alfa-2a, the majority of cases of abnormal laboratory values were managed with dose modifications (see section 4.2). With peginterferon alfa-2a and ribavirin combination treatment, up to 2% of patients experienced increased ALT levels that led to dose modification or discontinuation of treatment.

Haemolysis is the dose limiting toxicity of ribavirin therapy. A decrease in haemoglobin levels to <10 g/dl was observed in up to 15% of patients treated for 48 weeks with ribavirin 1000/1200 milligrams in combination with peginterferon alfa-2a and up to 19% of patients in combination with interferon alfa-2a. When ribavirin 800 milligram was combined with peginterferon alfa-2a for 24 weeks, 3% of patients had a decrease in haemoglobin levels to <10 g/dl. It is not expected that patients will need to discontinue therapy because of decrease in haemoglobin levels alone. In most cases the decrease in haemoglobin occurred early in the treatment period and stabilised concurrently with a compensatory increase in reticulocytes.

Most cases of anaemia, leucopenia and thrombocytopenia were mild (WHO grade 1). WHO grade 2 laboratory changes were reported for haemoglobin (4% of patients), leucocytes (24% of patients) and thrombocytes (2% of patients). Moderate (absolute neutrophil count (ANC): 0.749-0.5x109/L) and severe (ANC: <0.5x109/L) neutropenia was observed in 24% (216/887) and 5% (41/887) of patients receiving 48 weeks of ribavirin 1000/1200 milligrams in combination with peginterferon alfa-2a.

An increase in uric acid and indirect bilirubin values associated with haemolysis were observed in some patients treated with ribavirin used in combination with peginterferon alfa-2a or interferon alfa-2a and values returned to baseline levels within 4 weeks after the end of therapy. In rare cases (2/755) this was associated with clinical manifestation (acute gout).

Laboratory values for HIV-HCV co-infected patients

Although haematological toxicities of neutropenia, thrombocytopenia and anaemia occurred more frequently in HIV-HCV patients, the majority could be managed by dose modification and the use of growth factors and infrequently required premature discontinuation of treatment. Decrease in ANC levels below 500 cells/mm^3 was observed in 13% and 11% of patients receiving peginterferon alfa-2a monotherapy and combination therapy, respectively. Decrease in platelets below 50,000/mm^3 was observed in 10% and 8% of patients receiving peginterferon alfa-2a monotherapy and combination therapy, respectively. Anaemia (haemoglobin < 10g/dL) was reported in 7% and 14% of patients treated with peginterferon alfa-2a monotherapy or in combination therapy, respectively.

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 Yellow Card Scheme at: www.mhra.gov.uk/yellowcard.

4.9 Overdose

No cases of overdose of ribavirin have been reported in clinical trials. Hypocalcaemia and hypomagnesaemia have been observed in persons administered dosages greater than four times the maximal recommended dosages. In many of these instances ribavirin was administered intravenously. Due to the large volume of distribution of ribavirin, significant amounts of ribavirin are not effectively removed by haemodialysis.

5. Pharmacological properties

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Nucleosides and nucleotides (excl. reverse transcriptase inhibitors),

ATC code: J05AB04.

Mechanism of Action: Ribavirin is a synthetic nucleoside analog that shows *in vitro* activity against some RNA and DNA viruses. The mechanism by which ribavirin in combination with peginterferon alfa-2a or interferon alfa-2a exerts its effects against HCV is unknown.

HCV RNA levels decline in a biphasic manner in responding patients with hepatitis C who have received treatment with 180 micrograms peginterferon alfa-2a. The first phase of decline occurs 24 to 36 hours after the first dose of peginterferon alfa-2a and is followed by the second phase of decline which continues over the next 4 to 16 weeks in

patients who achieve a sustained response. ribavirin had no significant effect on the initial viral kinetics over the first 4 to 6 weeks in patients treated with the combination of Ribavirin and pegylated interferon alfa-2a or interferon alfa.

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

Ribavirin in combination with peginterferon alfa-2a

Study results in treatment-naive patients

Efficacy and safety of the combination of ribavirin and peginterferon alfa-2a were established in two pivotal studies (NV15801 + NV15942), including a total of 2405 patients. The study population comprised interferon-naïve patients with CHC confirmed by detectable levels of serum HCV RNA, elevated levels of ALT, and a liver biopsy consistent with chronic hepatitis C infection. Only HIV-HCV co-infected patients were included in the study NR15961 (see Table 12). These patients had stable HIV disease and mean CD4 T-cell count was about 500 cells/µl.

