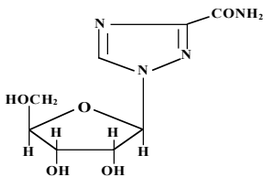
Ribazole™
(Ribavirin)

400mg, 500mg
Capsules & Tablets
Broad Spectrum Antiviral

DESCRIPTION
Ribazole (Ribavirin) is the product of an intensive search for antiviral chemotherapeutic agent with broad spectrum of activity and low toxicity. First synthesized in 1970 by Dr. Roland Robbins and his colleagues, it has since shown to be active *in vitro* against at least 20 different RNA and DNA viruses. The chemical name of ribavirin is 1-β-D-ribofuranosyl-1*H*-1,2,4-triazole-3-carboxamide and has the following structural formula :



RIBAZOLE is Getz Pharma's brand name for ribavirin, a nucleoside analog administered against Hepatitis viruses, Herpes viruses, Influenza A & B, Respiratory Syncytial Virus (RSV) and several of the viruses that produce hemorrhagic fever. Recently, it showed a mitigating effect for corona virus that caused SARS.

QUALITATIVE AND QUANTITATIVE COMPOSITION
Ribazole (Ribavirin) is available for oral administration containing:

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

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

ANTIVIRAL ACTION
Ribavirin inhibits a wide variety of viruses *in vitro* and in *animal models*. Once ribavirin is taken up into the cell it is phosphorylated by thymidine kinase and it may act in several sites including cellular enzymes to interfere with viral nucleic acid synthesis. The mono- and triphosphate derivatives are believed to be responsible for the antiviral activity of the compound. Susceptible DNA viruses include herpes viruses, adenoviruses, and poxviruses. Susceptible RNA viruses include Lassa virus, members of the bunyaviridae group, influenza, parainfluenza, measles, mumps, and respiratory syncytial viruses, and human immunodeficiency virus (HIV).

CLINICAL PHARMACOLOGY
Mechanism of Action
Ribavirin is a synthetic guanine analogue that acts in a manner similar to the other nucleoside analogues. It shows *in vitro* activity against some RNA and DNA viruses. RNA is essential in the synthesis of proteins, as the messenger with the genetic code of RNA and DNA viruses. Ribavirin blocks messenger RNA, prevents viral replication and stops the infection. Ribavirin suppresses viral replication without effect on normal cellular function.

Pharmacokinetics
Absorption
Ribavirin is rapidly and extensively absorbed following oral administration. However, due to first-pass metabolism, the absolute bioavailability averaged 64% (44%). There is no effect of food intake on gastrointestinal absorption of ribavirin. There was a linear relationship between dose and AUC_{tf} (AUC from time zero to last measurable concentration) following single doses 200-1200mg ribavirin. The relationship between dose and C_{max} was curve linear, tending to asymptote above single doses of 400-600mg.
Upon multiple dosing, based on AUC 12_{hr}, a six-fold accumulation of ribavirin was observed in plasma. Following oral dosing with 1200mg daily, steady state was reached by approximately 4 weeks, with mean steady plasma concentrations of 2200ng/mL (37%). Upon discontinuation of dosing, the mean half-life was 298 hours (30%), which probably reflects slow elimination from neoplasma compartments.

Distribution
Ribavirin is distributed throughout the body including red blood cells and cerebrospinal fluid. Red blood cells generally display a rapid uptake of drug and ribavirin concentration remains elevated long after plasma level declines to near-zero values. Distribution and elimination is triphasic.

Metabolism and Elimination
The β-phase half-life is about 2 hours, and the terminal elimination half-life is reported to be 20 to 50 hours depending on the sampling time. Excretion is almost entirely via the urine in the form of unchanged drug and the major metabolite 1,2,4 triazole-3-carboxamide. Insignificant amounts of drug are removed by haemodialysis. Ribavirin is still detectable in the plasma up to 4 weeks after cessation of therapy. In subjects with normal renal and liver functions, the unchanged drug was found to have a plasma half-life ranging from 18-164 hours. The half-life of ribavirin was 173 and 143 hours with impaired renal and liver functions respectively.

Special Populations:
Pediatric:
The pharmacokinetic properties for ribavirin are similar in adults and paediatric patients. Ribavirin C_{min} were similar following administration of ribavirin during 48 weeks of therapy in paediatric patients (3 to 16 years of age).

Geriatric:
Pharmacokinetic evaluations in elderly subjects have not been performed.

Renal Insufficiency:
Patients with creatinine clearance <50mL/min should not be treated with ribavirin. The multiple dose pharmacokinetics of ribavirin cannot be accurately predicted in patients with renal dysfunction. The increased AUC_{tf} appears to be due to reduction of renal and non-renal clearance in these patients.

