

28-04-2016

**RYBIO™** Tablets / Capsules  
(Ribavirin)

**DESCRIPTION:**

Ribavirin is a synthetic nucleoside analogue (purine analogue) with antiviral activity. The chemical name of ribavirin is 1--D-ribofuranosyl-1H-1,2,4-triazole-3-carboxamide. Its molecular formula is C<sub>8</sub>H<sub>12</sub>N<sub>4</sub>O<sub>5</sub>

**COMPOSITION:**

**RYBIO™ 600mg Tablets:**

Each film coated tablet contains:  
Ribavirin USP .....600mg

**RYBIO™ 400mg Capsules:**

Each capsule contains:  
Ribavirin USP .....400mg

**CLINICAL PHARMACOLOGY:**

**Pharmacodynamics**

Mechanism of action: Ribavirin is a synthetic nucleoside analog which has shown in-vitro activity against some RNA and DNA viruses. The mechanism by which ribavirin in combination with peg interferon alpha-2a or interferon alpha-2b exerts its effects against HCV is unknown. Ribavirin has direct antiviral activity in tissue culture against many RNA viruses. Ribavirin increases the mutation frequency in the genomes of several RNA viruses and ribavirin triphosphate inhibits HCV polymerase in a biochemical reaction

**Antiviral action:** Ribavirin inhibits many viruses in-vitro and in animal models. However, this activity has not necessarily correlated with activity against human infection. Ribavirin is phosphorylated but its mode of action is still unclear. It may act at several sites, including cellular enzymes, to interfere with viral nucleic acid synthesis. The mono and triphosphate derivatives are believed to be responsible for its antiviral activity. Susceptible DNA viruses include Herpes viruses, Adenoviruses and Pox viruses. Susceptible RNA viruses include Lassa virus, members of the bunyaviridae groups, influenza, parainfluenza, measles, mumps, RSV and HIV

**Pharmacokinetics**

**Absorption:** Ribavirin is absorbed rapidly following oral administration of a single dose of ribavirin (median T<sub>max</sub> = 12 hours). The mean terminal phase half-life of ribavirin ranges 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. Ribavirin does not bind to plasma proteins

Ribavirin has been shown to produce high inter and intra subject pharmacokinetic variability (intra subject variability of < 25% for both AUC and C<sub>max</sub>), which may be due to extensive first pass metabolism and transfer within and beyond the blood compartment

**Distribution:** Ribavirin transport in non-plasma compartments has been most extensively studied in red cells, and has been identified to be primarily via an es-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

**Metabolism and Excretion:** Ribavirin has two pathways of metabolism: 1) a reversible phosphorylation pathway, 2) a degradative pathway involving denitrosylation 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. Following oral dosing with 600mg BID, steady-state was reached by approximately 4 weeks, with mean steady-state plasma concentrations of approximately 2,200ng/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 ribavirin 600mg dose was increased by co-administration of a high fat meal. The ribavirin exposure parameters of AUC(0-192hr) and C<sub>max</sub> 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 peg interferon alpha-2a and ribavirin and interferon alpha-2b and ribavirin. In order to achieve optimal ribavirin plasma concentrations, it is recommended to take ribavirin with food

**INDICATIONS AND USAGE:**

Ribavirin is indicated in combination with other medicinal products, for the treatment of chronic hepatitis C (CHC)

**DOSAGE AND ADMINISTRATION:**

Ribavirin is to be administered orally each day in two divided doses (morning and evening) with food. Due to the teratogenic potential of ribavirin, the tablet/capsule should be swallowed whole with water

Table 1: Ribavirin dosing recommendation according to the medicinal product used in combination

Medicinal product used in combination	Body Weight & Total Dose	Daily Ribavirin Dose
Direct acting antivirals (DAA)	<75kg = 1000mg	400mg in the morning 600mg in the evening
	=>75kg = 1200mg	600mg in the morning 600mg in the evening
Peg INF Alpha-2a with DAA	<75kg = 1000mg	400mg in the morning 600mg in the evening
	=>75kg = 1200mg	600mg in the morning 600mg in the evening
Peg INF Alpha-2a without DAA	Genotype 2/3 treatment-naive Genotype 2/3/4 with HIV-coinfection 800mg	400mg in the morning 400mg in the evening
	Genotype 1/4 Genotype 2/3 treatment-experienced Genotype 1 HIV-coinfection <75kg = 1000mg =>75kg = 1200mg	400mg in the morning 600mg in the evening 600mg in the morning 600mg in the evening
	<75kg = 1000mg	400mg in the morning 600mg in the evening
	=>75kg = 1200mg	600mg in the morning 600mg in the evening
INF Alpha-2a without DAA	<75kg = 1000mg	400mg in the morning 600mg in the evening
	=>75kg = 1200mg	600mg in the morning 600mg in the evening
Peg INF Alpha-2a with or without DAA	<65kg = 800mg	400mg in the morning 400mg in the evening
	65-80kg = 1000mg	400mg in the morning 600mg in the evening
	81-105kg = 1200mg	600mg in the morning 600mg in the evening
	>105kg = 1400mg	600mg in the morning 800mg in the evening

210 mm

150 mm

**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, co-infection status, previous history of treatment, and on-treatment response

