Ribavirin

Class: Nucleosides and Nucleotides
VA Class: AM800
Chemical Name: 1-β-D-Ribofuranosyl-1H-1,2,4-triazole-3 carboxamide
CAS Number: 36791-04-5
Brands: Copegus, Rebetol, Ribasphere, Virazole

Warning(s)

Oral Ribavirin

- Ribavirin *not* effective *alone* for treatment of chronic HCV infection; do *not* use ribavirin monotherapy for this indication.[34e 37i 40i 40j]
- Principal toxicity of oral ribavirin is hemolytic anemia which may result in worsening of cardiac disease and has resulted in fatal and nonfatal MI.[34e 37i 40i 40k] Do not use ribavirin in patients with a history of clinically important or unstable cardiac disease.[34e 37i 40i 40j]
- Teratogenic and/or embryocidal effects demonstrated in all animal species exposed to ribavirin.[34e 37i 40i 40k] Ribavirin has a long half-life (12 days after multiple doses) and may persist in nonplasma compartments for as long as 6 months.[34e 37i 40i 40j]
- Contraindicated in pregnant women and male partners of pregnant women.[34e 37i 40i 40k] Extreme care must be used to avoid pregnancy during and for 6 months following ribavirin therapy in female patients and female partners of male patients receiving ribavirin.[34e 37i 40i 40j] Must use at least 2 reliable forms of contraception during and for 6 months following completion of treatment.[34e 37i 40i 40j]

Ribavirin Nasal and Oral Inhalation

- Aerosolized ribavirin (ribavirin for nasal and oral inhalation) should be used in patients requiring mechanical ventilator assistance only if clinicians and support staff are familiar with this mode of administration and the specific ventilator being used.[1] Strict attention must be directed to procedures that minimize accumulation of drug precipitate, which can result in mechanical ventilator dysfunction and associated increased pulmonary pressure.[1]
- Initiation of aerosolized ribavirin in infants has resulted in sudden deterioration of respiratory function.[1] Monitor respiratory function carefully during treatment.[1] If sudden deterioration of respiratory function occurs, discontinue the drug.[1] Reinstitute only with extreme caution and continuous monitoring; consider concomitant administration of a bronchodilator.[1]
- Ribavirin for nasal and oral inhalation is *not* indicated in adults.[1]

Introduction

Antiviral agent; nucleoside derivative.[1 4i 6i 7i 9i 11i 22i 166]

Uses for Ribavirin

Chronic HCV Infection

Treatment of chronic HCV infection in adults and pediatric patients with compensated liver disease.[9,11,34,34,36,37,40,40,41,42,42,42] Used in conjunction with peginterferon alfa (peginterferon alfa-2a, peginterferon alfa-2b)[11,34,34,36,37,37,38,38,40,40,41,42,42,42,42] or, less frequently, with nonconjugated interferon alfa-2b.[32,32,32,32,33,33,33,33,33,34,34,36,40,42]

Treatment of chronic HCV genotype 1 infection in adults with compensated liver disease; used in conjunction with peginterferon alfa (alfa-2a or alfa-2b) and an HCV nonstructural 3/4A (NS3/4A) protease inhibitor (i.e., boceprevir, telaprevir).[11,12,18,18,38]

Do *not* use alone for treatment of chronic HCV infection.[34,37,40,40]

Goal of antiviral therapy is sustained suppression of HCV replication and prevention of HCV-related complications (e.g., necroinflammation, fibrosis, cirrhosis, hepatocellular carcinoma) and death.[9,12] When making decisions regarding treatment, consider severity of liver disease, HCV genotype, treatment history, potential for serious adverse reactions, likelihood of treatment response, presence of coexisting conditions, and patient's readiness for treatment.[9,11,12,12]

American Association for the Study of Liver Diseases (AASLD) and other experts state peginterferon alfa used in conjunction with oral ribavirin is the standard of care for treatment of HCV infection (genotypes 2, 3, 4, 5, 6) in treatment-naive patients (have not previously received interferon alfa therapy) and also is recommended for previously treated patients following failure of prior therapy (nonconjugated interferon alfa monotherapy, concomitant nonconjugated interferon alfa and oral ribavirin).[9,11,12,12]

For initial treatment of chronic HCV genotype 1 infection in treatment-naive adults, AASLD and other experts state that an NS3/4A protease inhibitor (i.e., boceprevir, telaprevir) in conjunction with peginterferon alfa and oral ribavirin is the standard of care.[11,12] This regimen also recommended for retreatment in adults who had virologic relapse or were partial responders after prior treatment with other regimens (nonconjugated interferon alfa or peginterferon alfa with or without ribavirin).[11,12]

Safety and efficacy of ribavirin tablets (Copegus, Ribasphere) used in conjunction with peginterferon alfa-2a not established in patients who are previous nonresponders to interferon therapy.[37,40]

Safety and efficacy of oral ribavirin in conjunction with peginterferon alfa *not* established for treatment of chronic HCV infection in patients with decompensated liver disease,[34,37,40,40] HBV coinfection,[34,40] or liver or other organ transplants.[34,37,38,40,40]

Oral ribavirin in conjunction with peginterferon alfa-2a (Pegasys) is used for treatment of chronic HCV infection in adults with compensated liver disease who are coinfected with HIV and have clinically stable HIV disease and $CD4^+$ T-cell counts >100 cells/mm^3.[9,12,12,19,37,38,42] Safety and efficacy not established in HCV and HIV coinfected patients with $CD4^+$ T-cell counts <100 cells/mm^3.[37,40]

Manufacturers state safety and efficacy of oral ribavirin used in conjunction with peginterferon alfa-2b (PegIntron) or interferon alfa-2b (Intron A) not established in patients with HCV and HIV coinfection.[34,40]

Treatment of chronic HCV infection is complex and rapidly evolving; consult a specialist to obtain the most up-to-date information regarding patient selection criteria and preferred regimens.[9,11,12,12]

Respiratory Syncytial Virus (RSV) Infection

Ribavirin nasal and oral inhalation used for treatment of severe lower respiratory tract infections (i.e., bronchiolitis, pneumonia) caused by RSV in hospitalized infants and young children.[1,16,41,45,75,76,88,90,91,100,101,105,196,197,202,277,278,401,410,411,412,413,414,415,416,417,418]

Should be considered *only* for infants and small children with *severe* RSV lower respiratory tract infections; use in mechanically ventilated patients *only* if clinicians and support staff are familiar with the mode of administration and specific ventilator being used.[1]

AAP states ribavirin nasal and oral inhalation therapy should *not* be used routinely in children with bronchiolitis, but may be considered in children with documented severe RSV bronchiolitis that is potentially life-threatening and in those at risk for severe disease (e.g., immunocompromised, hemodynamically important cardiopulmonary disease).[105,405]

Not indicated for treatment of RSV infection in adults.[1]

Viral Hemorrhagic Fevers

Treatment of viral hemorrhagic fevers†, including Lassa fever, Hantavirus infections, infections caused by New World arenaviruses, and Crimean-Congo hemorrhagic fever.[105,337,340,344,351,388,392]