Study NV15801 (1121 patients treated) compared the efficacy of 48 weeks of treatment with peginterferon alfa-2a (180 µg once weekly) and Ribavirin (1000/1200 mg daily) with either peginterferon alfa-2a monotherapy or combination therapy with interferon-alfa-2b and ribavirin. The combination of peginterferon alfa-2a and Ribavirin was significantly more efficacious than either the combination of interferon alfa-2b and ribavirin or peginterferon alfa-2a monotherapy.

Study NV15942 (1284 patients treated) compared the efficacy of two durations of treatment (24 weeks with 48 weeks) and two dosages of Ribavirin (800 mg with 1000/1200 mg).

For HCV monoinfected patients and HIV-HCV co-infected patients, for treatment regimens, duration of therapy and study outcome see tables 4, 5, 6 and 12, respectively. Virological response was defined as undetectable HCV RNA as measured by the COBAS AMPLICOR™ HCV Test, version 2.0 (limit of detection 100 copies/ml equivalent to 50 International Units/ml) and sustained response as one negative sample approximately 6 months after the end of therapy.

Table 4 Virological Response in the overall population (including non-cirrhotic and cirrhotic patients)

	Study NV15942	**Study NV15801**	
	Ribavirin 1,000/1,200 mg & Peginterferon alfa-2a 180 micrograms	Ribavirin 1,000/1,200 mg & Peginterferon alfa-2a 180 micrograms	Ribavirin 1,000/1,200 mg & Interferon alfa-2b 3 MIU
	(N=436) 48 weeks	(N=453) 48 weeks	(N=444) 48 weeks
Response at End of Treatment	68%	69%	52%
Overall Sustained Response	63%	54%*	45%*

*95% CI for difference: 3% to 16% p-value (stratified Cochran-Mantel-Haenszel test) = 0.003

The virological responses of HCV monoinfected patients treated with ribavirin and peginterferon alfa-2a combination therapy in relation to genotype and pre-treatment viral load and in relation to genotype, pre-treatment viral load and rapid virological response at week 4 are summarized in Table 5 and Table 6 respectively. The results of study NV15942 provide the rationale for recommending treatment regimens based on genotype, baseline viral load and virological response at week 4 (see Tables 5 and 6).

The difference between treatment regimens was in general not influenced by presence/absence of cirrhosis; therefore treatment recommendations for genotype 1, 2 or 3 are independent of this baseline characteristic.

Table 5 Sustained Virological Response based on Genotype and Pre-treatment Viral Load after ribavirin Combination Therapy with peginterferon alfa-2a

	Study NV15942			**Study NV15801**		
	Ribavirin 800 mg & **PEG-IFN alfa-2a** 180µg 24 weeks	**Ribavirin** 1000/1200 mg & **PEG-IFN alfa-2a** 180 µg 24 weeks	**Ribavirin** 800 mg & **PEG-IFN alfa-2a** 180 µg	**Ribavirin** 1000/1200 mg & **PEG-IFN alfa-2a** 180 µg	**Ribavirin** 1000/1200 mg & **PEG-IFN alfa-2a** 180 µg 48 weeks	**Ribavirin** 1000/1200 mg & **Interferon alfa-2b** 3 MIU

			48 weeks	48 weeks		48 weeks
Genotype 1	29% (29/101)	42% (49/118)†	41%(102/250)*	52% (142/271)*†	45% (134/298)	36% (103/285)
Low viral load	41 % (21/51)	52 % (37/71)	55% (33/60)	65% (55/85)	53% (61/115)	44 % (41/94)
High viral load	16 % (8/50)	26 % (12/47)	36% (69/190)	47% (87/186)	40% (73/182)	33% (62/189)
Genotype 2/3	84 % (81/96)	81% (117/144)	79 % (78/99)	80 % (123/153)	71 % (100/140)	61% (88/145)
Low viral load	85 % (29/34)	83 % (39/47)	88 % (29/33)	77 % (37/48)	76% (28/37)	65 % (34/52)
High viral load	84 % (52/62)	80 % (78/97)	74 % (49/66)	82 % (86/105)	70% (72/103)	58 % (54/93)
Genotype 4	0 % (0/5)	67 % (8/12)	63 % (5/8)	82 % (9/11)	77 % (10/13)	45 % (5/11)