Hepatic Insufficiency:
The effect of hepatic dysfunction was assessed after a single oral dose of ribavirin 600mg. The mean AUC_{tf} values were not significantly different in subjects with mild, moderate or severe hepatic dysfunction (Child-Pugh Classification A, B, or C) when compared to control subjects. However, the mean C_{max} values were two-fold greater in subjects with severe hepatic dysfunction when compared to control subjects.

THERAPEUTIC INDICATIONS
Ribazole (Ribavirin) is indicated in combination with recombinant interferon alfa for the treatment of chronic hepatitis C in patients 3 years of age or older with compensated liver disease previously untreated with interferon alfa or in patients 18 years of age or older who have relapsed following interferon alfa therapy.

Pediatric Use:
Evidence of disease progression, such as hepatic inflammation and fibrosis, as well as prognostic factors for response, HCV genotype and viral load, should be considered when deciding to treat a pediatric patient. The benefits of treatment should be weighed against the safety findings observed for pediatric subjects.

DOSAGE AND ADMINISTRATION
Based on results of worldwide clinical trials on ribavirin monotherapy, it showed that it is not effective for the treatment of chronic hepatitis C virus infection; therefore, Ribazole (Ribavirin) must not be used alone. For the treatment of chronic hepatitis C refractory to interferon alone, ribavirin is given daily by mouth in doses determined according to body weight.
Treatment should be initiated and monitored by a physician experienced in the management of chronic hepatitis C.

Adults. The recommended dose of Ribazole (Ribavirin) depends on the patient's body weight. 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 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.

Ribavirin/Interferon Alfa-2b Combination Therapy in Adult Patients.
Previously Untreated and Relapse Patients.

Table 1. Recommended Dosing in Combination Countered Therapy.

Body Weight	Dose	Interferon alfa 2b
≤ 75 kg	500mg b.i.d. (1000mg/day)	3 miu, 3 times weekly
> 75 kg	400mg t.i.d. or 600mg b.i.d. (1200mg/day)	3 miu, 3 times weekly

Pediatrics. The recommended dose of Ribazole (Ribavirin) is 15mg/kg per day orally (divided dose AM and PM). Refer to Table 2 below for dosing recommendations to achieve the recommended dose.

Table 2. Pediatric Dosing		
Body Weight	**Ribazole (Ribavirin)**	**Uniferon (Interferon alfa-2b)**
25-36 kg	200mg caps. in the morning 200mg caps. in the evening daily	3 miu, 3 times weekly s.c.
37-49 kg	200mg caps. in the morning 400mg caps. in the evening daily	3 miu, 3 times weekly s.c.
50-61 kg	400mg caps. in the morning 400mg caps. in the evening daily	3 miu, 3 times weekly s.c.
> 61 kg	Refer to the adult dosing table	Refer to the adult dosing table

The recommended duration of treatment is 48 weeks for pediatric patients with genotype 1. After 24 weeks of treatment, virologic response should be assessed. The recommended duration of treatment for pediatric patients with genotype 2/3 is 24 weeks. There are no safety and efficacy data on treatment for longer than 48 weeks in pediatrics. Ribazole (Ribavirin) may be administered without regard to food, but should be administered in a consistent manner with respect to food intake.

Dose Modifications [Table 3]
If severe adverse reactions or laboratory anomalies develop during combination ribavirin/interferon alfa therapy, the dose should be modified or discontinued if appropriate, until the adverse reactions abate. If intolerance persists after dose adjustment, the combination therapy should be discontinued.

Table 3. Guidelines for Dose Modifications and Discontinuation for Anemia		
Hemoglobin	**Dose Reduction Ribazole (Ribavirin) 600mg daily adults 7.5mg/kg daily for pediatrics**	**Permanent Discontinuation of Ribazole (Ribavirin) Treatment**
No Cardiac History	<10 g/dL	< 8.5 g/dL
Cardiac History patients	≥ 2g/dL decrease during any 4 week period during treatment	< 12 g/dL after 4 weeks of dose reduction

For patients with a history of stable cardiovascular disease, a permanent dose reduction is required if the hemoglobin decreases by ≥ 2g/dL after 4 weeks on a reduced dose, the patient should discontinue combination ribavirin/interferon alfa therapy.

ADVERSE REACTIONS
Ribavirin monotherapy was reasonably well tolerated and not associated with severe adverse events.
The primary toxicity of ribavirin is hemolytic anemia. Patients receiving ribavirin by mouth have experienced hemolytic anemia, sometimes with associated increased serum concentrations of bilirubin and uric acid. The most commonly reported adverse reactions with ribavirin were mostly mild to moderate in severity and were manageable without the need for modification of dosesor discontinuation of therapy. They include depression, irritability, anxiety, alopecia, nausea/vomiting, and flu like symptoms such as fatigue, pyrexia, myalgia, headache and rigors.

