Tablets

Ribascot

رائباسکاٹ ٹیبلٹس

WARNING: RISK OF SERIOUS DISORDERS AND RIBAVIRIN-ASSOCIATED EFFECTS

RIBASCOT (ribavirin) monotherapy is not effective for the treatment of chronic hepatitis C virus infection and should not be used alone for this indication.

The primary clinical toxicity of ribavirin is hemolytic anemia. The anemia 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 RIBASCOT.

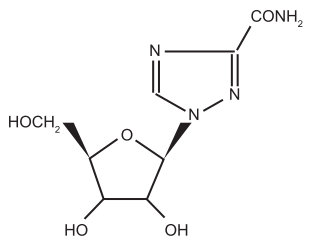
Significant teratogenic and/or embryocidal effects have been demonstrated in all animal species exposed to ribavirin. In addition, ribavirin has a multiple dose half-life of 12 days, and it may persist in non-plasma compartments for as long as 6 months. Therefore, ribavirin, including RIBASCOT, is contraindicated 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 therapy in both female patients and in female partners of male patients who are taking ribavirin therapy. At least two reliable forms of effective contraception must be utilized during treatment and during the 6-month post treatment follow-up period.

COMPOSITION

Each film coated tablet contains: Ribavirin BP/USP…..... 400 mg.

DESCRIPTION

RIBASCOT, ribavirin, is a nucleoside analogue with antiviral activity. The empirical formula of ribavirin is $C_8H_{12}N_4O_5$ and the molecular weight is 244.2. Ribavirin is a white to off-white powder. It is freely soluble in water and slightly soluble in anhydrous alcohol. The chemical name of ribavirin is 1-β-D ribofuranosyl-1H-1,2,4-triazole-3-carboxamide and has the following structural formula:



CLINICAL PHARMACOLOGY

Mechanism of Action:

The mechanism by which ribavirin contributes to its antiviral efficacy is not fully understood. 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.

Pharmacokinetics:

The average time to reach Cmax is 2 hours. The terminal half-life of ribavirin following administration of a single oral dose of ribavirin is about 120 to 170 hours. The total apparent clearance following administration of a single oral dose of ribavirin is about 26 L/h. There is extensive accumulation of ribavirin after multiple dosing.

Absorption:

Bioavailability of a single oral dose of ribavirin increases by co-administration with a high-fat meal. The absorption gets slower and the AUC and Cmax increases by 42% and 66%, respectively, when ribavirin is taken with a high-fat meal compared with fasting conditions.

Elimination and Metabolism:

The contribution of renal and hepatic pathways to ribavirin elimination after administration of ribavirin is not known.

INDICATIONS AND USAGE

RIBASCOT in combination with peginterferon alfa-2a is indicated for the treatment of patients 5 years of age and older with chronic hepatitis C (CHC) virus infection who have compensated liver disease and have not been previously treated with interferon alpha.

CONTRAINDICATIONS

Ribavirin is contraindicated in:

- Women who are pregnant. Ribavirin may cause fetal harm when administered to a pregnant woman. Ribavirin is contraindicated in women who are or may become pregnant. If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to the fetus.
- Men whose female partners are pregnant.
- Patients with hemoglobinopathies (e.g., thalassemia major or sickle-cell anemia).
- In combination with didanosine. Reports of fatal hepatic failure, as well as peripheral neuropathy, pancreatitis, and symptomatic hyperlactatemia/lactic acidosis have been reported.

Ribavirin and peginterferon alfa-2a combination therapy is contraindicated in patients with:

- Autoimmune hepatitis.
- Hepatic decompensation (Child-Pugh score greater than 6; class B and C) in cirrhotic CHC mono-infected patients before treatment.
- Hepatic decompensation (Child-Pugh score greater than or equal to 6) in cirrhotic CHC patients co-infected with HIV before treatment.

ADVERSE REACTIONS

Ribavirin in combination with peginterferon alfa-2a causes a broad variety of serious adverse reaction. The most common serious or life-threatening adverse reactions induced or aggravated by ribavirin/peginterferon alfa-2a include depression, suicide, relapse of drug abuse/overdose, and bacterial infections each occurring at a frequency of less than 1%. Hepatic decompensation occurred in 2% CHC/HIV patients. The most commonly reported adverse reactions are psychiatric reactions, including depression, insomnia, irritability, anxiety, and flu-like symptoms such as fatigue, pyrexia, myalgia, headache and rigors. Other common reactions are anorexia, nausea and vomiting, diarrhea, arthralgias, injection site reactions, alopecia, and pruritus.