Low viral load= ≤800,000 IU/ml; High viral load= > 800,000 IU/ml

*Ribavirin 1000/1200 mg + peginterferon alfa-2a 180 µg, 48 w vs. Ribavirin 800 mg + peginterferon alfa-2a 180 µg, 48 w: Odds Ratio (95% CI) = 1.52 (1.07 to 2.17) P-value (stratified Cochran-Mantel-Haenszel test) = 0.020

†Ribavirin 1000/1200 mg + peginterferon alfa-2a 180 µg, 48 w vs. Ribavirin 1000/1200 mg + peginterferon alfa-2a 180 µg, 24 w: Odds Ratio (95% CI) = 2.12 (1.30 to 3.46) P-value (stratified Cochran-Mantel-Haenszel test) = 0.002

The possibility to consider shortening treatment duration to 24 weeks in genotype 1 and 4 patients was examined based on a sustained rapid virological response observed in patients with rapid virological response at week 4 in studies NV15942 and ML17131 (see Table 6).

Table 6 Sustained Virological Response Based on Rapid Viral Response at week 4 for Genotype 1 and 4 after Ribavirin Combination Therapy with Peginterferon alfa-2a in HCV Patients

Study NV15942			**Study ML17131**
	Ribavirin 1000/1200 mg & **Peginterferon alfa-2a** 180 µg 24 weeks	**Ribavirin** 1000/1200 mg & **Peginterferon alfa-2a** 180 µg 48 weeks	**Ribavirin** 1000/1200 mg & **Peginterferon alfa-2a** 180 µg 24 weeks
Genotype 1 RVR	90% (28/31)	92% (47/51)	77% (59/77)
Low viral load	93% (25/27)	96% (26/27)	80% (52/65)
High viral load	75% (3/4)	88% (21/24)	58% (7/12)
Genotype 1 non RVR	24% (21/87)	43% (95/220)	-
Low viral load	27% (12/44)	50% (31/62)	-
High viral load	21% (9/43)	41% (64/158)	-
Genotype 4 RVR	(5/6)	(5/5)	92% (22/24)
Genotype 4 non RVR	(3/6)	(4/6)	-

Low viral load= ≤800,000 IU/ml; High viral load= > 800,000 IU/ml

RVR = rapid viral response (HCV RNA undetectable) at week 4 and HCV RNA undetectable at week 24

Although limited, data indicated that shortening treatment to 24 weeks might be associated with a higher risk of relapse (see Table 7).

Table 7 Relapse of Virological Response at the End of Treatment for Rapid Virological Response Population

	Study NV15942		**Study NV15801**
	Ribavirin 1000/1200 mg & **Peginterferon alfa-2a** 180 µg	**Ribavirin** 1000/1200 mg & **Peginterferon alfa-2a** 180 µg	**Ribavirin** 1000/1200 mg & **Peginterferon alfa-2a** 180 µg

	24 weeks	48 weeks	48 weeks
Genotype 1 RVR	6.7% (2/30)	4.3% (2/47)	0% (0/24)
Low viral load	3.8% (1/26)	0% (0/25)	0% (0/17)
High viral load	25% (1/4)	9.1% (2/22)	0% (0/7)
Genotype 4 RVR	(0/5)	(0/5)	0% (0/4)

The possibility of shortening treatment duration to 16 weeks in genotype 2 or 3 patients was examined based on the sustained rapid virological response observed in patients with rapid virological response by week 4 in study NV17317 (see Table 8).

In study NV17317 in patients infected with viral genotype 2 or 3, all patients received peginterferon alfa-2a 180 µg sc qw and a ribavirin dose of 800 mg and were randomised to treatment for either 16 or 24 weeks. Overall treatment for 16 weeks resulted in lower sustained viral response (65%) than treatment for 24 weeks (76%) ($p < 0.0001$).

The sustained viral response achieved with 16 weeks of treatment and with 24 weeks of treatment was also examined in a retrospective subgroup analysis of patients who were HCV RNA negative by week 4 and had a LVL at baseline (see Table 8).