Ribavirin/Interferon alfa Combination Therapy
There are significant adverse events caused by ribavirin/interferon alfa combination therapy, which includes severe depression and suicidal ideation, hemolytic anemia, suppression of bone marrow function, autoimmune and infectious disorders, pulmonary dysfunction, pancreatitis, and diabetes. It is recommended that patients be carefully monitored by the prescribing physician.
Other less frequent adverse reactions were pruritis, dermatitis, dizziness, arthralgia, neutropenia, insomnia, diarrhoea, dyspnea, dry skin and skin rashes.

Pediatric Patients
Conversely, pediatric patients experienced less fatigue, dyspepsia, arthralgia, insomnia, irritability, impaired concentration, dyspnea, and pruritis compared to adult patients.

CONTRAINDICATIONS
- Patients with a history of known hypersensitivity to ribavirin or any of its components.
- Ribavirin therapy is contraindicated for use in pregnant women or in women expected to be pregnant.
- Patients with autoimmune hepatitis must not be treated with combination of ribavirin and interferon alfa therapy because use of these medicines can worsen the hepatitis.
- Patients with hemoglobinopathies (e.g. thalassemia major, sickle-cell anemia) should not be treated with ribavirin.
- Patients with a history of severe pre-existing cardiac disease, including unstable or uncontrolled cardiac disease.

SPECIAL WARNINGS & PRECAUTIONS
Haemolysis and cardiovascular system
– The primary toxicity of ribavirin is haemolytic anemia, which was observed in approximately 10% ribavirin/interferon alfa combination therapy treated patients. The anemia associated with ribavirin therapy occurs within 1-2 weeks of initiation therapy. Because the initial drop in hemoglobin may be significant, it is advised that hemoglobin or hematocrit be obtained pre-treatment and at week 2 and week 4 of therapy, or more frequently if clinically indicated. Patients should then be followed as clinically appropriate.
– Although ribavirin has no direct cardiovascular effects, anemia 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; 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.

Liver function: In patients who develop evidence of hepatic decompensation during treatment, ribavirin in combination with interferon alfa 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.

Psychiatric and Central Nervous System (CNS): Severe CNS effects such as depression, suicidal ideation, suicide, aggressive behaviour, confusion and alterations of mental status have been observed in some patients during ribavirin combination therapy with interferon alfa. If patients develop psychiatric or CNS problems, including clinical depression, it is recommended that patients be carefully monitored by the prescribing physician. If symptoms persist or worsen, discontinue both ribavirin and/or interferon alfa.

Renal impairment: The pharmacokinetics of ribavirin is altered in patients with renal dysfunction due to reduction of apparent clearance. 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.
There is insufficient data on the safety and efficacy of ribavirin in such patients to support recommendations for dose adjustments. Ribavirin therapy should not be initiated (or continued if renal impairment occurs while on treatment) in such patients, whether or not on hemodialysis, unless it is considered to be essential. Extreme caution is required. Uric acid may increase with ribavirin due to hemolysis and therefore the potential development of gout must be carefully monitored in predisposed patients.

Pregnancy: Extreme care must be taken to avoid pregnancy in female patients and in partners of male patients. Ribavirin accumulates intracellularly and is cleared from the body very slowly. 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 and their partners must use 2 forms of effective contraception simultaneously, during treatment and for 6 months after treatment has been concluded. Routine monthly pregnancy tests must be performed during this time.

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
There is no clinically relevant interaction when ribavirin is concomitantly administered with antacids.

Nucleoside analogues
Zidovudine and stavudine: 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): Ribavirin potentiated the antiretroviral effect of didanosine (ddI) *in vitro* and in animals by increasing the formation of the active triphosphate anabolite (ddATP). This observation also raised the possibility that concomitant administration of ribavirin and ddI might increase the risk of adverse reactions related to ddI (such as peripheral neuropathy, pancreatitis, and hepatic steatosis with lactic acidosis). While the clinical significance of these findings is unknown, one study of concomitant ribavirin and ddI in patients with HIV disease did not result in further reductions in viraemia or an increase in adverse reactions. Plasma pharmacokinetics of ddI was not significantly affected by concomitant ribavirin, although intracellular ddATP was not measured.

STORAGE
Store below 30°C.
Protect from sunlight & moisture.

The expiration date refers to the product correctly stored in the required conditions.

HOW SUPPLIED
1. Ribazole (Ribavirin) 400mg Capsules are available in blister packs of 10 capsules.
2. Ribazole (Ribavirin) 500mg Tablets are available in blister packs of 10 tablets.

Keep out of reach of children.

Getz pharma (PVT) LIMITED
www.getzpharma.com
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