Only antiviral identified to date that exhibits potential efficacy for management of viral hemorrhagic fevers; however, ribavirin provides benefit only in some (not all) of these infections.[340,344,351] Has some activity against Arenaviridae and Bunyaviridae, but is inactive against Filoviridae and most Flaviviridae.[340,344,351]

Considered the drug of choice for treatment of Lassa fever†.[59,104,105,177,178,219,257,259,340,351] Previously recommended for postexposure prophylaxis of Lassa fever in high-risk contacts,[219] but CDC no longer recommends such prophylaxis.[397] Instead, exposed individuals or contacts should be placed under medical surveillance for 21 days and treated presumptively with ribavirin if clinical evidence of viral hemorrhagic fever develops.[397]

Treatment of hemorrhagic fever with renal syndrome† (HFRS)[105,270,271,272,276] (designated an orphan drug by FDA for this use).[273]

Treatment of Crimean-Congo hemorrhagic fever† (CCHF).[105,347,388,392] Although experience limited, CDC states use of ribavirin to treat the disease and prevent infection in high-risk contacts is reasonable based on in vitro susceptibility data for this and other Bunyaviridae.[219]

Treatment of clinically evident viral hemorrhagic fever in the context of biologic warfare or bioterrorism† when the disease is caused by Arenavirus (e.g., Lassa fever, New World hemorrhagic fever) or Bunyavirus (e.g., Rift Valley fever) or is of unknown etiology.[340,351,357] Preemptive administration of ribavirin or postexposure prophylaxis with ribavirin not recommended following known or presumed exposure to hemorrhagic fever virus in the context of biologic warfare or bioterrorism.[351] Those with known or presumed exposure, including high-risk contacts (i.e., individuals with mucous membrane contact with infected patient) and close contacts (i.e., individuals who live with, shake hands or hug, process laboratory specimens from, or care for infected patients [prior to initiation of appropriate precautions]) should be placed under medical surveillance for 21 days and treated presumptively with ribavirin if fever ≥38.3°C develops.[351]

Information on diagnosis and management of viral hemorrhagic fevers is available from Special Pathogens Branch of CDC at or at 404-639-1115 or 404-639-2888.[337,397] Clinicians should immediately notify CDC's Special Pathogens Branch of any suspected cases of viral hemorrhagic fever occurring in individuals residing in or requiring evacuation to the US.[337] In addition, state health departments should notify Division of Global Migration and Quarantine (DGMQ) at CDC regarding possible travel-related exposures to ensure that prompt risk assessments, notifications, and appropriate containment measures are implemented for exposed

travelers.[397]

Adenovirus Infections

Has been used for treatment of infections caused by adenovirus† in immunocompromised adults and children, including bone marrow or stem cell transplant recipients, solid organ transplant recipients (e.g., liver, kidney), and patients with leukemia or severe combined immunodeficiency.[393 394 395 396]

Safety and efficacy not established;[340 377] only limited experience to date.[393 394 395 396]

Generally has been used in critically ill patients with severe adenovirus infections (e.g., hemorrhagic cystitis, nephritis, respiratory tract infections, GI infections, disseminated disease) who received multiple treatment modalities.[393 395 396] Not all patients respond;[393 394 396] unlikely to be of benefit if initiated late in the course of severe infections.[393]

Has been used for preemptive therapy in immunocompromised patients who were asymptomatic but had clinical cultures positive for adenovirus.[395] Possible benefits and risks in such patients not determined; asymptomatic adenovirus infections often resolve spontaneously.[395]

Severe Acute Respiratory Syndrome (SARS)

Has been used empirically in some adults and a limited number of children with severe acute respiratory syndrome† (SARS), alone or in conjunction with systemic corticosteroids; [367 368 369 370 371 372 380 381 382] clinical benefit of the various anti-infective regimens employed to date, including ribavirin, have been disappointing.[368 369 373]

Ribavirin Dosage and Administration

Administration

Administer orally[340 377 402 403] or by nasal and oral inhalation.[1] Also has been administered IV†.[102 270 271 272 276 389 390 394 395 396 397]

Oral Administration

Administer ribavirin capsules,[340 402] tablets,[377 402] and oral solution[340] with food.

Do not open, crush, or break capsules.[340 403]

Oral solution containing 40 mg of ribavirin per mL recommended (instead of capsules) in children ≥3 years of age weighing <47 kg.[349] The oral solution may be used in any patient ≥3 years of age, regardless of weight.[349]

Patients should be well hydrated, especially during initial treatment.[340 377 402 403]

Nasal and Oral Inhalation

Ribavirin sterile powder (Virazole) must be reconstituted and diluted and administered as a solution *only* via nasal and oral inhalation using the Valeant small-particle aerosol generator (SPAG) Model SPAG-2 available from the manufacturer.[1 162] *Do not administer using any other aerosol generator and do not administer concomitantly with other drug solutions for nebulization.*[1]

Consult the SPAG-2 manual for detailed administration instructions.[1 162]

In patients not requiring mechanical ventilation, ribavirin solution for nebulization should be administered from the SPAG-2 aerosol generator via an oxygen hood.[1,162] If an oxygen hood cannot be used, the solution may be administered from the SPAG-2 aerosol generator via a face mask or oxygen tent;[1,162] because the volume and condensation area of the solution for nebulization are larger in an oxygen tent, this may alter delivery dynamics of the drug.[1]

When ribavirin inhalation therapy is used in patients who require assisted ventilation, constantly monitor the patient and apparatus (e.g., in an intensive care setting).[182,183] Use either a pressure or volume cycle ventilator in conjunction with the SPAG-2.[1] For pressure or volume cycle ventilators, heated wire connective tubing and bacterial filters in series in the expiratory limb of the system must be used to minimize the risk of ribavirin precipitation in the system and risk of ventilator dysfunction; the filters should be changed frequently (e.g., every 4 hours).[1] Water column pressure release valves should be used in the ventilator circuit for pressure cycle ventilators and may be used in the ventilator circuit for volume cycle ventilators.[1] The endotracheal tube should be suctioned every 1–2 hours; monitor pulmonary pressure frequently (every 2–4 hours).[1]

Reconstitution and Dilution

Add a minimum of 75 mL of sterile water for injection or inhalation (additive free) to the vial containing 6 g of ribavirin; shake well.[1,162] Transfer reconstituted solution to the sterile 500-mL reservoir of the SPAG-2 aerosol generator; further dilute with sterile water for injection or inhalation (additive free) to a final volume of 300 mL to provide a solution containing 20 mg/mL.[1,162]

Solutions that have been placed into the SPAG-2 reservoir should be discarded at least every 24 hours and prior to the addition of freshly reconstituted solution whenever the amount of solution remaining in the reservoir is low.[1,162]

Rate of Administration

When 20-mg/mL solution is delivered using the SPAG-2 aerosol generator according to the manufacturer's instructions, the average aerosol concentration for a 12-hour delivery period is 190 mcg/L.[1]

Administer the 20-mg/mL solution via the SPAG-2 aerosol generator at a rate of about 15 L/minute when using an oxygen hood or tent or about 12 L/minute when using a face mask.[162]