Table 8 Sustained Virological Response Overall and Based on Rapid Viral Response by Week 4 for Genotype 2 or 3 after ribavirin Combination Therapy with Peginterferon alfa-2a in HCV Patients

	Study NV17317			
	ribavirin 800 mg & **Peginterferon alfa-2a** 180 µg 16 weeks	**ribavirin** 800 mg & **Peginterferon alfa-2a** 180 µg 24 weeks	**Treatment difference 95% CI**	**p value**
Genotype 2 or 3	65% (443/679)	76% (478/630)	-10.6% [-15.5% ; -0.06%]	P<0.0001
Genotype 2 or 3 RVR	82% (378/461)	90% (370/410)	-8.2% [-12.8% ; -3.7%]	P=0.0006
Low viral load	89% (147/166)	94% (141/150)	-5.4% [-12% ; 0.9%]	P=0.11
High viral load	78% (231/295)	88% (229/260)	-9.7% [-15.9% ; -3.6%]	P=0.002

Low viral load= ≤ 800,000 IU/ml at baseline; High viral load= > 800,000 IU/ml at baseline

RVR = rapid viral response (HCV RNA negative) by week 4

It is presently not clear whether a higher dose of ribavirin (e.g.1000/1200 mg/day based on body weight) results in higher SVR rates than does the 800 mg/day, when treatment is shortened to 16 weeks.

The data indicated that shortening treatment to 16 weeks is associated with a higher risk of relapse (see Table 9)

Table 9 Relapse of Virological Response after the End of Treatment in Genotype 2 or 3 Patients with a Rapid Viral Response

	Study NV17317			
	ribavirin 800 mg & **Peginterferon alfa-2a** 180 µg 16 weeks	**ribavirin** 800 mg & **Peginterferon alfa-2a** 180 µg 24 weeks	**Treatment difference 95% CI**	**p value**
Genotype 2 or 3 RVR	15% (67/439)	6% (23/386)	9.3% [5.2% ; 13.6%]	P<0.0001
Low viral load	6% (10/155)	1% (2/141)	5% [0.6% ; 10.3%]	P=0.04
High viral load	20% (57/284)	9% (21/245)	11.5% [5.6% ; 17.4%]	P=0.0002

Chronic hepatitis C prior treatment non-responder patients

In study MV17150, patients who were non-responders to previous therapy with pegylated interferon alfa-2b plus ribavirin were randomised to four different treatments:

- peginterferon alfa-2a 360 µg/week for 12 weeks, followed by 180 µg/week for a further 60 weeks
- peginterferon alfa-2a 360 µg/week for 12 weeks, followed by 180 µg/week for a further 36 weeks
- peginterferon alfa-2a 180 µg/week for 72 weeks
- peginterferon alfa-2a 180 µg/week for 48 weeks

All patients received ribavirin (1000 or 1200 mg/day) in combination with peginterferon alfa-2a. All treatment arms had 24 week treatment-free follow-up.

Multiple regression and pooled group analyses evaluating the influence of treatment duration and use of induction dosing clearly identified treatment duration for 72 weeks as the primary driver for achieving a sustained virological response. Differences in sustained virological response (SVR) based on treatment duration, demographics and best responses to previous treatment are displayed in Table 10.

Table 10 Week 12 Virological Response (VR) and Sustained Virological Response (SVR) in Patients with Virological Response at Week 12 after Treatment with ribavirin and Peginterferon alfa-2a Combination Therapy in Non-Responders to Peginterferon alfa-2b plus Ribavirin

	ribavirin 1000/1200 mg & Peginterferon alfa-2a 360/180 or 180 µg 72 or 48 Weeks (N = 942) Pts with VR at Wk 12 [a] (N = 876)	ribavirin 1000/1200 mg & Peginterferon alfa-2a 360/180 or 180 µg 72 Weeks (N = 473) SVR in Pts with VR at Wk 12 [b] (N = 100)	ribavirin 1000/1200 mg & Peginterferon alfa-2a 360/180 or 180 µg 48 Weeks (N = 469) SVR in Pts with VR at Wk 12 [b] (N = 57)
Overall	18% (157/876)	57% (57/100)	35% (20/57)
Low viral load	35% (56/159)	63% (22/35)	38% (8/21)
High viral load	14% (97/686)	54% (34/63)	32% (11/34)
Genotype 1/4	17% (140/846)	55% (52/94)	35% (16/46)
Low viral load	35% (54/154)	63% (22/35)	37% (7/19)
High viral load	13% (84/663)	52% (30/58)	35% (9/26)
Genotype 2/3	58% (15/26)	(4/5)	(3/10)
Low viral load	(2/5)	—	(1/2)
High viral load	(11/19)	(3/4)	(1/7)
Cirrhosis Status	8% (19/239)	(6/13)	(3/6)
Cirrhosis	22% (137/633)	59% (51/87)	34% (17/50)
Noncirrhosis			
Best Response during Previous Treatment			
≥2log$_{10}$ decline in HCV RNA	28% (34/121)	68% (15/22)	(6/12)
<2log$_{10}$ decline in HCV RNA	12% (39/323)	64% (16/25)	(5/14)
Missing best previous response	19% (84/432)	49% (26/53)	29% (9/31)

