

Ribavirin 200 mg film-coated tablets

Summary of Product Characteristics Updated 09-Aug-2017 | Aurobindo Pharma - Milpharm Ltd.

1. Name of the medicinal product

Ribavirin 200 mg film-coated tablets

2. Qualitative and quantitative composition

Each film-coated tablet contains 200 mg of ribavirin.

For the full list of excipients, see section 6.1.

3. Pharmaceutical form

Film-coated tablet.

Light pink colored, capsule shaped, film-coated tablets debossed with 'F' on one side and '10' on the other side. The size is 13.1 mm x 6.1 mm.

4. Clinical particulars

4.1 Therapeutic indications

Ribavirin is indicated in combination with other medicinal products except peginterferon alfa-2a and peginterferon alfa-2b, for the treatment of chronic hepatitis C

4.2 Posology and method of administration

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

Refer also to the SmPC of the medicinal products that are used in combination with Ribavirin for the treatment of 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

Dose to be administered

The dose of Ribavirin is based on patient body weight, viral genotype and the medicinal product that is used in combination (see Table 1). Ribavirin tablets are to be administered orally each day in two divided doses (morning and evening) with food.

Table 1. Ribavirin dosing recommendation according to the medicinal product used in combination		
Medicinal product used in combination	Daily Ribavirin Dose	Number of 200/400mg tablets
Direct acting antivirals (DAA)	<75kg=1000mg	5 x 200 mg (2 morning, 3 evening)
	≥75 kg = 1200 mg	6 x 200 mg (3 morning, 3 evening)
IFN alfa-2a without DAA	<75kg=1000mg	5 x 200 mg (2 morning, 3 evening)
	≥75 kg = 1200 mg	6 x 200 mg (3 morning, 3 evening)

Duration of treatment

Duration of treatment depends on medicinal products that it is being combined with and may depend on several patients or virus characteristics including genotype, previous history of treatment, on-treatment response.

Refer to the SPC of the medicinal product that is used in combination with Ribavirin Aurobindo.

Dosage modification for adverse reactions

Dose modification of Ribavirin depends on medicinal products that it is being combined with.

If a patient has a severe adverse reaction potentially related to ribavirin, the ribavirin dose should be modified or discontinued, if appropriate, until the adverse reaction abates or decreases in severity. Table 2 provides guidelines for dose modifications and discontinuation based on the patient's haemoglobin concentration and cardiac status.

Table 2 Dosage Modification Guidelines for Management of Treatment-Emergent Anaemia

Laboratory Values	Reduce only ribavirin dose to [1] 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

[1] For patients receiving a 1000mg (<75kg) or 1200mg (>75kg) dose, Ribavirin dose should be reduced to 600mg/day (administered as 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.

Refer to the SmPCs of interferon alfa for dose modification and/or discontinuation in case of serious adverse reaction potentially related to these drugs."

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. The total daily dose of Ribavirin should be reduced for patients with creatinine clearance less than or equal to 50 ml/min as shown in Table 3 (see also section 5.2).

Table 3 Dosage Modification for Renal Impairment

Creatinine Clearance	Ribavirin Dose (daily)
30 to 50 ml/min	Alternating doses, 200 mg and 400 mg every other day
Less than 30 ml/min	200 mg daily
Hemodialysis	200 mg daily

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).

If severe adverse reactions or laboratory abnormalities develop, ribavirin should be discontinued, if appropriate, until the adverse reactions abate or decrease in severity. If intolerance persists after restarting ribavirin, ribavirin therapy should be discontinued. No data are available for pediatric subjects with renal impairment.

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.

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 other medicinal products for the treatment of hepatitis C. Only limited safety and efficacy data are available in children and adolescents (6-18 years) in combination with peginterferon alfa-2a. A case by case benefit/risk assessment with respect to the use of ribavirin in children is needed (see section 4.4).