**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

Laboratory Values	Reduce Ribavirin dose to [1] [2] if:	Discontinue Ribavirin if:
Haemoglobin in Patients with No Cardiac Disease	<10g/dl	<8.5g/dl
Haemoglobin: Patients with History of Stable Cardiac Disease	< 2g/dl decrease in haemoglobin during any 4 weeks period during treatment (permanent dose reduction)	<12g/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. If the abnormality is reversed, ribavirin may be restarted at 600mg daily, and further increased to 800mg daily at the discretion of the treating physician. However, a return to higher doses is not recommended

[2] For patients receiving an 800mg (<65kg)-1000mg (65 - 80kg)-1200mg (81 - 105kg) or 1400mg (>105kg) dose, 1st dose reduction of ribavirin is by 200mg/day (except in patients receiving the 1400mg, dose reduction should be by 400mg/day). If needed, 2nd dose reduction of ribavirin is by an additional 200mg/day

**OR**  
As directed by the physician

#### ADVERSE EFFECTS:

##### Combination therapy of ribavirin with peg interferon alpha

There are several severe adverse reactions associated with the combination therapy of ribavirin with peg interferon alpha

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

The salient safety issue of ribavirin is hemolytic anaemia occurring within the first weeks of therapy. The hemolytic anaemia 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

**Chronic hepatitis C:** The most frequently reported adverse events with ribavirin in combination with peg interferon alpha-2a 180-g were mostly mild to moderate in severity. Most of them were manageable without the need for discontinuation of therapy

**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<sup>3</sup> was observed in 13% and 11% of patients receiving peg interferon alpha-2a monotherapy and combination therapy, respectively. Decrease in platelets below 50,000/mm<sup>3</sup> was observed in 10% and 8% of patients receiving peg interferon alpha-2a monotherapy and combination therapy, respectively. Anaemia (haemoglobin <10g/dl) was reported in 7% and 14% of patients treated with peg interferon alpha-2a monotherapy or in combination therapy, respectively

#### CONTRAINDICATIONS:

Ribavirin is contraindicated in the following:

- Hypersensitivity to ribavirin or to any of the excipients
- Pregnant women: 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 breastfeeding
- 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)

#### WARNING:

##### RISK OF SERIOUS DISORDERS AND RIBAVIRIN ASSOCIATED EFFECTS

- Ribavirin monotherapy is not effective for the treatment of chronic hepatitis C virus infection
- The hemolytic anaemia associated with ribavirin therapy may result in worsening of cardiac disease and lead to fatal and nonfatal myocardial infarctions. Patients with a history of significant or unstable cardiac disease should not be treated with ribavirin
- Significant teratogenic and embryocidal effects have been demonstrated in all animal species exposed to ribavirin. Therefore, ribavirin is contraindicated in women who are pregnant and in the male partners of women who are pregnant. Extreme care must be taken to avoid pregnancy during therapy and for 6 months after completion of treatment in both female patients and in female partners of male patients who are taking ribavirin therapy

#### PRECAUTIONS:

Ribavirin monotherapy must not be used

**Teratogenic risk:** 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

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

**Haemolysis and Cardiovascular system:** A decrease in haemoglobin levels to <10g/dl was observed in up to 15% of patients treated for 48 weeks with ribavirin 1000/1200mg in combination with peg interferon alpha-2a and up to 19% of patients in combination with interferon alpha-2a. When ribavirin 800mg was combined with peg interferon alpha-2a for 24 weeks, 3% of patients had a decrease in haemoglobin levels to <10g/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 the start of therapy and monitored clinically during therapy; if any deterioration occurs, stop therapy. 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

**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 is 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 >2mg/dl or with creatinine clearance <50ml/minute, therefore ribavirin dose adjustments are recommended in these patients. Haemoglobin concentrations should be monitored intensively during treatment and corrective action taken as necessary

**Laboratory tests:** Standard haematologic tests and blood chemistry (complete blood count [CBC] and differential, platelet count, electrolytes, glucose, 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

**SPECIAL POPULATIONS:**

Use in renal impairment: The recommended dose regimens (adjusted by the body weight cutoff of 75kg) 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 50ml/min as shown in Table 3

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

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 paediatric subjects with renal impairment

**Use in hepatic impairment:** Hepatic function does not affect the pharmacokinetics of ribavirin. 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 peg interferon alpha-2a. A case by case benefit/risk assessment with respect to the use of ribavirin in children is needed

**Pregnancy:** 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. 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

**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

**DRUG INTERACTIONS:**

Interaction studies have been conducted with ribavirin in combination with peg interferon alpha-2a, interferon alpha-2b and antacids. Ribavirin concentrations are similar when given alone or concomitantly with interferon alpha-2b or peg interferon alpha-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. 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 600mg was decreased by co-administration with an antacid containing magnesium, aluminium and methicone; AUCt 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 hyperlactemia/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 peg interferon alpha-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

**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

**STABILITY:**

See expiry on the pack

**PRESENTATION:**

**RYBIO™** 600mg tablets in a pack of 10's

**RYBIO™** 400mg capsules in a pack of 10's

**INSTRUCTIONS:**

Keep out of reach of children

Avoid exposure to heat, light and humidity

Store between 15 to 30°C

Improper storage may deteriorate the medicine

**رائیو™**  
ٹیبلٹ / کیپسول  
(رائیو اورن)

خوراک: ڈاکٹر کی ہدایت کے مطابق استعمال کریں

بچوں کی پہنچ سے دور رکھیں

دوا کو دھوپ، گرمی اور نمی سے محفوظ ۱۵ سے ۳۰ ڈگری سینٹی گریڈ

کے درمیان میں رکھیں ورنہ دوا خراب ہو جائیگی



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