Parenteral Administration

Although not commercially available, parenteral ribavirin is available for compassionate use protocols for treatment of viral hemorrhagic fevers† such as Lassa fever†, Hantavirus infections†, and Congo-Crimean hemorrhagic fever†.[337] To obtain IV ribavirin for emergency use, contact FDA for compassionate use authorization and also contact the manufacturer (Valeant Pharmaceuticals) at 800-548-5100.[337]

Dosage

Pediatric Patients

Treatment of Chronic HCV Infection

Must be used in conjunction with peginterferon alfa or nonconjugated interferon alfa.[34,37,403]

Concomitant Ribavirin Capsules (Rebetol, Ribasphere) or Oral Solution (Rebetol) and Peginterferon Alfa-2b (PegIntron) or Interferon Alfa-2b (Intron A)

Oral

Children 3–17 years of age: 15 mg/kg daily in 2 divided doses in conjunction with sub-Q peginterferon alfa-2b or interferon alfa-2b.[349 403] (See Table 1.) Use oral solution in those weighing <47 kg.[349] If patient reaches 18th birthday during treatment, complete treatment using pediatric dosage.[349 403]

Recommended treatment duration is 24 weeks for HCV genotype 2 or 3 and 48 weeks for genotype 1.[349 403]

With the exception of HCV genotypes 2 and 3, consider discontinuing HCV treatment if HCV RNA levels have not decreased ≥2 $\log_{10}$ from baseline at week 12 or remain detectable after 24 weeks of treatment.[349 403]

Table 1. Pediatric Dosage of Ribavirin Capsules (Rebetol, Ribasphere) or Oral Solution (Rebetol) for Concomitant Use with Peginterferon Alfa-2b (PegIntron) or Nonconjugated Interferon Alfa-2b (Intron A)349403

Weight	Ribavirin Dosage (Capsules, Oral Solution)
<47 kg	15 mg/kg daily, given as oral solution in 2 divided doses
47–59 kg	400 mg in morning and 400 mg in evening
60–73 kg	400 mg in morning and 600 mg in evening
>73 kg	600 mg in morning and 600 mg in evening

Concomitant Ribavirin Tablets (Copegus) and Peginterferon Alfa-2a (Pegasys)

Oral

Children ≥5 years of age: Approximately 15 mg/kg daily in 2 divided doses in conjunction with sub-Q peginterferon alfa-2a.[377] (See Table 2.) If patient reaches 18th birthday during treatment, complete treatment using pediatric dosage.[377]

Recommended treatment duration is 24 weeks for HCV genotype 2 or 3 and 48 weeks for other HCV genotypes.[377]

Table 2. Pediatric Dosage of Ribavirin Tablets (Copegus) for Concomitant Use with Peginterferon Alfa-2a (Pegasys)377

Weight	Copegus Dosage (Tablets)
23–33 kg	200 mg in morning and 200 mg in evening
34–46 kg	200 mg in morning and 400 mg in evening
47–59 kg	400 mg in morning and 400 mg in evening
60–74 kg	400 mg in morning and 600 mg in evening
>75 kg	600 mg in morning and 600 mg in evening

Dosage Modification for Toxicity

Oral

If serious adverse effects or laboratory changes occur when oral ribavirin used in conjunction with

peginterferon alfa or nonconjugated interferon alfa, modify dosage of one or both drugs, if appropriate, until adverse effects abate.[349 377 403] If intolerance persists after dosage adjustment, discontinue both drugs.[349 377 403]

Concomitant ribavirin *capsules* or *oral solution* (Rebetol, Ribasphere) and peginterferon alfa-2b or nonconjugated interferon alfa-2b in children 3–17 years of age: If hemoglobin <10 g/dL, decrease ribavirin dosage from 15 mg/kg daily to 12 mg/kg daily and, if needed, to 8 mg/kg daily.[349 401] If hemoglobin <8.5 g/dL, leukocyte count <1000/mm^3, neutrophil count <500/mm^3, or platelet count <50,000/mm^3, permanently discontinue both drugs.[349 401] In pediatric patients with preexisting cardiac conditions, closely monitor with weekly hematology evaluations if hemoglobin decreases by ≥2 g/dL during any 4-week period; discontinue if hemoglobin concentration <8.5 g/dL (or <12 g/dL after 4 weeks of reduced dosage).[349]

Concomitant ribavirin *tablets* (Copegus) and peginterferon alfa-2a in children ≥5 years of age without cardiac disease: If hemoglobin <10 g/dL, decrease ribavirin dosage to 200 mg daily (200 mg in morning) in those weighing 23–33 kg, 400 mg daily (200 mg in morning and 200 mg in evening) in those weighing 34–59 kg, or 600 mg daily (200 mg in morning and 400 mg in evening) in those weighing ≥60 kg.[377] If hemoglobin <8.5 g/dL, discontinue both drugs.[377]

Concomitant ribavirin *tablets* (Copegus) and peginterferon alfa-2a in children ≥5 years of age with history of stable cardiac disease: If hemoglobin decreases by ≥2 g/dL during any 4-week period, decrease ribavirin dosage to 200 mg daily (200 mg in morning) in those weighing 23–33 kg, 400 mg daily (200 mg in morning and 200 mg in evening) in those weighing 34–59 kg, or 600 mg daily (200 mg in morning and 400 mg in evening) in those weighing ≥60 kg.[377] If hemoglobin <12 g/dL after 4 weeks of reduced dosage, discontinue both drugs.[377]

Consult manufacturer's information for more specific recommendations regarding dosage modification for hematologic or other adverse effects.[349 377 403]

Treatment of Respiratory Syncytial Virus (RSV) Infection

Inhalation

Using a solution containing 20 mg/mL and SPAG-2 aerosol generator with an oxygen hood, face mask, or oxygen tent, deliver mist continuously for 12–18 hours daily for 3–7 days.[1 162] Manufacturer recommends mist be delivered at a rate of about 15 L/minute when using an oxygen hood or tent or about 12 L/minute when using a face mask.[162] The average aerosol concentration for a 12-hour delivery period is 190 mcg/L.[1]

Dose and administration schedule for infants requiring mechanical ventilation is the same as that for infants not requiring assisted ventilation.[1]

Viral Hemorrhagic Fevers†

Treatment of Viral Hemorrhagic Fevers in Context of Biologic Warfare or Bioterrorism†

Oral

US Army Medical Research Institute of Infectious Diseases (USAMRIID) and US Working Group on Civilian Biodefense recommend initial loading dose of 30 mg/kg, followed by 15 mg/kg daily given in 2 divided doses.[343 351] Duration of treatment is 10 days.[349 351]

IV regimen usually preferred.[349 351] Oral regimen may be used when parenteral preparation cannot be obtained or would be impractical (e.g., when large numbers of individuals require treatment in a mass casualty setting).[349 351]

IV†

US Working Group on Civilian Biodefense recommends initial loading dose of 30 mg/kg (maximum 2 g), followed by 15 mg/kg (maximum 1 g) every 6 hours for 4 days and then 8 mg/kg (maximum 500 mg) every 8 hours for 6 days.[351]

IV regimen recommended for contained casualty settings if parenteral preparation can be obtained.[351]

Treatment of Adenovirus Infections†

IV†

Severe infections in immunocompromised children: 25 mg/kg daily in 3 divided doses on day 1 followed by 15 mg/kg daily in 3 divided doses on days 2–10 has been used.[393] Alternatively, 15 mg/kg daily for 10 days has been used.[396]

Adults

Treatment of Chronic HCV Infection

Must be used in conjunction with peginterferon alfa or nonconjugated interferon alfa.[340, 377, 402, 403]

Concomitant Ribavirin Capsules (Rebetol, Ribasphere) and Peginterferon Alfa-2b (PegIntron)

Oral

800–1400 mg daily (based on body weight) in 2 divided doses in conjunction with sub-Q peginterferon alfa-2b.[340, 402] (See Table 3.) Duration of treatment depends on history of prior treatment, HCV genotype, and treatment response.[340, 402] (See Table 4.)