4.3 Contraindications

Ribavirin is contraindicated in the following:

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

Refer also to the SmPC of the medicinal products that are used in combination with ribavirin for contraindications related to those products.

4.4 Special warnings and precautions for use

Ribavirin monotherapy must not be used.

Combination therapy of ribavirin with (peg) interferon alfa.

There are several severe adverse reactions associated with the combination therapy of ribavirin with (peg) interferon alfa. These include:

- Severe psychiatric and central nervous system effects (such as depression, suicidal ideation, attempted suicide and aggressive behavior, etc.)
- Severe ocular disorders
- Dental and periodontal disorders
- Growth inhibition in children and adolescents that may be irreversible in some patients

Please refer to the SPC of (peg) interferon alfa for details on the recommendations of monitoring and management regarding these adverse reactions before initiating therapy.

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 other medicinal products 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 in patients with serum creatinine >2 mg/dl or with creatinine clearance <50 ml/minute, therefore ribavirin dose adjustments are recommended in these patients (see section 4.2 and 5.2).

Haemoglobin concentrations should be monitored intensively during treatment and corrective action taken as necessary (see section 4.2).

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 ribavirin and the other medicinal products. 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:

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

In patients co-infected with HIV-HCV, limited efficacy and safety data are available in subjects with CD4 counts less than 200 cells/ μ L. 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.

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; AUC₀₋₁₂ 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 or interferon alfa or other medicinal products used in combination with ribavirin may have an effect. Refer to the SmPC of medicinal products that are used in combination with Ribavirin for further information.

4.8 Undesirable effects

The salient safety issue of ribavirin is hemolytic anemia occurring within the first weeks of therapy. The hemolytic anemia associated with ribavirin therapy may result in deterioration of cardiac function and/or worsening of pre-existing cardiac disease. An increase in uric acid and indirect bilirubin values associated with haemolysis were also observed in some patients (see below and section 4.4).

The adverse events listed in this section are reported in clinical trials and/or as adverse drug reactions from spontaneous reports primarily when ribavirin was used in combination with interferon alfa-2a or peginterferon alfa-2a.

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.

Refer also to the SmPC of the medicinal products that are used in combination with ribavirin for additional undesirable effects reported with these products.

Chronic Hepatitis C

The most frequently reported adverse events with ribavirin in combination with peginterferon alfa-2a 180 µg were mostly mild to moderate in severity. Most of them were manageable without the need for 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 fibrosis 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 are available in co-infected patients with CD4+ cell counts ≤ 200/μl. (see peginterferon alfa-2a SmPC).

Table 4 shows the undesirable effects reported in patients who have received ribavirin and peginterferon alfa-2a or interferon alfa-2a therapy.

Table 4 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		
Blood and lymphatic system disorders	Anaemia, neutropenia	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,	Peripheral neuropathy	Coma, convulsions, facial palsy	Cerebral ischaemia	

		migraine, hyposensitivity, hyperaesthesia, paraesthesia, tremor, taste disturbance, nightmares, somnolence				
Eye disorders		Vision blurred, eye pain, eye inflammation, xerophthalmia	Retinal haemorrhage	Optic neuropathy, papilloedema, retinal vascular disorder, retinopathy, corneal ulcer	Vision loss	Serious retinal detachment
Ear and labyrinth disorders		Vertigo, earache, tinnitus	Hearing loss			
Cardiac disorders		Tachycardia, palpitations, oedema peripheral		Myocardial infarction, congestive heart failure, angina, Supraventricular tachycardia arrhythmia, atrial fibrillation, pericarditis		
Vascular disorders		Flushing, hypotension	Hypertension	Cerebral haemorrhage, vasculitis		
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		Colitis ischaemic, colitis ulcerative, tongue pigmentation
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		Myositis		Rhabdomyolysis

		pain, muscle cramps				
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, injection site reaction, irritability	Chest pain, influenza like illness, malaise, 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. 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/mm³ was observed in 13% and 11% of patients receiving peginterferon alfa-2a monotherapy and combination therapy, respectively. Decrease in platelets below 50,000/mm³ 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 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 µg 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 DAA

Please refer to the SmPC of the corresponding direct antiviral agent for a full description of the clinical data with such combination. Only the description of the use of ribavirin with interferon are detailed in the current SmPC

Study results in treatment-naïve patients

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.