High viral load = >800,000 IU/ml, low viral load = ≤ 800,000 IU/ml.

[a] Patients who achieved viral suppression (undetectable HCV RNA, <50 IU/ml) at week 12 were considered to have a virological response at week 12. Patients missing HCV RNA results at week 12 have been excluded from the analysis.

[b] Patients who achieved viral suppression at week 12 b ut were missing HCV RNA results at the end of follow-up were considered to be non-responders

In the HALT-C study, patients with chronic hepatitis C and advanced fibrosis or cirrhosis who were non-responders to previous treatment with interferon alfa or pegylated interferon alfa, monotherapy or in combination therapy with ribavirin, were treated with peginterferon alfa-2a 180 µg/week and ribavirin 1000/1200 mg daily. Patients who achieved undetectable levels of HCV RNA after 20 weeks of treatment remained on peginterferon alfa-2a plus ribavirin combination therapy for a total of 48 weeks and were then followed for 24 weeks after the end of treatment. The probability for sustained virological response varied depending upon the previous treatment regimen (see Table 11).

Table 11 Sustained Virological Response in HALT-C by Previous Treatment Regimen in Non-Responder Population

Previous Treatment	**ribavirin** 1000/1200 mg & **Peginterferon alfa-2a** 180 µg 48 weeks
Interferon	27% (70/255)
Pegylated interferon	34% (13/38)
Interferon plus ribavirin	13% (90/692)
Pegylated interferon plus ribavirin	11% (7/61)

HCV patients with normal ALT

In study NR16071, HCV patients with normal ALT values were randomised to receive peginterferon alfa-2a 180 micrograms/week with a Ribavirin dose of 800 milligrams/day for either 24 or 48 weeks followed by a 24 week treatment free follow-up period or an untreated control group for 72 weeks. The SVRs reported in the treatment arms of this study were similar to the corresponding treatment arms from study NV15942.

Children and adolescents

In the investigator sponsored CHIPS study (Chronic Hepatitis C International Paediatric Study), 65 children and adolescents (6-18 years) with chronic HCV infection were treated with peginterferon alfa-2a 100 µg/m2 sc once weekly and ribavirin 15 mg/kg/day, for 24 weeks (genotypes 2 and 3) or 48 weeks (all other genotypes). Preliminary and limited safety data demonstrated no obvious departure from the known safety profile of the combination in adults with chronic HCV infection, but, importantly, the potential impact on growth has not been reported. Efficacy results were similar to those reported in adults.

HIV-HCV co-infected patients

The virological responses of patients treated with Ribavirin and peginterferon alfa-2a combination therapy in relation to genotype and pre-treatment viral load for HIV-HCV co-infected patients are summarised below in Table 12.

Table 12 Sustained Virological Response based on Genotype and Pre-treatment Viral Load after Ribavirin Combination Therapy with peginterferon alfa-2a in HIV-HCV co-infected patients

	Study NR15961		
	Interferon alfa-2a 3 MIU & **Ribavirin 800 mg** 48 weeks	**Peginterferon alfa-2a** 180 µg & **Placebo** 48 weeks	**Peginterferon alfa-2a** 180 µg & **Ribavirin 800 mg** 48 weeks
All patients	12% (33/285)*	20% (58/286)*	40% (116/289)*
Genotype 1	7% (12/171)	14% (24/175)	29% (51/176)
Low viral load	19% (8/42)	38% (17/45)	61% (28/46)
High viral load	3% (4/129)	5% (7/130)	18% (23/130)
Genotype 2-3	20% (18/89)	36% (32/90)	62% (59/95)
Low viral load	27% (8/30)	38% (9/24)	61% (17/28)
High viral load	17% (10/59)	35% (23/66)	63% (42/67)