Table 3. Adult Dosage of Ribavirin Capsules (Rebetol, Ribasphere) for Concomitant Use with Peginterferon Alfa-2b (PegIntron) for Chronic HCV Infection.349403

Weight	Total Daily Dosage of Ribavirin (Capsules)	Recommended Ribavirin Dosage Regimen (Capsules)
≤65 kg	800 mg	400 mg in morning and 400 mg in evening
66–80 kg	1 g	400 mg in morning and 600 mg in evening
81–105 kg	1.2 g	600 mg in morning and 600 mg in evening
>105 kg	1.4 g	600 mg in morning and 800 mg in evening

Table 4. Duration of Treatment with Ribavirin Capsules (Rebetol, Ribasphere) and Peginterferon Alfa-2b (PegIntron) in Adults for Chronic HCV Infection.349403

Patient Type and Response	HCV Genotype	Duration	Considerations
Treatment-naive	1	48 weeks	Consider discontinuing HCV treatment if HCV RNA has not decreased ≥2 $\log_{10}$ by week 12 or remains detectable after 24

			weeks of treatment[34c 403]
Treatment-naive	2,3	24 weeks	
Prior failure	Any	48 weeks	Consider discontinuing HCV treatment if HCV RNA still detectable at week 12 or remains detectable after 24 weeks of treatment[34c 403]

Concomitant Ribavirin Capsules (Rebetol, Ribasphere) and Interferon Alfa-2b (Intron A)

Oral

Adults weighing ≤75 kg: 1 g daily (400 mg in morning and 600 mg in evening) in conjunction with sub-Q interferon alfa-2b.[34c 403]

Adults weighing >75 kg: 1.2 g daily (600 mg in morning and 600 mg in evening) in conjunction with sub-Q interferon alfa-2b.[34c 403]

Duration of treatment depends on history of prior treatment, HCV genotype, and treatment response.[34c 403] In treatment-naive adults, usual duration is 24–48 weeks; consider discontinuing if HCV RNA levels are not below the limit of detection at 24 weeks.[34c 403] If used in adults who relapsed after prior nonconjugated interferon monotherapy, manufacturers recommend treatment duration of 24 weeks.[34c 403]

Concomitant Ribavirin Tablets (Copegus, Ribasphere) and Peginterferon Alfa-2a (Pegasys)

Oral

Adults with HCV monoinfection (without coexisting HIV infection): 800–1200 mg daily in 2 divided doses in conjunction with sub-Q peginterferon alfa-2a.[377i 402] Treatment duration depends on HCV genotype.[377i 402] (See Table 5.)

Table 5. Adult Dosage of Ribavirin Tablets (Copegus, Ribasphere) for Concomitant Use with Peginterferon Alfa-2a (Pegasys) for Chronic HCV Monoinfection377402

HCV Genotype	Ribavirin Dosage (Tablets)	Duration
1,4	1 g daily (500 mg twice daily) in those weighing <75 kg	48 weeks
	1.2 g daily (600 mg twice daily) in those weighing ≥75 kg	
2,3	800 mg daily (400 mg twice daily)	24 weeks
5,6	Data insufficient to make dosage recommendations	–

Adults with HCV and HIV coinfection: 800 mg daily in 2 divided doses in conjunction with sub-Q peginterferon alfa-2a for 48 weeks, regardless of HCV genotype.[377i 402] Some experts suggest HIV-infected adults with HCV coinfection types 1, 4, 5, or 6 receive weight-based ribavirin dosage: 1 g daily (600 mg in morning and 400 mg in evening) for those weighing <75 kg or 1.2 g daily (600 mg in morning and 600 mg in evening) for those weighing ≥75 kg.[190]

Consider discontinuing HCV treatment if HCV RNA levels have not decreased ≥2 $\log_{10}$ from baseline at week 12 or are still detectable after 24 weeks of treatment.[377i 402]

Manufacturer states safety and efficacy beyond 48 weeks of therapy not established.[377i 402]

Dosage Modification for Toxicity

Oral

If serious adverse effects or laboratory changes occur when oral ribavirin used in conjunction with peginterferon alfa or nonconjugated interferon alfa, modify dosage of one or both drugs, if appropriate, until adverse effects abate.[34e 37i 40i 40s] If intolerance persists after dosage adjustment, discontinue both drugs.[34e 37i 40i 40s]

Ribavirin *capsules* (Rebetol, Ribasphere) and peginterferon alfa-2b or interferon alfa-2b in adults: If hemoglobin decreases to <10 g/dL, decrease ribavirin dosage by 200 mg daily (or by 400 mg daily in those originally receiving 1.4 g daily); an additional dosage reduction of 200 mg daily may be used if needed.[34e 40s] If hemoglobin <8.5 g/dL, leukocyte count <1000/mm^3, neutrophil count <500/mm^3, or platelet count <25,000/mm^3, permanently discontinue both drugs.[34e 40s] In those with history of stable cardiovascular disease, decrease ribavirin dosage by 200 mg daily if hemoglobin decreases by ≥2 g/dL during any 4-week period; discontinue if hemoglobin <8.5 g/dL (or <12 g/dL after 4 weeks of reduced dosage).[34g]

Ribavirin *tablets* (Copegus, Ribasphere) and peginterferon alfa-2a in adults: In those without cardiac disease, decrease ribavirin dosage to 600 mg daily (200 mg in morning and 400 mg in evening) if hemoglobin decreases to <10 g/dL; discontinue the drug if hemoglobin decreases to <8.5 g/dL.[37i 40i] In those with history of stable cardiac disease, decrease ribavirin dosage to 600 mg daily (200 mg in morning and 400 mg in evening) if hemoglobin decreases by ≥2 g/dL during any 4-week period; discontinue the drug if hemoglobin decreases to <12 g/dL after 4 weeks of reduced dosage.[37i 40i] If ribavirin tablets have been withheld and toxicity resolves or decreases in severity, may attempt reinitiation using ribavirin dosage of 600 mg daily; may then increase ribavirin dosage to 800 mg daily if tolerated.[37i 40i] Do *not* resume usual maximum recommended adult dosage of 1–1.2 g daily (see Table 5).[37i 40i]

Consult manufacturer's information for more specific recommendations regarding dosage modification for hematologic or other adverse effects.[34e 37i 40i 40s]

Viral Hemorrhagic Fevers†

Treatment of Lassa Fever†

IV†

CDC and USAMRIID recommend initial loading dose of 30 mg/kg (up to 2 g), followed by 16 mg/kg (up to 1 g) every 6 hours for 4 days and then 8 mg/kg (up to 500 mg) every 8 hours for 6 days for total treatment duration of 10 days.[21e 34s]

Treatment of Hantavirus Infections†

IV†

Hemorrhagic fever with renal syndrome† (HFRS): Initial loading dose of 33 mg/kg, followed by 16 mg/kg every 6 hours for 4 days and then 8 mg/kg every 8 hours for 3 days for a total treatment duration of 7 days has been used.[27c 27i 27s]

Treatment of Crimean-Congo Hemorrhagic Fever†

Oral

Initial loading dose of 30 mg/kg, followed by 15 mg/kg every 6 hours for 4 days and then 7.5 mg/kg every 8 hours for 6 days has been used.[39e]

IV†

CDC and USAMRIID recommend initial loading dose of 30 mg/kg (up to 2 g), followed by 16 mg/kg (up to 1 g) every 6 hours for 4 days and then 8 mg/kg (up to 500 mg) every 8 hours for 6 days for a total treatment duration of 10 days.[219,343]

Treatment of Viral Hemorrhagic Fevers in Context of Biologic Warfare or Bioterrorism†

Oral

USAMRIID and US Working Group on Civilian Biodefense recommend initial loading dose of 2 g, followed by 1.2 daily given in 2 divided doses for those weighing >75 kg or 1 g daily (400 mg in morning and 600 mg in evening) for those weighing ≤75 kg.[340,351] Duration of treatment is 10 days.[340,351]

IV regimen usually preferred.[340,351] Oral regimen may be used when parenteral preparation cannot be obtained or would be impractical (e.g., when large numbers of individuals require treatment in a mass casualty setting).[340,351]

IV†

USAMRIID and US Working Group on Civilian Biodefense recommend initial loading dose of 30 mg/kg (maximum 2 g), followed by 15 mg/kg (maximum 1 g) every 6 hours for 4 days and then 8 mg/kg (maximum 500 mg) every 8 hours for 6 days.[340,351]

IV regimen recommended for contained casualty settings if parenteral preparation can be obtained.[340,351]

Treatment of Adenovirus Infections†

IV†

Severe infections in immunocompromised adults: Initial 33-mg/kg loading dose followed by 16 mg/kg every 6 hours for 4 days and then 8 mg/kg every 8 hours for another 3 days or longer until relevant cultures are negative for adenovirus.[394,396]

Special Populations

Hepatic Impairment

Effect of hepatic impairment on pharmacokinetics of oral ribavirin not fully evaluated;[340,377,402,403] peak concentrations are increased depending on severity of hepatic impairment.[340,403] (See Pharmacokinetics.)

Renal Impairment

Ribavirin tablets (Copegus): Reduce dosage in adults with Cl_{cr} ≤50 mL/minute.[377] For treatment of chronic HCV infection, use alternating doses of 200 mg and 400 mg every other day in adults with Cl_{cr} 30–50 mL/minute and use 200 mg daily in adults with Cl_{cr} <30 mL/minute or undergoing hemodialysis.[377] Do not reduce dosage any further; if severe adverse effects or laboratory abnormalities occur, discontinue drug.[377] Data insufficient to make dosage recommendations for pediatric patients with renal impairment.[377]

Ribavirin capsules (Rebetol, Ribasphere),[340,403] tablets (Ribasphere),[402] oral solution (Rebetol) and peginterferon alfa-2b or interferon alfa-2b therapy:[340] Contraindicated in adults with Cl_{cr} <50 mL/minute.[340,402,403]

Pediatric patients with renal impairment: Discontinue ribavirin capsules or oral solution (Rebetol) and

peginterferon alfa-2b or interferon alfa-2b if S_{cr} concentrations >2 mg/dL.[349]

Geriatric Patients

Cautious dosage selection because of age-related decreases in renal, hepatic, and/or cardiac function.[346 403] Initiate therapy at the lower end of the dosing range.[346 403] (See Geriatric Precautions under Cautions.)

Cautions for Ribavirin

Contraindications

Oral Ribavirin

- Hypersensitivity to ribavirin or any ingredient in the formulation.[346 377 402 403] (See Sensitivity Reactions under Cautions.)
- Women who are or may become pregnant.[346 377 402 403] (See Fetal/Neonatal Morbidity and Mortality under Cautions.)
- Male partners of pregnant women.[346 377 402 403]
- Patients with hemoglobinopathies (e.g., thalassemia major, sickle cell anemia).[346 377 402 403]
- Concomitant use with didanosine.[346 377 402 403] (See Interactions.)
- Use of ribavirin capsules (Rebetol, Ribasphere), tablets (Ribasphere), and oral solution (Rebetol) in patients with Cl_{cr} <50 mL/minute.[346 402 403]
- Use of concomitant oral ribavirin and peginterferon alfa in patients with autoimmune hepatitis.[346 377 402 403]
- Use of concomitant oral ribavirin tablets (Copegus, Ribasphere) and peginterferon alfa-2a in cirrhotic patients with chronic HCV monoinfection (without coexisting HIV infection) who have hepatic decompensation (Child-Pugh score >6; class B and C) prior to or during treatment.[377 402]
- Use of concomitant oral ribavirin tablets (Copegus, Ribasphere) and peginterferon alfa-2a in cirrhotic patients with chronic HCV infection who are coinfected with HIV and have hepatic decompensation (Child-Pugh score ≥6) prior to or during treatment.[377 402]

Ribavirin Nasal and Oral Inhalation

- Hypersensitivity to ribavirin or any ingredient in the formulation.[1] (See Sensitivity Reactions under Cautions.)
- Women who are or may become pregnant.[1] (See Fetal/Neonatal Morbidity and Mortality under Cautions.)

Warnings/Precautions

Warnings

Concomitant Peginterferon Alfa or Interferon Alfa

Must *not* be used alone for treatment of chronic HCV infection.[346 377 402 403]

When used in conjunction with peginterferon alfa or interferon alfa, consider cautions, precautions, and contraindications associated with both oral ribavirin and peginterferon alfa or interferon alfa.[346 377 402 403]

When used in conjunction with peginterferon alfa *and* an HCV NS3/4A protease inhibitor (i.e., boceprevir, telaprevir), also consider cautions, precautions, and contraindications associated with the HCV NS3/4A protease inhibitor.[184 185] If serious skin reaction occurs during oral ribavirin, peginterferon alfa, and telaprevir therapy, immediately discontinue all 3 drugs and promptly refer patient for urgent medical care.[14 184]

Ribavirin in conjunction with peginterferon alfa or interferon alfa is associated with substantial adverse effects including severe depression and suicidal ideation, hemolytic anemia, bone marrow suppression, autoimmune and infectious disorders, pulmonary dysfunction, pancreatitis, and diabetes.[34 377 402 403] Review prescribing information and medication guide prior to initiation of therapy.[34 377 402 403]