For HCV monoinfected patients, for treatment regimens, duration of therapy and study outcome see tables 5, 6 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 5 Virological Response in the overall population (including non-cirrhotic and cirrhotic patients)		
	Study NV15801	
	Ribavirin 1,000/1,200 mg & Peginterferon alfa-2a 180 µg	Ribavirin 1,000/1,200 mg & Interferon alfa-2b 3 MIU
	(N=453) 48 weeks	(N=444) 48 weeks
Response at End of Treatment	69%	52%
Overall Sustained Response	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 or interferon alfa-2b combination therapy in relation to genotype and pre-treatment viral load are summarized in Table 5

Table 6 Sustained Virological Response based on Genotype and Pre-treatment Viral Load after ribavirin Combination Therapy with peginterferon alfa-2a		
	Study NV15801	
	Ribavirin 1000/1200 mg & PEG-IFN alfa-2a 180 µg 48 weeks	Ribavirin 1000/1200 mg & Interferon alfa-2b 3 MIU 48 weeks
Genotype 1	45% (134/298)	36% (103/285)
Low viral load	53% (61/115)	44 % (41/94)
High viral load	40% (73/182)	33% (62/189)
Genotype 2/3	71 % (100/140)	61% (88/145)

Low viral load	76% (28/37)	65 % (34/52)
High viral load	70% (72/103)	58 % (54/93)
Genotype 4	77 % (10/13)	45 % (5/11)

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

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 naive (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 naive 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_{tr} following single doses of 200-1,200 milligrams ribavirin. Mean apparent oral clearance of ribavirin following single 600 mg doses of ribavirin ranges from 22 to 29 litres/hour. Volume of distribution is approximately 4,500 litres 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 carboxylic acid 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 20 to 30% higher compared to patients with normal renal function (creatinine clearance >80 ml/min) receiving the standard ribavirin dose. In patients with ESRD on chronic haemodialysis and who received 200 mg daily doses of ribavirin, mean ribavirin exposure (AUC) was found to be approximately 20% lower compared to 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.

Based on pharmacokinetic modelling and simulation, dose adjustments are recommended in patients with significant renal impairment (see section 4.2). These adjusted doses are expected to provide ribavirin plasma exposures

comparable to those achieved in patients with normal renal function receiving the standard ribavirin dose. Most of the recommended doses were derived from PK modelling and simulation and have not been studied in clinical trials.

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: Refer to the SmPC of the medicinal products that are indicated in combination with ribavirin for this population.

No ribavirin pharmacokinetic analysis has been performed in patients under the age of 18 years

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:

HPMC 2910/ Hypromellose (15cP) (E464)

Titanium dioxide (E171)

Triacetin (E1518)
Iron oxide red (E172)
Iron oxide yellow (E172)
Ethyl cellulose (10cP) (E462)

6.2 Incompatibilities

Not applicable

6.3 Shelf life

2 years

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

Ribavirin film-coated tablets are available in clear PVC - Aluminium foil blister pack and HDPE bottle packs with polypropylene closure.

Pack sizes:

Blister pack: 14, 20, 28, 42, 56, 84, 112, 140 and 168 film-coated tablets

HDPE bottle pack: 28, 42, 56, 112, 168 and 500 film-coated tablets

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. Marketing authorisation holder

Milpharm Limited
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United Kingdom

8. Marketing authorisation number(s)

PL 16363/0407

9. Date of first authorisation/renewal of the authorisation

25/11/2014

10. Date of revision of the text

19/10/2015

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