Low viral load= ≤800,000 IU/ml; High viral load=> 800,000 IU/ml

* peginterferon alfa-2a 180 µg Ribavirin 800mg vs. Interferon alfa-2a 3MIU + ribavirin 800mg: Odds Ratio (95% CI) = 5.40 (3.42 to 8.54), P-value (stratified Cochran-Mantel-Haenszel test) = < 0.0001

* peginterferon alfa-2a 180 µg + Ribavirin 800mg vs. peginterferon alfa-2a 180µg: Odds Ratio (95% CI) = 2.89 (1.93 to 4.32), P-value (stratified Cochran-Mantel-Haenszel test) = < 0.0001

* Interferon alfa-2a 3MIU + Ribavirin 800mg vs. peginterferon alfa-2a 180µg: Odds Ratio (95% CI) = 0.53 (0.33 to 0.85), P-value (stratified Cochran-Mantel-Haenszel test) = < 0.0084.

A subsequent study (NV18209) in patients co-infected with HCV genotype 1 and HIV compared treatment using peginterferon alfa-2a 180 µg week and either ribavirin 800 mg or 1000 mg (<75 kg/1200 mg (≥75 kg) daily for 48 weeks. The study was not powered for efficacy considerations. The safety profiles in both ribavirin groups were consistent with the known safety profile of peginterferon alfa-2a plus ribavirin combination treatment and not indicative of any relevant differences, with the exception of a slight increase in anaemia in the high dose ribavirin arm.

Ribavirin in combination with interferon alfa-2a

The therapeutic efficacy of interferon alfa-2a alone and in combination with oral ribavirin was compared in clinical trials in naïve (previously untreated) and relapsed patients who had virologically, biochemically and histologically documented chronic hepatitis C. Six months after end of treatment sustained biochemical and virological response as well as histological improvement were assessed.

A statistically significant 10-fold increase (from 4% to 43%; p <0.01) in sustained virological and biochemical response was observed in relapsed patients (M23136; N=99). The favourable profile of the combination therapy was also reflected in the response rates relative to HCV genotype or baseline viral load. In the combination and interferon monotherapy arms, respectively, the sustained response rates in patients with HCV genotype-1 were 28% versus 0% and with genotype non-1 were 58% versus 8%. In addition the histological improvement favoured the combination therapy. Supportive favourable results (monotherapy vs combination; 6% vs 48%, p<0.04) from a small published study in naïve patients (N=40) were reported using interferon alfa-2a (3 MIU 3 times per week) with ribavirin.

5.2 Pharmacokinetic properties

Ribavirin is absorbed rapidly following oral administration of a single dose of Ribavirin (median T_{max} = 1-2 hours). The mean terminal phase half-life of ribavirin following single doses of Ribavirin range from 140 to 160 hours. Ribavirin data from the literature demonstrates 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 an approximately linear relationship between dose and AUC_{tf} following single doses of 200-1,200 milligrams ribavirin. Mean apparent oral clearance of ribavirin following single 600 milligram doses of ribavirin ranges from 22 to 29 litres/hour. Volume of distribution is approximately 4,500 1itres following administration of ribavirin. Ribavirin does not bind to plasma proteins.

Ribavirin has been shown to produce high inter- and intra-subject pharmacokinetic variability following single oral doses of ribavirin (intra-subject variability of ≤25% for both AUC and C_{max}), which may be due to extensive first pass metabolism and transfer within and beyond the blood compartment.

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.

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. Ribavirin and both its triazole carboxamide and triazole carboxylic acid metabolites are excreted renally.

Upon multiple dosing, ribavirin accumulates extensively in plasma with a six-fold ratio of multiple-dose to single-dose AUC_{12hr}based on literature data. Following oral dosing with 600 milligrams BID, steady-state was reached by approximately 4 weeks, with mean steady state plasma concentrations of approximately 2,200 ng/ml. Upon discontinuation of dosing the half-life was approximately 300 hours, which probably reflects slow elimination from non-plasma compartments.

Food effect: The bioavailability of a single oral 600 mg dose Ribavirin was increased by co-administration of a high fat meal. The ribavirin exposure parameters of $AUC_{(0-192h)}$ and C_{max} increased by 42% and 66%, respectively, when ribavirin was taken with a high fat breakfast compared to being taken in the fasted state. The clinical relevance of results from this single dose study is unknown. Ribavirin exposure after multiple dosing when taken with food was comparable in patients receiving peginterferon alfa-2a and ribavirin and interferon alfa-2b and ribavirin. In order to achieve optimal ribavirin plasma concentrations, it is recommended to take ribavirin with food.