Respiratory Effects

Use of aerosolized ribavirin for treatment of RSV in infants has resulted in sudden deterioration of respiratory function.[1] Monitor respiratory function carefully.[1] If sudden deterioration of respiratory function occurs, discontinue therapy.[1] Reinstitute with extreme caution and continuous monitoring; consider concomitant administration of a bronchodilator.[1]

Optimum monitoring and attention to respiratory and fluid status needed in patients with severe lower respiratory tract infection due to RSV.[1]

Use of oral ribavirin has been associated with adverse pulmonary effects, including dyspnea, pulmonary infiltrates, pulmonary hypertension, pneumonitis, and pneumonia (sometimes fatal).[34 377 402 403] Sarcoidosis or exacerbation of sarcoidosis reported rarely with oral ribavirin.[34 377 402 403]

Closely monitor patients who experience pulmonary infiltrates or deterioration in pulmonary function; if appropriate, discontinue ribavirin.[34 377 402 403]

Mechanically Ventilated Patients

Administer aerosolized ribavirin under the supervision of and by qualified clinicians and support staff experienced with the specific ventilator and mode of administration.[1] (See Nasal and Oral Inhalation under Dosage and Administration.)

Fetal/Neonatal Morbidity and Mortality

Teratogenic and/or embryocidal.[34 377 402 403] Exercise extreme care to avoid pregnancy in female patients and in female partners of male patients.[34 377 402 403] Women of childbearing potential and men must use 2 forms of effective contraception during therapy and for 6 months following completion of therapy.[34 377 402 403]

Do not initiate therapy until a report of a negative pregnancy test has been obtained; the pregnancy test should be performed immediately prior to initiating therapy.[34 377 402 403] Perform pregnancy testing monthly during therapy and for 6 months after therapy is completed.[34 377 402 403]

If pregnancy occurs in a patient or in the partner of a patient during oral ribavirin therapy or during the 6 months following completion of therapy, report such cases to the pregnancy registry at 800-593-2214.[34 377 402 403]

Hematologic Effects

Hemolytic anemia reported in patients receiving oral ribavirin in conjunction with interferon alfa; anemia usually occurs 1–2 weeks after initiation of therapy.[34 377 402 403] Use with caution in patients with baseline risk of severe anemia (e.g., spherocytosis, history of GI bleeding).[377 402]

Monitor hemoglobin or hematocrit before initiating therapy, at week 2 and 4 (or more frequently if needed),

and during therapy as appropriate.[34] [37] [40] [40] Dosage modification may be necessary.[34] [37] [40] [40] (See Treatment of Chronic HCV Infection under Dosage and Administration.)

Cardiovascular Effects

Fatal and nonfatal MI reported in patients with anemia due to oral ribavirin.[34] [37] [40] [40]

Assess patient for cardiac disease before initiating therapy and monitor during therapy.[34] [37] [40] [40] Obtain an electrocardiogram in patients with known cardiac disease.[34] [37] [40] [40]

Temporarily interrupt or discontinue therapy if cardiovascular status deteriorates.[34] [37] [40] [40] Dosage modification may be necessary.[34] [37] [40] [40] (See Treatment of Chronic HCV Infection under Dosage and Administration.)

Not recommended in those with substantial or unstable cardiac disease.[34] [37] [40] [40]

Hepatic Failure

Patients with chronic HCV infection and cirrhosis may be at risk of hepatic decompensation and death during interferon alfa (including peginterferon alfa) therapy.[34] [37] [40] [40] Such patients who are coinfected with HIV and receiving highly active antiretroviral therapy (HAART) in conjunction with interferon alfa-2a therapy (with or without ribavirin) appear to be at increased risk for development of hepatic decompensation compared with patients not receiving HAART.[34] [37] [40] [40]

Closely monitor clinical status and hepatic function.[34] [37] [40] [40] Decrease dosage or immediately discontinue peginterferon alfa if decompensation (Child-Pugh score ≥6) occurs.[34] [37] [40] [40]

Sensitivity Reactions

Serious skin reactions, including Stevens-Johnson syndrome, toxic epidermal necrolysis, and erythema multiforme, reported in patients receiving peginterferon with or without oral ribavirin.[34] [37] [40] [40]

If acute hypersensitivity reactions (urticaria, angioedema, bronchoconstriction, anaphylaxis) occur, discontinue immediately and initiate appropriate medical intervention.[37] [40]

General Precautions

Other Viral Infections

Safety and efficacy of oral ribavirin in the treatment of HIV infection, adenovirus infection, RSV infection, parainfluenzae virus infection, or influenza virus infection have not been established; oral ribavirin should not be used for these indications.[34] [37] [40] [40]

Pancreatitis

Temporarily interrupt oral ribavirin in patients with manifestations of pancreatitis; discontinue in patients with confirmed pancreatitis.[34] [37] [40] [40]

Dental and Periodontal Disorders

Dental and periodontal disorders reported in patients receiving oral ribavirin in conjunction with peginterferon alfa or interferon alfa; dry mouth may contribute to damage of teeth and oral mucous membranes during long-term treatment.[34] [40]

Advise patients to have regular dental examinations during treatment, brush their teeth thoroughly twice daily,

and rinse their mouth thoroughly after vomiting.[349,403]

Environmental Exposure of Health-care Personnel and Visitors

The potential risks, particularly for long-term and cumulative effects, associated with environmental exposure to aerosolized ribavirin by health-care personnel and visitors while in contact with patients undergoing inhalation therapy with the drug have not been elucidated; acute effects do not appear to be substantial.[187,188,189,192,195,200,216,217,227,228,229,234,235,236,237,238,239,240,241,242,243,247,261,266,267] Exposure of pregnant women[187,188,216,217,218,228,227,228,234,238,239,240,241,242,243,244,247,266,268,267] and possibly those who may become pregnant[187,188,216,268] may represent a risk to the fetus. Consult specialized sources (e.g., National Institute for Occupational Safety and Health [NIOSH]) for recommended procedures to minimize environmental exposure.

Specific Populations

Pregnancy

Category X.[1,349,377,402,403] (See Fetal/Neonatal Morbidity and Mortality under Cautions.)

Pregnancy Registry at 800-593-2214 to monitor pregnancy outcomes of female patients and female partners of male patients exposed to ribavirin.[349,377,402,403]

Lactation

Not known whether ribavirin is distributed into human milk.[349,377,402,403] Discontinue nursing or delay or discontinue the drug.[349,377,402,403]

Pediatric Use

Nasal and oral inhalation: Safety and efficacy established for treatment of RSV infection in infants and young children.[1]

Ribavirin oral capsules (Rebetol, Ribasphere) and oral solution (Rebetol): Safety and efficacy in conjunction with peginterferon alfa-2b or nonconjugated interferon alfa-2b for treatment of chronic HCV infection not established in children <3 years of age.[349,403] When deciding whether to use such regimens in HCV-infected children, consider evidence of disease progression (hepatic inflammation, fibrosis), prognostic factors for response, HCV genotype, and viral load.[349,403] Weigh benefits against adverse effects reported in pediatric patients.[349,403] Do not use concomitant ribavirin capsules or oral solution (Rebetol) and peginterferon alfa-2b or nonconjugated interferon alfa-2b in pediatric patients with S_{cr} >2 mg/dL.[349]

Ribavirin tablets (Copegus): Safety and efficacy in conjunction with peginterferon alfa-2b for treatment of chronic HCV infection not established in children <5 years of age.[377]

Ribavirin tablets (Ribasphere): Safety and efficacy not established in patients <18 years of age.[402]

Adverse effects reported with oral ribavirin in pediatric patients generally similar to those reported in adults.[349,377] Suicidal ideation or attempts reported more frequently during or after oral ribavirin in pediatric patients (primarily adolescents) than in adults receiving the drug.[349] Other adverse psychiatric effects (depression, emotional lability, somnolence), anemia, and neutropenia reported as in adults.[349]

Decreased weight and height for age z-scores as well as percentiles of the normative population reported in pediatric patients receiving peginterferon alfa and oral ribavirin therapy;[349,377,403] generally return to baseline normative growth curve percentiles for weight and height at end of 2-year follow-up after completion of

treatment.[346,377,403]

Geriatric Use

Insufficient experience in patients ≥65 years of age to determine whether geriatric patients respond differently than younger adults.[346,377,402,403] Higher incidence of anemia reported in geriatric patients compared with younger adults.[346,403]

Caution advised; start at the lower end of the dosing range due to greater frequency of decreased renal, hepatic, and/or cardiac function and of concomitant disease and drug therapy observed in the elderly.[346,403]

Substantially eliminated by kidneys; risk of adverse effects increased in patients with renal impairment.[346,403] Monitor renal function and consider age-related decreases in renal function when selecting dosage.[346,403] (See Renal Impairment under Dosage.)

Hepatic Impairment

Do not use in patients with autoimmune hepatitis or hepatic decompensation.[346,377,402,403] (See Contraindications under Cautions.)

Monitor liver function before and during therapy.[346,377,402]

Renal Impairment

Capsules (Rebetol, Ribasphere),[346,403] tablets (Ribasphere),[402] oral solution (Rebetol)[349]: Contraindicated in patients with Cl_{cr} <50 mL/minute.[346,403]

Tablets (Copegus): Use reduced dosage in adults with Cl_{cr} <50 mL/minute.[377] (See Renal Impairment under Dosage.)

Common Adverse Effects

Oral: Fatigue/asthenia, headache, fever, rigors, nausea, myalgia, emotional lability/irritability.[346,377,402,403]

Nasal and oral inhalation: Respiratory and cardiovascular effects.[1]

Interactions for Ribavirin

Does not inhibit and is not a substrate for CYP450 isoenzymes.[346,377] Interactions with drugs affecting or metabolized by CYP enzymes unlikely.[346,377]

Specific Drugs

Drug	Interaction	Comments
Antacids containing magnesium, aluminum, and simethicone (Mylanta)	Decreased ribavirin concentrations[349]	Clinical importance unknown[349]

Antiretrovirals, nucleoside reverse transcriptase inhibitors (NRTIs)	Possible increased risk of potentially fatal hepatic decompensation in cirrhotic patients with chronic HCV coinfected with HIV who are receiving peginterferon alfa (with or without ribavirin) and antiretroviral regimens that include NRTIs[371,387] Didanosine: Fatal hepatic failure, peripheral neuropathy, pancreatitis, symptomatic hyperlactatemia/lactic acidosis reported[346,377] Zidovudine: Possible increased risk of severe neutropenia (ANC <500/mm^3) and severe anemia (hemoglobin <8 g/dL) if used concomitantly with peginterferon alfa and ribavirin[371,387] Ribavirin can reduce phosphorylation of lamivudine, stavudine, and zidovudine; no evidence of pharmacokinetic or pharmacodynamic interaction when ribavirin used concomitantly with these drugs in patients coinfected with HCV and HIV[346,377] Stavudine and zidovudine: In vitro evidence of antagonistic antiretroviral effects; possibility of increased risk of adverse effects[173,222,275,346,352,355,364,377]	If used in patients coinfected with HIV who are receiving NRTIs, closely monitor for toxicities;[371,387] if worsening toxicities are observed, consider discontinuing or reducing dosage of peginterferon and/or ribavirin;[371,387] if decompensation occurs (Child-Pugh score ≥6), discontinue[387] Didanosine: Concomitant use contraindicated[200,346,371,402,403] Stavudine: Use concomitantly with caution[220,349,371,402,403] Zidovudine: Avoid concomitant use or use with caution and increased monitoring[200,222,346,377,402,403]
Azathioprine	Severe pancytopenia and bone marrow suppression reported in patients receiving peginterferon alfa and oral ribavirin;[346,371,402,403] may be due to interaction with ribavirin which may increase accumulation of azathioprine metabolite associated with myelotoxicity[346,371,402,403]	If used concomitantly with oral ribavirin and peginterferon alfa, perform CBCs (including platelet counts) weekly for first month, twice monthly during second and third months, and then monthly or more frequently if necessary[349,371,402,403] If pancytopenia develops, discontinue all 3 drugs (azathioprine, ribavirin, peginterferon alfa) and do not reinitiate peginterferon alfa and ribavirin concomitantly with azathioprine[349,371,402,403]
Interferons (interferon alfa, peginterferon alfa)	Hepatic decompensation, including some fatalities, reported in cirrhotic HCV patients coinfected with HIV receiving ribavirin, peginterferon alfa, and NRTIs[346,371,402,403] Ribavirin may potentiate hematologic effects of interferons (anemia, neutropenia, lymphocytopenia);[387,388] no evidence of pharmacokinetic interaction[377]	

Ribavirin Pharmacokinetics

Absorption

Bioavailability

Absorbed rapidly from GI tract; peak plasma concentrations achieved within 1–3 hours.[34,37] Bioavailability is 64%.[34,49]

Following nasal and oral inhalation, absorbed systemically from the respiratory tract.[1] Concentrations achieved in respiratory tract secretions are likely to be substantially greater than those achieved in plasma.[1,4,16]

Food

Administration with a high-fat meal increases oral bioavailability.[34,37]

Special Populations

Mean peak plasma concentrations increased with severity of hepatic impairment; mean AUCs in individuals with mild, moderate, or severe hepatic impairment similar to AUCs in controls.[34,49]

Following a single oral dose of ribavirin, AUC increased twofold or threefold in non-HCV-infected individuals with Cl_{cr} 30–60 or 10–30 mL/minute, respectively.[34,49]

In HCV-infected individuals with end-stage renal disease requiring hemodialysis, ribavirin 200 mg daily (Copegus tablets) produced plasma exposures about 20% lower than exposures achieved with 1–1.2 g daily in individuals with normal renal function.[37,77]

Distribution

Extent

Ribavirin and/or its metabolites accumulate in erythrocytes.[1,4,16,22,61,132,133,134,140,193]

Distributes slowly into CSF.[76,166] CSF concentrations approximately 70% of concurrent plasma concentrations reported in HIV-infected patients.[78]

Not known whether ribavirin crosses the placenta[152] or distributes into milk in humans.[1]

Plasma Protein Binding

Not bound.[34,49]

Elimination

Metabolism

Undergoes reversible phosphorylation in nucleated cells and deribosylation and amide hydrolysis.[34,49]

Elimination Route

Following oral administration, eliminated in urine (61%) and feces (12%) as metabolites and unchanged drug (17%).[34,49]

Half-life

Rebetol capsules: 43.6 hours (single dose) and 298 hours (multiple doses).[349]

Copegus tablets: 120–170 hours (single dose).[377]

Special Populations

Clearance reduced in patients with renal impairment.[349]

Stability

Storage

Nasal and Oral Inhalation

For Inhalation Solution

25°C (may be exposed to 15–30°C).[1] Following reconstitution, store solution under sterile conditions at 20–30°C for up to 24 hours.[1]

After placement in SPAG-2 reservoir, discard unused solution within 24 hours and prior to adding any newly reconstituted solution (e.g., when remaining amount of solution in reservoir is low).[1]

Oral

Capsules

25°C (may be exposed to 15–30°C).[349,403]

Oral solution

2–8°C or 25°C (may be exposed to 15–30°C).[349]

Tablets

25°C (may be exposed to 15–30°C).[377,402]

Actions and Spectrum

- Exact mechanism of antiviral activity not fully elucidated,[1,3,4] but appears to interfere with RNA[3,7,21,22,34,35,140,149,166] and DNA synthesis[3,7,35,36,38,140,149,166] and subsequently inhibit protein synthesis[21,22] and viral replication.[3,15,16,22,33,148,157]
- Antiviral activity appears to depend principally on intracellular conversion to ribavirin-5′-triphosphate[3,4,6,7,16,20,22,24,140,149,161] and -monophosphate.[3,4,7,16,24,25,140,149,161]
- Ribavirin is active in vitro against many RNA viruses including respiratory syncytial virus (RSV);[1,44,60,61,64] many strains of influenza A[1,7,16,22,31,40,44,50,55,56,61,66,68,70,166] and B[1,7,16,22,31,40,44,50,55,56,61,66,68,166] viruses; measles virus;[7,16,18,22,31,44,46,68,82,141,166] subacute sclerosing panencephalitis virus;[16,19,22,31,61,68,82,166] parainfluenzae viruses;[7,16,22,31,44,46,50,61,62,68,82,166] mumps virus;[7,40,61,68,69] enterovirus 72 (formerly hepatitis A virus);[43,148] human rhinoviruses;[7,16,22,31,40,68,82,166] human reovirus 1,[7,40,46] 2,[40] and 3;[40] human rotavirus;[7] Colorado tick fever virus;[57,61] human immunodeficiency virus (HIV);[15,46,48,54,175,195] Crimean-Congo hemorrhagic fever virus;[215] Junin virus (causes Argentine hemorrhagic fever);[68,198,186] various hantaviruses (including those causing Korean hemorrhagic fever and

hantavirus pulmonary syndrome);[164 165] yellow fever virus;[66] Lassa fever virus;[81] and Machupo virus (causes Bolivian hemorrhagic fever).[66] The drug also has antiviral activity in vivo against hantavirus,[51 66 163] Lassa fever virus,[16 22 40 51 61 71 81] and Rift Valley fever virus.[40 51 66 71] Some viruses, including arboviruses,[7 31 40 66 71 144] rhinoviruses,[7] and rotaviruses,[7 40 144] that are inhibited in vitro by ribavirin may not be inhibited in vivo.

- Ribavirin has antiviral activity in vitro against many DNA viruses including herpes simplex types 1 (HSV-1)[16 22 31 40 45 50 61 65 67 68 82 166] and 2 (HSV-2);[7 16 22 31 40 50 52 61 67 68 82 166] human cytomegalovirus;[7 16 22 31 40 67 68 166] and human adenovirus.[7 16 22 31 40 50 67 68 82 166] Cytomegalovirus may not be susceptible to the drug in vivo.[7 31 40 144] In vitro, ribavirin has some activity against variola virus,[383] vaccinia virus[7 16 22 31 38 40 50 67 68 82 85 166 176 383] and other orthopoxviruses including camelpox,[85] cowpox,[85 383] and monkeypox.[85 383] Although ribavirin was active against cowpox virus in a mouse model, the in vivo activity of the drug against poxvirus infections (including smallpox) in humans has not been evaluated to date.[176]

Advice to Patients

- Advise patient of the benefits and risks of therapy for chronic HCV infection.[34 37 402 403] Importance of reading the medication guide.[34 37 402 403]
- Effect of therapy on transmission of HCV unknown; appropriate precautions to prevent transmission should be used.[34 37]
- Possibility of anemia; necessity of laboratory monitoring.[34 37 402 403]
- Importance of adequate hydration, especially during the initial phase of therapy.[34 37 402 403]
- Importance of taking ribavirin as instructed; importance of taking with food.[34 37 402 403]
- Potential for the drug to impair mental alertness or physical coordination; use caution when driving or operating machinery until effects on individual known.[37 402]
- Importance of informing clinician of existing or contemplated concomitant therapy, including prescription and OTC drugs and dietary or herbal products, and any concomitant illnesses.[34 37]
- Importance of women informing clinicians if they are or plan to become pregnant or plan to breast-feed.[34 37 402 405] Advise men and women of importance of using effective contraception during and for 6 months after ribavirin therapy.[34 37 402 405] (See Fetal/Neonatal Morbidity and Mortality under Cautions.)
- Importance of advising patients of other important precautionary information.[34 37] (See Cautions.)

Preparations

Excipients in commercially available drug preparations may have clinically important effects in some individuals; consult specific product labeling for details.

* available from one or more manufacturer, distributor, and/or repackager by generic (nonproprietary) name

Ribavirin

Routes	Dosage Forms	Strengths	Brand Names	Manufacturer
Nasal and Oral Inhalation	For inhalation solution	6 g	Virazole	Valeant
Oral	Capsules	200 mg*	Rebetol	Merck
			Ribasphere	Kadmon

			Ribavirin Capsules	
	Solution	40 mg/mL	Rebetol	Merck
	Tablets, film-coated	200 mg*	Copegus	Genentech
			Ribasphere	Kadmon
			Ribavirin Tablets	
		400 mg*	Ribasphere	Kadmon
			Ribavirin Tablets	
		600 mg*	Ribasphere	Kadmon
			Ribavirin Tablets	

Comparative Pricing

This pricing information is subject to change at the sole discretion of DS Pharmacy. This pricing information was updated 02/2014. Actual costs to patients will vary depending on the use of specific retail or mail-order locations and health insurance copays.

Rebetol 200MG Capsules (SCHERING): 60/$554.02 or 180/$1,633.06

Rebetol 40MG/ML Solution (SCHERING): 100/$223.98 or 300/$614.94

Ribasphere 200MG Capsules (KADMON PHARMACEUTICALS): 30/$135.61 or 90/$360.96

Ribavirin 200MG Capsules (SANDOZ): 56/$260.01 or 168/$776.02

† Use is not currently included in the labeling approved by the US Food and Drug Administration.

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