Ribavirin *(Copegus, Rebetol, Ribasphere)*

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Drug Summary

Ribavirin has been an integral component of hepatitis C therapy. The use of ribavirin with interferon or peginterferon for the treatment of hepatitis C is no longer recommended due to the poor efficacy and high rate of adverse effects with this regimen. Currently, still plays a role on a limited basis in combination with some direct-acting antiviral agents and combinations. Dosing of ribavirin is somewhat complicated and includes fixed-dose and weight-based ribavirin, with dosing depending on the genotype and brand of ribavirin used. In addition, ribavirin can cause severe anemia and dose adjustment is required in some patients who develop anemia.

Adverse Effects

Two potentially serious ribavirin-associated adverse effects are listed as black box warnings.

- Hemolytic Anemia: Ribavirin can cause a potentially severe hemolytic anemia. The hemolytic anemia can occur suddenly and can result in worsening of cardiac disease, even leading to myocardial infarction. The hemolytic anemia most often occurs within 1 to 2 weeks after starting therapy. Accordingly, patients should have a hematocrit and/or hemoglobin checked prior to starting therapy and at week 2 and 4 of therapy.
- Birth Defects: Ribavirin can cause significant teratogenic and embyocidal effects, including potential birth defects and fetal death. Ribavirin should not be used by women during pregnancy or in male partners of women who are pregnant. For women who will receive treatment with ribavirin, a documented negative pregnancy test is required immediately prior to starting ribavirin therapy and women should use two or more forms of birth control and have monthly pregnancy testing during treatment and for 6 months thereafter. Further, pregnancy should be avoided for at least 6 months after completing ribavirin therapy (for females who have taken ribavirin and for females partners

of males who have taken ribavirin).

Other less serious adverse effects have been observed with ribavirin, including fatigue, nausea, rash, and itching. To report suspected adverse reactions, contact (1) the ribavirin manufacturer or (2) the FDA at 1-800-FDA-1088.

Class and Mechanism

Ribavirin is a purine nucleoside analog that has an incompletely understood mechanism of action against hepatitis C virus. Investigators have proposed four main potential sites of ribavirin action against hepatitis C virus: (1) augmentation of host T-cell immune clearance of HCV, (2) inhibition of the host enzyme inosine monophosphate dehydrogenase (IMPDH) that results in depleted pools of guanosine triphosphate, an essential substrate for viral RNA synthesis (3) direct inhibition of HCV replication, and (4) induction of RNA virus mutagenesis that drives HCV to an abonormally high error rate.

Indications

The indications for ribavirin depend on the brand of ribavirin used, with the major distinction whether ribavirin is approved for use with peginterferon alfa-2a or peginterferon alfa-2b.

- Ribavirin (*Copegus*) is approved for use with peginterferon alfa-2a (*Pegasys*) for the treatment of chronic hepatitis C with compensated liver disease.
- Ribavirin (*Rebetol*) tablet formulation is approved for use with peginterferon alfa-2a (*Pegasys*) for the treatment of chronic hepatitis C with compensated liver disease.
- Ribavirin (*Ribasphere*) capsule formulation is approved for use with interferon alfa-2b (*Intron A*) and peginterferon alfa-2b (*PegIntron*) for the treatment of chronic hepatitis C.Ribavirin (*Ribasphere*) is approved for use with interferon alfa-2b (*Intron A*) and peginterferon alfa-2b (*PegIntron*) for the treatment of chronic hepatitis C.
- Recently, the NS5a polymerase inhibitor sofosbuvir (*Sovaldi*) was approved by the FDA for use with ribavirin to treat chronic hepatitis C genotype 2 and 3 infection, and for patients with genotype 1 who are interferon ineligible.
- Ribavirin should never be used as monotherapy for the treatment of hepatitis C virus.
- For all preparations, ribavirin is contraindicated in (1) pregnant women and male partners of females who are pregnant, (2) patients with hemoglobinopathies, and (3) coadministration with didanosine (*Videx*).

Dosing

Ribavirin is available in 200 mg, 400 mg, 500 mg, and 600 mg capsules and tablets. In addition, ribavirin is available in an oral (liquid) solution. The availability of specific strength depends on the brand of the ribavirin.

- Ribavirin (*Copegus*) is available in 200 mg tablets and should be taken with food. The daily dose when given as fixed dosing is 800 mg per day in two divided doses. When given as weight-based, the dose

is 1000 mg/day for persons less than 75 kg and 1200 mg/day for those 75 kg or greater.
- Ribavirin (*Rebetol*) is available in 200 mg capsules and oral solution (40 mg/ml) taken with food. The daily dose of ribavirin ranges from 800 to 1400 mg given in two divided doses. The daily dose when given as fixed dosing is 800 mg in two divided doses. When given as weight-based, the dose is 800 mg/day for body weight less than 66 kg, 1000 mg/day for 66 to 80 kg, 1200 mg/day for 81 to 105 kg, and 1400 mg/day for those greater than 105 kg; in all instances, the ribavirin is given in two divided doses.
- Ribavirin (*Ribasphere*) is available in 200 mg, 400 mg, and 600 mg tablets and 200 mg capsules and should be taken with food. The daily dose of ribavirin ranges from 800 mg to 1200 mg/day when given with peginterferon alfa-2a. If given with peginterferon alfa-2b, the dose of ribavirin ranges from 800 mg to 1400 mg/day.
- The levels of ribavirin increase significantly in patients with renal insufficiency. Patients with a creatinine clearance 30 to 60 mL/min have a twofold increase in ribavirin area under the curve (AUC) and those with a creatinine clearance 10 to 30 mL/min have a threefold increase in ribavirin AUC. Ribavirin is not significantly removed by dialysis.
- Ribavirin requires dosage modification in patients who have a creatinine clearance less than 50 mL/min and the exact dosage adjustment should be made based on the prescribing information for the specific brand of ribavirin used.
- Ribavirin levels are not significantly impacted by mild, moderate, or severe hepatic dysfunction.

Cost and Medication Access

Rebetol Patient Assistance: For information regarding reimbursement support services for ribavirin (*Rebetol*), see the ACT Program website or call 866-363-6379. This is the same patient assistance program for peginterferon alfa-2b (*Pegintron*).

Copegus Patient Assistance: For information regarding coverage, reimbursement, and patient assistance for *Copegus*), visit the Access Solutions website or call 888-941-3331. This is the same patient assistance program for peginterferon alfa-2a (*Pegasys*).

Ribasphere, RibapakPatient Assistance: For information regarding reimbursement support services for ribavirin (*Rebetol*), contact the Kadmon Enabling Your Success (K.E.Y.S.) Program at 888-668-3393.

Key Drug Interactions

For complete information on ribavirin-related drug interactions, see the Drug Interactions section in the Ribavirin (*Copegus, Rebetol, Ribasphere*) Prescribing Information.

Full Prescribing Information

Full Prescribing Information for *Rebetol* capsules and oral soluation.

Prescribing Information for *Copegus* tablets.

Full Prescribing Information for *Ribasphere* tablets

Full Prescribing Information for *Ribasphere* capsules

Figures

Figure 1. Bottle - Ribavirin (*Copegus*)

Photo: Andrew Karpenko, University of Washington

Figure 1. Tablets - Ribavirin (*Copegus*)

Photo: Andrew Karpenko, University of Washington

Figure 2. Tablets - Ribavirin (Generic from Sandoz)

Photo: Andrew Karpenko, University of Washington

Figure 3. Capsules - Ribavirin (Generic from Teva)

Photo: Andrew Karpenko, University of Washington