Laboratory Test Abnormalities:

Anemia due to hemolysis is the most significant toxicity of ribavirin therapy. Decreases in hemoglobin, neutrophils and platelets may require dose reduction or permanent discontinuation from treatment. Most laboratory abnormalities return to baseline levels shortly after discontinuation of treatment.

DRUG INTERACTIONS

There is no pharmacokinetic interaction between ribavirin and peginterferon alfa-2a.

Nucleoside Reverse Transcriptase Inhibitors (NRTIs):

Ribavirin reduces phosphorylation of lamivudine, stavudine, and zidovudine. However, no pharmacokinetic or pharmacodynamic interaction occurs when ribavirin and lamivudine, stavudine, or zidovudine are co-administered as part of a multi-drug regimen to HCV/HIV co-infected patients. Patients receiving ribavirin/peginterferon alfa-2a and NRTIs should be closely monitored for treatment-associated toxicities.

Didanosine: Co-administration of ribavirin and didanosine is contraindicated. Didanosine or its active metabolite (dideoxyadenosine 5'-triphosphate) concentrations are increased when didanosine is co- administered with ribavirin, which could cause or worsen clinical toxicities. Reports of fatal hepatic failure as well as peripheral neuropathy, pancreatitis, and symptomatic hyperlactatemia/lactic acidosis have been reported.

Zidovudine: Patients who are administered zidovudine in combination with ribavirin/peginterferon alfa-2a develop severe neutropenia and severe anemia more frequently than similar patients not receiving zidovudine. Discontinuation of zidovudine should be considered as medically appropriate.

Azathioprine:

The use of ribavirin to treat chronic hepatitis C in patients receiving azathioprine has been reported to induce severe pancytopenia and may increase the risk of azathioprine-related myelotoxicity. Inosine monophosphate dehydrogenase (IMDH) is required for one of the metabolic pathways of azathioprine. Ribavirin is known to inhibit IMDH, thereby leading to accumulation of an azathioprine metabolite, 6-methylthioinosine monophosphate (6-MTITP), which is associated with myelotoxicity (neutropenia, thrombocytopenia, and anemia). Patients receiving azathioprine with ribavirin should have complete blood counts, including platelet counts, monitored weekly for the first month, twice monthly for the second and third months of treatment, then monthly or more frequently if dosage or other therapy changes are necessary.

USE IN SPECIFIC POPULATION

Pregnancy: Pregnancy Category X. Ribavirin is known to accumulate in intracellular components from where it is cleared very slowly. Because of the potential human teratogenic effects of ribavirin, male patients should be advised to take every precaution to avoid risk of pregnancy for their female partners.Ribavirin should not be used by pregnant women or by men whose female partners are pregnant. Female patients of childbearing potential and male patients with female partners of childbearing potential should not receive ribavirin unless the patient and his/her partner are using effective contraception (two reliable forms) during therapy and for 6 months post therapy.

Nursing Mothers: It is not known whether ribavirin is excreted in human milk. Because many drugs are excreted in human milk and to avoid any potential for serious adverse reactions in nursing infants from ribavirin, a decision should be made either to discontinue nursing or therapy with ribavirin, based on the importance of the therapy to the mother.

Pediatric Use: Safety and effectiveness of ribavirin have not been established in patients below the age of 5 years.

Geriatric Use: Specific pharmacokinetic evaluations for ribavirin in the elderly have not been performed. The risk of toxic reactions to this drug may be greater in patients with impaired renal function.

Renal Impairment: Renal function should be evaluated in all patients prior to initiation of ribavirin by estimating the patient's creatinine clearance. Patients with CLcr less than or equal to 50 mL/min should receive a reduced dose of ribavirin; and patients with CLcr less than 30 mL/min should receive a reduced dose of peginterferon alfa-2a. The clinical and hematologic status of patients with CLcr less than or equal to 50 mL/min receiving ribavirin should be carefully monitored. Patients with clinically significant laboratory abnormalities or adverse reactions which are persistently severe or worsening should have therapy withdrawn.

Hepatic Impairment: The effect of hepatic impairment on the pharmacokinetics of ribavirin has not been evaluated.

WARNINGS AND PRECAUTIONS

Pregnancy: Ribavirin may cause birth defects and/or death of the exposed fetus. Ribavirin therapy should not be started unless a report of a negative pregnancy test has been obtained immediately prior to planned initiation of therapy.

Anemia: The primary toxicity of ribavirin is hemolytic anemia. Anemia associated with ribavirin occurs within 1 to 2 weeks of initiation of therapy. Because the initial drop in hemoglobin may be significant, it is advised that hemoglobin or hematocrit be obtained pretreatment and at week 2 and week 4 of therapy or more frequently if clinically indicated. Patients should then be followed as clinically appropriate. Caution should be exercised in initiating treatment in any patient with baseline risk of severe anemia.

Fatal and nonfatal myocardial infarctions have been reported in patients with anemia caused by ribavirin. Patients should be assessed for underlying cardiac disease before initiation of ribavirin therapy. Patients with pre-existing cardiac disease should have electrocardiograms administered before treatment, and

should be appropriately monitored during therapy. If there is any deterioration of cardiovascular status, therapy should be suspended or discontinued.

Hepatic Failure: Cirrhotic CHC patients co-infected with HIV receiving highly active antiretroviral therapy (HAART) and interferon alfa-2a with or without ribavirin appear to be at increased risk for the development of hepatic decompensation compared to patients not receiving HAART. During treatment, patients' clinical status and hepatic function should be closely monitored for signs and symptoms of hepatic decompensation. Treatment with ribavirin/peginterferon alfa-2a should be discontinued immediately in patients with hepatic decompensation.

Hypersensitivity: Severe acute hypersensitivity reactions have been observed during alpha interferon and ribavirin therapy. If such a reaction occurs, therapy with ribavirin/peginterferon alfa-2a should be discontinued immediately and appropriate medical therapy instituted.

Pulmonary Disorders: Occasional cases of fatal pneumonia have occurred. If there is evidence of pulmonary infiltrates or pulmonary function impairment, patients should be closely monitored and, if appropriate, combination ribavirin/peginterferon alfa-2a treatment should be discontinued.

Bone Marrow Suppression:

Pancytopenia (marked decreases in RBCs, neutrophils and platelets) and bone marrow suppression have been reported in the literature to occur within 3 to 7 weeks after the concomitant administration of peginterferon/ribavirin and azathioprine. Peginterferon/ribavirin and azathioprine should be discontinued for pancytopenia, and peginterferon/ribavirin should not be re-introduced with concomitant azathioprine.

Pancreatitis: Peginterferon/ribavirin therapy should be suspended in patients with signs and symptoms of pancreatitis, and discontinued in patients with confirmed pancreatitis.

Laboratory Tests:

Before beginning ribavirin/peginterferon combination therapy, standard hematological and biochemical laboratory tests are recommended for all patients. Pregnancy screening for women of childbearing potential must be performed. Patients who have pre-existing cardiac abnormalities should have ECG administered before treatment with ribavirin/peginterferon. After initiation of therapy, hematological tests should be performed at 2 weeks and 4 weeks and biochemical tests should be performed at 4 weeks. Additional testing should be performed periodically during therapy. Monthly pregnancy testing should be performed during combination therapy and for 6 months after discontinuing therapy.

DOSAGE AND ADMINISTRATION

RIBASCOT should be taken with food. RIBASCOT should be given in combination with peginterferon alfa-2a; it is important to note that RIBASCOT should never be given as monotherapy.

Chronic Hepatitis C Mono-infection:

Adult Patients: The recommended dose of RIBASCOT tablets is provided in Table 1. The recommended duration of treatment for patients previously untreated with ribavirin and interferon is 24 to 48 weeks. The daily dose of RIBASCOT is 800 mg to 1200 mg administered orally in two divided doses. The dose should be individualized to the patient depending on baseline disease characteristics, response to therapy, and tolerability of the regimen (see Table 1).

Table 1 Peginterferon Alfa-2a and RIBASCOT Dosing Recommendations

Hepatitis C Virus (HCV) Genotype	Peginterferon Alfa-2a Dose* (Once weekly)	RIBASCOT Dose (Daily)	Duration
Genotypes 1, 4	180 mcg	<75 kg = 1000 mg ≥75 kg = 1200 mg	48 Weeks 48 Weeks
Genotypes 2, 3	180 mcg	800 mg	24 Weeks

Genotypes 2 and 3 showed no increased response to treatment beyond 24 weeks.

*See details on Peginterferon Alfa-2a dosing and administration.

Pediatric Patients:

RIBASCOT should be given in combination with peginterferon alfa-2a. The recommended doses for RIBASCOT are provided in Table 2. Patients who initiate treatment prior to their 18th birthday should maintain pediatric dosing through the completion of therapy.

Table 2 RIBASCOT Dosing Recommendations for Pediatric Patients

Body weight in kilograms (kg)	RIBASCOT Daily Dose
23-33	400 mg
34-46	600 mg
47-59	800 mg
60-74	1000 mg
≥75	1200 mg

*approximately 15 mg/kg/day

Chronic Hepatitis C with HIV Co-infection:

Adult Patients: The recommended dose for treatment of chronic hepatitis C in patients co-infected with HIV is peginterferon alfa-2a 180 mcg subcutaneous once weekly and RIBASCOT 800 mg by mouth daily for a total duration of 48 weeks, regardless of HCV genotype.

Dose Modifications:

Adult and Pediatric Patients:

If severe adverse reactions or laboratory abnormalities develop during combination RIBASCOT/peginterferon alfa-2a therapy, the dose should be modified or discontinued, if appropriate, until the adverse reactions abate or decrease in severity. If intolerance persists after dose adjustment, RIBASCOT/peginterferon alfa-2a therapy should be discontinued. Table 3 provides guidelines for dose modifications and discontinuation based on the patient's hemoglobin concentration and cardiac status.

Body weight in kilograms (kg)	Laboratory Values	
	Hemoglobin <10 g/dL in patients with no cardiac disease, or Decrease in hemoglobin of ≥2 g/dL during any 4 week period in patients with history of stable cardiac disease.	Hemoglobin <8.5 g/dL in patients with no cardiac disease, or Decrease in hemoglobin of <12 g/dL despite 4 weeks at reduced dose in patients with history of stable cardiac disease.
Adult Patients older than 18 years of age		
Any weight	600 mg/day	Discontinue RIBASCOT.
Pediatric Patients 5 to 18 years of age		
23-33	200 mg/day	Discontinue RIBASCOT.
34-46	400 mg/day	
47-59	400 mg/day	
60-74	600 mg/day	
≥75	600 mg/day	

Renal Impairment:

The total daily dose of RIBASCOT should be reduced for patients with CLcr ≤50 mL/min; and the weekly dose of peginterferon alfa-2a should be reduced for creatinine clearance < 30 mL/min as follows in Table 4.

Table 4 Dosage Modification for Renal Impairment

Creatinine Clearance (CLcr)	Peginterferon Alfa-2a Dose (Once weekly)	RIBASCOT Dose (Daily)
30-50 mL/min	180 mcg	Alternating doses, 200 mg and 400 mg every other day
<30 mL/min	135 mcg	200 mg
Hemodialysis	135 mcg	200 mg

The dose of RIBASCOT should not be further modified in patients with renal impairment. If severe adverse reactions or laboratory abnormalities develop, RIBASCOT should be discontinued, if appropriate, until the adverse reactions abate or decrease in severity. If intolerance persists after restarting RIBASCOT, RIBASCOT/peginterferon alfa-2a therapy should be discontinued. No data is available for pediatric patients with renal impairment.

Discontinuation of Dosing:

Discontinuation of RIBASCOT/peginterferon alfa-2a therapy should be considered if the patient has failed to demonstrate at least a 2 log10 reduction from baseline in HCV RNA by 12 weeks of therapy, or undetectable HCV RNA levels after 24 weeks of therapy. RIBASCOT/peginterferon alfa-2a therapy should be discontinued in patients who develop hepatic decompensation during treatment.

OVERDOSAGE

No cases of overdose with ribavirin have been reported. Hypocalcemia and hypomagnesemia have been observed in persons administered greater than the recommended dosage of ribavirin.

STORAGE/PRECAUTIONS: Store in a cool, dry and dark place between 15 - 30 °C. Keep all medicines out of the reach of children. To be used on the prescription of Registered Medical Practitioners.

PRESENTATION: RIBASCOT Tablets 400 mg are available in packing containing 10 tablets.

خوراک: ڈاکٹر کی ہدایت کے مطابق۔
احتیاط: روشنی، نمی اور گرمی سے بچائیں۔ 15 سے 30 ڈگری سینٹی گریڈ کے درمیان محفوظ کریں۔ تمام ادویات بچوں کی پہنچ سے دور رکھیں۔ مستند ڈاکٹر کے نسخہ پر فروخت اور استعمال کریں۔

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