Renal function: The apparent clearance of ribavirin is reduced in patients with creatinine clearance ≤50 ml/min, including patients with ESRD on chronic haemodialysis, exhibiting approximately 30% of the value found in patients with normal renal function. Based on a small study in patients with moderate or severe renal impairment (creatinine clearance ≤50 ml/min) receiving reduced daily doses of 600 mg and 400 mg of ribavirin, respectively ribavirin plasma exposure (AUC) was found to be higher compared to patients with normal renal function (creatinine clearance >80 ml/min) receiving the standard ribavirin dose. Patients with ESRD on chronic haemodialysis and who received 200 mg daily doses of ribavirin, exhibited mean ribavirin exposure (AUC) approximately 80% of the value found in patients with normal renal function receiving the standard 1000/1200 mg ribavirin daily dose. Plasma ribavirin is removed by haemodialysis with an extraction ratio of approximately 50%; however, due to the large volume of distribution of ribavirin, significant amounts

of ribavirin are not effectively removed from the body by haemodialysis. Increased rates of adverse drug reactions were observed in patients with moderate and severe renal impairment receiving the doses evaluated in this study. Though the dose of ribavirin would need to be reduced if used in patients with significant renal impairment, there are insufficient data on the safety and efficacy of ribavirin in such patients to support specific recommendations for dose adjustments (see section 4.2 and 4.4).

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.

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

Patients under the age of 18 years: The pharmacokinetic properties of ribavirin have not been fully evaluated in patients under the age of 18 years. Ribavirin in combination with peginterferon alfa-2 or interferon alfa-2a is indicated for the treatment of chronic hepatitis C only in patients 18 years of age or older.

Population Pharmacokinetics: A population pharmacokinetic analysis was performed using plasma concentration values from five clinical trials. While body weight and race were statistically significant covariates in the clearance model, only the effect of body weight was clinically significant. Clearance increased as a function of body weight and was predicted to vary from 17.7 to 24.8 L/h over a weight range of 44 to 155 kg. Creatinine clearance (as low as 34 ml/min) did not affect ribavirin clearance.

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

5.3 Preclinical safety data

Ribavirin is embryotoxic and/or teratogenic at doses well below the recommended human dose in all animal species in which adequate 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 is reduced.

Erythrocytes are a primary target of toxicity for ribavirin in animal studies, including studies in dogs and monkeys. Anaemia occurs shortly after initiation of dosing, but is rapidly reversible upon cessation of treatment. Hypoplastic anaemia was observed only in rats at the high dose of 160 milligrams/kg/day in the subchronic study.

Reduced leucocyte and/or lymphocyte counts were consistently noted in the repeat-dose rodent and dog toxicity studies with ribavirin and transiently in monkeys administered ribavirin in the subchronic study. Repeat-dose rat toxicity studies showed thymic lymphoid depletion and/or depletion of thymus-dependent areas of the spleen (periarteriolar lymphoid sheaths, white pulp) and mesenteric lymph node. Following repeat-dosing of dogs with ribavirin, increased dilatation/necrosis of the intestinal crypts of the duodenum was noted, as well as chronic inflammation of the small intestine and erosion of the ileum.

In repeat dose studies in mice to investigate ribavirin-induced testicular and sperm effects, abnormalities in sperm occurred at doses in animals well below therapeutic doses. Upon cessation of treatment, essentially total recovery from ribavirin-induced testicular toxicity occurred within one or two spermatogenic cycles.

Genotoxicity studies have demonstrated that ribavirin does exert some genotoxic activity. Ribavirin was active in an *in vitro* Transformation Assay. Genotoxic activity was observed in *in vivo* mouse micronucleus assays. A dominant lethal assay in rats was negative, indicating that if mutations occurred in rats they were not transmitted through male gametes. Ribavirin is a possible human carcinogen.

Administration of ribavirin and peginterferon alfa-2a in combination did not produce any unexpected toxicity in monkeys. The major treatment-related change was 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

Tablet core:

Cellulose, microcrystalline

Starch, pregelatinised (Maize starch)

Sodium starch glycolate (Type A)

Povidone (K-30)

Silica, colloidal anhydrous

Magnesium stearate

Film coating: