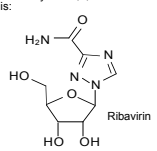
Ribazole®

(R i b a v i r i n)

100mg, 200mg, 400mg Capsules
500mg, 600mg Tablets

ريبازول

DESCRIPTION
RIBAZOLE (Ribavirin) is a synthetic nucleoside analogue (purine analogue) with antiviral activity. The chemical name of ribavirin is 1-ß-D-ribofuranosyl-1H-1,2,4-triazole-3-carboxamide. Its molecular formula is $C_8H_{12}N_4O_5$ and the structural formula is:



QUANTITATIVE & QUALITATIVE COMPOSITION
RIBAZOLE (Ribavirin) is available for oral administration as:

Ribazole Capsules 100mg
Each capsule contains:
Ribavirin USP… 100mg

Ribazole Capsules 200mg
Each capsule contains:
Ribavirin USP… 200mg

Ribazole Capsules 400mg
Each capsule contains:
Ribavirin USP… 400mg

Ribazole Tablets 500mg
Each film-coated tablet contains:
Ribavirin USP… 500mg

Ribazole Tablets 600mg
Each film-coated tablet contains:
Ribavirin USP… 600mg

CLINICAL PHARMACOLOGY
Mechanism of Action
Ribavirin is a synthetic nucleoside analogue which has shown *in-vitro* activity against some RNA and DNA viruses. The mechanism by which ribavirin in combination with Peginterferon alfa-2a or Interferon alfa 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 infections. 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 herpesviruses, adenoviruses and poxviruses. Susceptible RNA viruses include Lassa virus, members of the bunyaviridae group, influenza, parainfluenza, measles, mumps, RSV and HIV.

Pharmacokinetics
Absorption
Ribavirin was rapidly and extensively absorbed following oral administration. However, due to first-pass metabolism, the absolute bioavailability averaged 64%. There was a linear relationship between dose and AUC_{SS} (AUC from time zero to last measurable concentration) following single doses of 200mg to 1200mg ribavirin. The relationship between dose and C_{max} was curvilinear, tending to asymptote above single doses of 400mg to 600mg. Upon multiple oral dosing, based on AUC_{12hr}, a 6-fold accumulation of ribavirin was observed in plasma. Following oral dosing with 600mg twice daily, steady-state was reached by approximately 4 weeks, with mean steady-state plasma concentrations of 2200ng/mL. Upon discontinuation of dosing, the mean half-life was 298 hours, which probably reflects slow elimination from nonplasma compartments.

Effect of Food on Absorption of Ribavirin
Bioavailability of a single oral dose of ribavirin was increased by co-administration with a high-fat meal. The absorption was slowed (T_{max} was doubled) and the $AUC_{0-192hr}$ and C_{max} increased by 42% and 66%, respectively, when ribavirin was taken with a high-fat meal compared with fasting conditions.

Distribution
Ribavirin transport into nonplasma compartments has been most extensively studied in red blood 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 extensive volume of distribution. Ribavirin does not bind to plasma proteins. 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:(i) a reversible phosphorylation pathway in nucleated cells; and (ii) a degradative pathway involving deribosylation and amide hydrolysis to yield a triazole carboxylic acid metabolite. Ribavirin and its triazole carboxamide and triazole carboxylic acid metabolites are excreted renally. After oral administration of 600mg of ^{14}C-ribavirin, approximately 61% and 12% of the radioactivity was eliminated in the urine and feces, respectively, in 336 hours. Unchanged ribavirin accounted for 17% of the administered dose. After a single oral dose the terminal half life is about 120 to 170 hours. Insignificant amounts of the drug are removed by hemodialysis.

Special Population
Pediatric
The pharmacokinetics of ribavirin are similar in adults, children and adolescents.

Renal Impairment
The pharmacokinetics of ribavirin were assessed after administration of a single oral dose (400mg) of ribavirin to non HCV-infected subjects with varying degrees of renal dysfunction. The mean AUC_∞ value was threefold greater in subjects with creatinine clearance values between 10 to 30mL/min when compared to control subjects (creatinine clearance > 90mL/min). In subjects with creatinine clearance values 61kg is 3million IU/ml three times weekly between 30 to 60mL/min; AUC_∞ was twofold greater when compared to control subjects. The increased AUC_∞ appears to be due to reduction of renal and non renal clearance in these subjects. Ribavirin is not effectively removed by hemodialysis.

Hepatic Impairment
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.

THERAPEUTIC INDICATIONS
RIBAZOLE (Ribavirin) in combination with Interferon alfa-2b and Peginterferon alfa-2a is indicated for the treatment of patients 3 years of age and older with chronic Hepatitis C (CHC) who have compensated liver disease. RIBAZOLE (Ribavirin) monotherapy must not be used.

DOSAGE AND ADMINISTRATION
Ribavirin with Interferon alfa-2b Combination Therapy

Adults
Duration of Treatment - Interferon alfa-2b-naïve Patients.
The recommended dose of Interferon alfa-2b is 3 million IU three times weekly subcutaneously. The recommended dose of Ribazole (Ribavirin) depends on the patient's body weight (see table 1). The recommended duration of treatment for patients previously untreated with interferon is 24 to 48 weeks. The duration of treatment should be individualized to the patient depending on baseline disease characteristics, response to therapy and tolerability of the regimen. After 24 weeks of treatment, virologic response should be assessed. Treatment discontinuation should be considered in any patient who has not achieved an HCV-RNA below the limit of detection of the assay by 24 weeks. There are no safety and efficacy data on treatment for longer than 48 weeks in the previously untreated patient population.

Duration of Treatment - Retreatment with interferon alfa / Ribazole (Ribavirin) in Relapse Patients
In patients who relapse following nonpegylated interferon monotherapy, the recommended duration of treatment is 24 weeks.

Table 1: Recommended Dosing

Body Weight	Ribazole (Ribavirin)
≤ 75kg	400mg in the morning 600mg in the evening Daily orally
> 75kg	400mg in the morning 600mg in the evening Daily orally

Pediatrics
The recommended dose of Ribazole (Ribavirin) is 15mg/kg per day orally (divided dose in the morning and in the evening). *See table 2* for Pediatric Dosing of Ribazole (Ribavirin) in combination with Interferon alfa-2b. Interferon alfa-2b Injection by body weight of 25kg to 61kg is 3million IU/m^2 three times weekly.

Table 2: Recommend Ribavirin Dosing in Combination Therapy (Pediatrics)

Body Weight kg (lbs)	Ribavirin Daily Dose	Ribavirin
< 47 (< 103)	15mg/kg/day	Use Ribavirin Oral Solution
47 - 59 (103 - 131)	800mg/day	400mg in the morning 400mg in the evening
60 - 73 (132 - 162)	1000mg/day	400mg in the morning 600mg in the evening
> 73 (> 162)	1200mg/day	600mg in the morning 600mg in the evening

The recommended duration of treatment is 48 weeks for pediatric patients with genotype 1. After 24 weeks of treatment, virologic response should be assessed. Treatment discontinuation should be considered in any patient who has not achieved an HCV-RNA below the limit of detection of the assay by this time. The recommended duration of treatment for pediatric patients with genotype 2/3 is 24 weeks.

Ribavirin with Peginterferon alfa-2a Combination Therapy

Dose to be administered
The recommended dose of ribavirin in combination with Peginterferon alfa-2a solution for injection depends on viral genotype and the patient's body weight. (see table 3)

Table 3: Ribavirin Dosing Recommendations in Combination with Peginterferon alfa-2a for HCV patients.

Genotype	Daily Ribavirin Dose	Duration of treatment
Genotype 1 LVL with RVR*	< 75 kg = 1000mg (400mg morning, 600mg evening) ≥75 kg = 1200mg (600mg morning, 600mg evening)	24 weeks or 48 weeks
Genotype 1 HVL with RVR*	<75 kg = 1000mg (400mg morning, 600mg evening) ≥75 kg = 1200mg (600mg morning, 600mg evening)	48 weeks
Genotype 4 with RVR*	<75 kg = 1000mg (400mg morning, 600mg evening) ≥75 kg = 1200mg (400mg morning, 800mg evening)	24 weeks or 48 weeks
Genotype 1 or 4 without RVR*	<75 kg = 1000mg (400mg morning, 600mg evening) ≥75 kg = 1200mg (600mg morning, 600mg evening)	48 weeks
Genotype 2 or 3 LVL with RVR**	800mg [a] (400mg morning, 400mg evening)	16 weeks[a] or 24 weeks
Genotype 2 or 3 HVL with RVR**	800mg (400mg morning, 400mg evening)	24 weeks
Genotype 2 or 3 without RVR**	800mg (400mg morning, 400mg evening)	24 weeks

*RVR = rapid viral response (HCV RNA undetectable) at week 4 and HCV RNA undetectable at week 24
**RVR = rapid viral response (HCV RNA negative) by week 4
LVL= ≤800,000 IU/mL; HVL= > 800,000 IU/mL
(a) It is presently not clear whether a higher dose of ribavirin (e.g.1000/1200mg/day based on body weight) results in higher SVR rates than does the 800mg/day, when treatment is shortened to 16 weeks.

The ultimate clinical impact of a shortened initial treatment of 16 weeks instead of 24 weeks is unknown, taking into account the need for retreating non-responding and relapsing patients.

Duration of treatment
The duration of combination therapy with Peginterferon alfa 2a depends on viral genotype. Patients infected with HCV genotype 1 who have detectable HCV RNA at week 4 regardless of pre-treatment viral load should receive 48 weeks of therapy.

Treatment for 24 weeks may be considered in patients infected with:
- genotype 1 with low viral load (LVL) (≤800,000 IU/mL) at baseline or
- genotype 4 who become HCV RNA negative at week 4 and remain HCV RNA negative at week 24.

Chronic hepatitis C - treatment-experienced patients
The recommended dose of ribavirin, in combination with 180micrograms once weekly of Peginterferon alfa-2a, is 1000 milligrams daily or 1200 milligrams daily for patients <75 kg and ≥75 kg, respectively, regardless of genotype.

Patients who have detectable virus at week 12 should stop therapy. The recommended total duration of therapy is 48 weeks. If patients infected with virus genotype 1, not responding to prior treatment with Peginterferon and ribavirin are considered for treatment, the recommended total duration of therapy is 72 weeks.

HIV-HCV Co-infection
The recommended dosage for ribavirin in combination with 180 micrograms once weekly of Peginterferon alfa-2a is 800mg, daily for 48 weeks, regardless of genotype.

Predictability of response and non-response - treatment-naïve patients
Early virological response by week 12, defined as a 2 log viral load decrease or undetectable levels of HCV RNA has been shown to be predictive for sustained response. (see table 4)

Table 4: Predictive Value of Week 12 Virological Response at the Recommended Dosing Regimen while receiving Ribavirin and Peginterferon Combination Therapy

Genotype	Negative			Positive		
	No response by week 12	No sustained response	Predictive Value	Response by week 12	Sustained response	Predictive Value
Genotype 1	102	97	95%	467	271	58%
Genotype 2 and 3	3	3	100%	93	81	87%

A similar negative predictive value has been observed in HIV-HCV co-infected patients treated with Peginterferon alfa-2a monotherapy or in combination with ribavirin (100% or 98%, respectively). Positive predictive values of 45% and 70% were observed for genotype 1 and genotype 2/3 HIV-HCV co-infected patients receiving combination therapy.

Predictability of response and non-response - treatment-experienced patients
In non-responder patients re-treated for 48 or 72 weeks, viral suppression at week 12 (undetectable HCV RNA defined as <50 IU/mL) has been shown to be predictive for sustained virological response. The probabilities of not achieving a sustained virological response with 48 or 72 weeks of treatment if viral suppression was not achieved at week 12 were 96% and 96%, respectively. The probabilities of achieving a sustained virological response with 48 or 72 weeks of treatment if viral suppression was achieved at week 12 were 35% and 57%, respectively.

Dose modification and discontinuation of therapy
If severe adverse reactions or laboratory abnormalities develop during combination Ribavirin/Interferon alfa 2b therapy or Ribavirin/Peginterferon alfa 2a therapy, modify, or discontinue the dose until the adverse reaction abates or decreases in severity. If intolerance persists after dose adjustment, combination therapy should be discontinued.

Laboratory Values	Reduce only ribavirin dose to 600 mg/day if:	Discontinue ribavirin if:
Hemoglobin in Patients with No Cardiac Disease	<10 g/dl	<8.5 g/dl
Hemoglobin: Patients with History of Stable Cardiac Disease	>2 g/dl decrease in hemoglobin during any 4 week period during treatment (permanent dose reduction)	<12 g/dl despite 4 weeks at reduced dose

Adult patients: 1st dose reduction of ribavirin is by 200 mg/day (except in patients receiving the 1,400 mg, dose reduction should be by 400 mg/day). If needed, 2nd dose reduction of ribavirin is by an additional 200 mg/day. Patients whose dose of ribavirin is reduced to 600 mg daily receive 200mg in the morning and 400mg in the evening. Pediatric patients: 1st dose reduction of ribavirin is to 12 mg/kg/day, 2nd dose reduction of ribavirin is to 8 mg/kg/day.

Discontinuation of Dosing
Adults
In HCV genotype 1, interferon-alfa-naïve patients receiving Peginterferon in combination with ribavirin, discontinuation of therapy is recommended if there is not at least a 2 log10 drop or loss of HCV-RNA at 12 weeks of therapy, or if HCV-RNA levels remain detectable after 24 weeks of therapy. Regardless of genotype, previously treated patients who have detectable HCV-RNA at Week 12 or 24 are highly unlikely to achieve SVR and discontinuation of therapy should be considered.

Pediatrics (3-17 years of age)
It is recommended that patients receiving Ribavirin/Peginterferon combination (excluding HCV Genotype 2 and 3) be discontinued from therapy at 12 weeks if their treatment Week 12 HCV-RNA dropped less than 2 log10 compared to a pretreatment or at 24 weeks if they have detectable HCV-RNA at treatment Week 24.

CONTRAINDICATIONS
Ribavirin is contraindicated in:
- Patients with known hypersensitivity to ribavirin or any component of the product.
- Women who are or may become pregnant.
- Men whose female partners are pregnant.
- Nursing mothers.
- Patients with known hypersensitivity reactions such as Stevens-Johnson syndrome, toxic, epidermal necrolysis, and erythema multiforme to ribavirin or any component of the product.
- Patients with hemoglobinopathies (e.g., thalassemia major, sickle-cell anemia).
- Patients with chronic renal failure, patients with creatinine clearance < 50 mL/min and/or on hemodialysis.
- Patients with a history of severe pre-existing cardiac disease, including unstable or uncontrolled cardiac disease, in the previous six months.
- Patients with Severe hepatic impairment (Child-Pugh Classification B or C) or decompensated cirrhosis of the liver.
- Patients with severe, debilitating medical condition.
- Initiation of Peginterferon alfa-2a is contraindicated in HCV/HIV patients with cirrhosis and a Child-Pugh score ≥6.
- Combination with didanosine and zidovudine.

Children and adolescent
- Existence of or history of severe psychiatric condition, particularly severe depression, suicidal ideation, or suicide attempt.

Because of co-administration with peginterferon alfa-2a or interferon alfa-2b:
- Autoimmune hepatitis or history of autoimmune disease.

ADVERSE REACTIONS
The most common adverse effects reported by patients taking oral ribavirin, with either interferon alfa or peginterferon alfa, are psychiatric reactions (such as anxiety, depression, insomnia, and irritability) and flulike symptoms. Life-threatening or fatal adverse effects include severe depression, suicidal ideation, relapse of drug abuse or overdose and bacterial infection.
Severe adverse effects include hemolytic anemia, leucopenia, thrombocytopenia, aplastic anemia, diabetes mellitus, auto-immune disorders, gastrointestinal symptoms, pancreatitis, pulmonary embolism, chest pain, liver dysfunction and interstitial pneumonitis. Lupus erythematosus, rash (including very rarely Stevens-Johnson syndrome and toxic epidermal necrolysis), and photosensitivity have also been reported. Growth retardation (including decrease in height and weight) has been reported in children.

Ribavirin/Interferon alfa-2b Combination Therapy
Injection site inflammation, injection site reaction, headache, fatigue, rigors, fever, influenza-like symptoms, asthenia, chest pain, dizziness, nausea, anorexia, dyspepsia, vomiting, myalgia, arthralgia, musculoskeletal pain, insomnia, irritability, depression, emotional lability, concentration impaired, nervousness, dyspnea, sinusitis, alopecia, rash, pruritus and taste perversion.

Ribavirin/Peginterferon alfa-2a Combination Therapy
Upper respiratory infection, bronchitis, oral candidiasis, herpes simplex, anemia, thrombocytopenia, lymphadenopathy, hypothyroidism, hyperthyroidism, anorexia, depression, insomnia, mood alteration, emotional disorders, anxiety, aggression, nervousness, libido decreased, headache, dizziness, concentration impaired, memory impairment, syncope, weakness, migraine, hypoaesthesia, hyperaesthesia, paraesthesia, tremor, taste disturbance, nightmares, somnolence, vision blurred, eye pain, eye inflammation, xerophthalmia, vertigo, earache, tachycardia, palpitations, oedema peripheral, flushing, dyspnoea, cough, dyspnoea, exertional, epistaxis, nasopharyngitis, sinus congestion, nasal congestion, rhinitis, sore throat, diarrhea, nausea, abdominal pain vomiting, dyspepsia, dysphagia, mouth ulceration, gingival bleeding, glossitis, stomatitis, flatulence, constipation, dry mouth, alopecia, dermatitis, pruritus, dry skin rash, sweating increased, psoriasis, urticaria, eczema, skin disorder, photosensitivity reaction, night sweats, myalgia, arthralgia, back pain, arthritis, muscle weakness, bone pain, neck pain, musculoskeletal pain, muscle cramps, impotence, pyrexia, rigors, pain, asthenia, fatigue, injection site reaction, irritability, chest pain, influenza like illness, malaise, lethargy, hot flushes, thirst and weight decreased.

PRECAUTIONS
Psychiatric and Central Nervous System (CNS)
Patients should be closely monitored for any signs or symptoms of psychiatric disorders. It is recommended that treatment with ribavirin and peginterferon alfa-2a or interferon alfa-2b be discontinued, and the patient followed, with psychiatric intervention as appropriate.

Patients with substance use/abuse
If treatment with alfa 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. Patients should be closely monitored during therapy and even after treatment discontinuation.

Growth and development (children and adolescents)
The expected benefit of treatment should be carefully weighed against the safety findings observed for children and adolescents. Whenever possible the child should be treated after the pubertal growth spurt, in order to reduce the risk of growth inhibition.

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
Any patient developing significant liver function abnormalities during treatment must be monitored closely. Discontinue treatment in patients who develop prolongation of coagulation markers which might indicate liver decompensation.

Anemia
The primary toxicity of ribavirin is hemolytic 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 ECG administered before treatment and should be appropriately monitored during therapy. If there is any deterioration of cardiovascular status, therapy should be suspended or discontinued.

Pancreatitis
Ribavirin and Interferon therapy should be suspended in patients with signs and symptoms of pancreatitis and discontinued in patients with confirmed pancreatitis.

Pulmonary Disorders
If there is evidence of pulmonary infiltrates or pulmonary function impairment, patients should be closely monitored and, if appropriate, combination treatment should be discontinued.

Ophthalmologic Disorders
All patients should have a baseline eye examination. Patients with pre-existing ophthalmologic disorders (e.g., diabetic or hypertensive retinopathy) should receive periodic ophthalmologic exams during combination therapy with alfa interferons. Combination therapy with alfa interferons should be discontinued in patients who develop new or worsening ophthalmologic disorders.

Laboratory Tests
Before beginning 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 electrocardiograms administered before treatment.

Dental and Periodontal Disorders
Dental and periodontal disorders have been reported in patients receiving combination therapy. Patients should brush their teeth thoroughly twice daily and have regular dental examinations.

Thyroid supplemental monitoring specific for children and adolescents
If thyroid abnormalities are detected, the patient's thyroid status should be evaluated and treated as clinically appropriate. Children and adolescents should be monitored every 3 months for evidence of thyroid dysfunction (e.g., TSH).

HCV/HIV Co-infection
Caution should be taken in HIV-positive subjects co- infected with HCV who receive nucleoside reverse transcriptase inhibitor (NRTI) treatment (especially ddI and d4T) and associated Interferon alfa-2b/Ribavirin treatment. In the HIV-positive population receiving an NRTI regimen, physicians should carefully monitor markers of mitochondrial toxicity and lactic acidosis when ribavirin is administered.

Drug Interactions
Azathioprine
The use of ribavirin for the treatment of chronic hepatitis C in patients receiving azathioprine has been reported to induce severe pancytopenia and may increase the risk of azathioprine-related myelotoxicity.

OVERDOSAGE
No cases of overdose with ribavirin have been reported. Hypocalcemia and hypomagnesemia have been observed in persons administered greater than the recommended dosages of ribavirin. In most of these cases, ribavirin was administered intravenously at dosage up to and in some cases exceeding four times the recommended maximum oral daily dose.

STORAGE
Store at 25°C (Excursions permitted between 15°C - 30°C).
Protect from sunlight and moisture.
The expiration date refers to the product correctly stored at the required conditions.

HOW SUPPLIED
Ribazole (Ribavirin) Capsules 100mg is available in blister pack of 10 capsules.
Ribazole (Ribavirin) Capsules 200mg is available in blister pack of 10 capsules.
Ribazole (Ribavirin) Capsules 400mg is available in blister pack of 10 capsules.
Ribazole (Ribavirin) Tablets 500mg is available in blister pack of 10 tablets.
Ribazole (Ribavirin) Tablets 600mg is available in blister pack of 10 tablets.

Keep out of reach of children.

To be sold on prescription of a registered medical practitioner only.

Please read the contents carefully before use.
This package insert is continually updated from time to time.

Manufactured by:
Getz pharma (PVT) LIMITED
www.getzpharma.com
29-30/27, K.I.A., Karachi, Pakistan
200007814