VENTURA COUNTY
HEALTH CARE PLAN

Prior Authorization DRUG Guidelines

RIBAVIRIN (Copegus, Rebetol, Ribapak, Ribasphere, Ribatab)

Effective Date: 1/28/14

Date Developed: 1/28/14 by Catherine Sanders, MD
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Ribavirin is an antiviral agent used in the treatment of Hepatitis C and Respiratory syncytial viral infections in children. It Inhibits replication of RNA and DNA viruses; inhibits influenza virus RNA polymerase activity and inhibits the initiation and elongation of RNA fragments resulting in inhibition of viral protein synthesis.

Pre-Authorization Criteria:
Ribavirin in oral capsule form is indicated, in combination with interferon alfa 2b (pegylated or nonpegylated) injection, for the treatment of chronic hepatitis C in interferon alfa-naive or experienced-patients with compensated liver disease. Patients likely to fail retreatment after a prior failed course include previous nonresponders, those who received previous pegylated interferon treatment, patients who have significant bridging fibrosis or cirrhosis, or those with genotype 1 infection.

Ribavirin in oral solution form is indicated, in combination with interferon alfa-2b (pegylated or nonpegylated) injection, for the treatment of chronic hepatitis C in interferon alfa-naive or experienced patients ≥3 years of age with compensated liver disease. Patients likely to fail retreatment after a prior failed course include previous nonresponders, those who received previous pegylated interferon treatment, patients who have significant bridging fibrosis or cirrhosis, or those with genotype 1 infection.

Ribavirin in oral tablet form is indicated, in combination with peginterferon alfa-2a (Pegasys®) injection, for the treatment of chronic hepatitis C in patients with compensated liver disease who were previously untreated with alpha interferons, and in adult chronic hepatitis C patients coinfected with HIV.

Ribavirin for inhalation use is applicable for treatment of hospitalized infants and young children with respiratory syncytial virus (RSV) infections, specifically those patients with severe lower respiratory tract RSV infections with an underlying compromising condition of prematurity, cardiopulmonary disease or immunosuppression.

Ribarin unlabeled uses include treatment for RSV in adult hematopoietic stem cell or heart/lung transplant recipients and in other viral infections including influenza A and B and adenovirus and are not covered.

VCHCP requires that Ribavirin be prescribed by a gastroenterologist or a Hepatitis C Clinic physician or, in the case of use for pediatric patients with RSV, a Pediatric Pulmonologist or Intensivist.

Medication Guide:
An FDA-approved patient medication guide, which is available with the product information and as follows, must be dispensed with this medication:
Copegus®: http://www.fda.gov/downloads/Drugs/DrugSafety/ucm088576.pdf,
Rebetol®: http://www.fda.gov/downloads/Drugs/DrugSafety/ucm089017.pdf
Ribasphere®: http://www.fda.gov/downloads/Drugs/DrugSafety/ucm111342.pdf

Dosing: Adult:
Note: Oral solution may be used those unable to swallow capsules.
Chronic hepatitis C monoinfection (in combination with peginterferon alfa-2b): *Oral capsule, oral solution (Rebetol®, Ribasphere®):* Note: Recommended therapy duration [manufacturer labeling]: Genotype 1: 48 weeks; genotypes 2,3: 24 weeks); recommended therapy duration for patients who previously failed therapy: 48 weeks [regardless of genotype])
≤65 kg: 800 mg daily (400 mg in the morning and evening)
66-80 kg: 1000 mg daily (400 mg in the morning, 600 mg in the evening)
81-105 kg: 1200 mg daily (600 mg in the morning, 600 mg in the evening)
>105 kg: 1400 mg daily (600 mg in the morning, 800 mg in the evening)

Chronic hepatitis C monoinfection (in combination with interferon alfa-2b): *Oral capsule (Rebetol®, Ribasphere®):* Note: Individualized therapy duration [manufacturer labeling] 24-48 weeks):
≤75 kg: 1000 mg daily (400 mg in the morning, 600 mg in the evening)
>75 kg: 1200 mg daily (600 mg in the morning, 600 mg in the evening)

Chronic hepatitis C monoinfection (in combination with peginterferon alfa-2a): *Oral tablet (Copegus®, Ribasphere®):*
Genotype 1,4:
<75 kg: 1000 mg daily in 2 divided doses for 48 weeks
≥75 kg: 1200 mg daily in 2 divided doses for 48 weeks
Genotype 2,3: 800 mg daily in 2 divided doses for 24 weeks

Chronic hepatitis C coinfection with HIV (in combination with peginterferon alfa-2a): *Oral tablet (Copegus®, Ribasphere®):* 800 mg daily in 2 divided doses for 48 weeks (regardless of genotype)

Alternative recommendation: American Association for the Study of Liver Diseases (AASLD) guidelines: Adults with chronic hepatitis C infection (Ghany, 2009): Treatment of choice: Ribavirin plus peginterferon; clinical condition and ability of patient to tolerate therapy should be evaluated to determine length and/or likely benefit of therapy. Recommended treatment duration (AASLD guidelines): Genotypes 1,4: 48 weeks; Genotypes 2,3: 24 weeks; Coinfection with HIV: 48 weeks.

RSV infection in hematopoietic cell or heart/lung transplant recipients (unlabeled use): Aerosol inhalation: 2000 mg (over 2 hours) every 8 hours (Boeckh, 2007; Liu, 2010)
Note: Heart/lung transplant recipients also received IVIG, methylprednisolone and palivizumab. Dosage and protocol may be institution specific. (Boeckh, 2007; Chemaly, 2006; Liu, 2010).

Dosing: Pediatric:
Chronic hepatitis C monoinfection (in combination with pegylated or nonpegylated interferon alfa-2b):

Children ≥3 years: *Oral capsule or solution (Rebetol®, Ribasphere®):* Note: Oral solution should be used in children <47 kg, or those unable to swallow capsules. Children who start treatment prior to age 18 years should continue on pediatric dosing regimen through therapy completion. Recommended therapy duration (manufacturer labeling): Genotypes 2,3: 24 weeks; all other genotypes: 48 weeks
Oral capsule, oral solution dosing recommendations:
<47 kg: 15 mg/kg/day in 2 divided doses (morning and evening) as oral solution
47-59 kg: 800 mg daily (400 mg in morning and evening)
60-73 kg: 1000 mg daily (400 mg in morning and 600 mg in the evening)
>73 kg: 1200 mg daily (600 mg in morning and evening)

Alternative recommendations: American Association for the Study of Liver Diseases (AASLD) guidelines:
Children 2-17 years with chronic hepatitis C infection (Ghany, 2009): Treatment of choice: Ribavirin 15 mg/kg daily (in combination with SubQ peginterferon alfa-2b) once weekly for 48 weeks
Chronic hepatitis C monoinfection (in combination with peginterferon alfa-2a):
Children ≥5 years: *Oral tablet (Copegus®):* Note: Assess child's ability to swallow tablet; children who start treatment prior to age 18 years should continue on pediatric dosing regimen through therapy completion. Recommended therapy duration (manufacturer labeling): Genotypes 2,3: 24 weeks; all other genotypes: 48 weeks
23-33 kg: 400 mg daily (200 mg in the morning and evening)
34-46 kg: 600 mg daily (200 mg in the morning and 400 mg in the evening)
47-59 kg: 800 mg daily (400 mg in the morning and evening)
60-74 kg: 1000 mg daily (400 mg in the morning and 600 mg in the evening)
≥75 kg: 1200 mg daily (600 mg in the morning and evening)

RSV infection: Infants and Children: *Aerosol inhalation:* Use with Viratek® small particle aerosol generator (SPAG-2): A concentration of 20 mg/mL (6 g reconstituted with 300 mL of sterile water without preservatives) administered for 12-18 hours/day for 3 days, up to 7 days in length.

Dosing: Geriatric:
Refer to adult dosing.

Dosing: Renal Impairment:
CHC infection: Oral:
Rebetol® capsules/solution, Ribasphere® capsules: Adults:
Cl_{cr} ≥50 mL/minute: No dosage adjustment necessary.
Cl_{cr} <50 mL/minute: Use is contraindicated.
Ribasphere® tablets: Adults:
Cl_{cr} ≥50 mL/minute: No dosage adjustment necessary.
Cl_{cr} <50 mL/minute: Use is not recommended.
Copegus® tablets: Adults:
Cl_{cr} >50 mL/minute: No dosage adjustment necessary.
Cl_{cr} 30-50 mL/minute: Alternate 200 mg and 400 mg every other day.
Cl_{cr} <30 mL/minute: 200 mg once daily.
ESRD requiring hemodialysis: 200 mg once daily.
Note: The dose of Copegus® should not be further modified in patients with renal impairment. If severe adverse reactions or laboratory abnormalities develop it should be discontinued, if appropriate, until the

adverse reactions resolve or decrease in severity. If abnormalities persist after restarting, therapy should be discontinued.

Dosing: Hepatic Impairment:
CHC infection: Hepatic decompensation (Child-Pugh class B and C): Manufacturer's labeling: Oral tablets: Use contraindicated.

Dosing: Adjustment for Toxicity:
Patient without cardiac history:
Hemoglobin <10 g/dL:
Children ≥3 years: Oral capsules, oral solution:
First reduction: Decrease to 12 mg/kg/day
Second reduction: Decrease to 8 mg/kg/day
Children ≥5 years: Oral tablets (Copegus®):
23-33 kg: Decrease dose to 200 mg daily (in the morning)
34-59 kg: Decrease dose to 400 mg daily (200 mg in the morning and evening)
≥60 kg: Decrease dose to 600 mg daily (200 mg in the morning and 400 mg in the evening)
Adults:
Oral capsules, oral solution:
First reduction: ≤105 kg: Decrease by 200 mg daily; >105 kg: Decrease by 400 mg daily
Second reduction: Decrease by an additional 200 mg daily (not weight-based)
Oral tablets: Decrease dose to 600 mg daily (200 mg in the morning, 400 mg in the evening)
Hemoglobin <8.5 g/dL: Children and Adults: Oral capsules, solution, tablets: Permanently discontinue treatment.
WBC <1000 mm^3, neutrophils <500 mm^3: Children and Adults: Oral capsules, solution: Permanently discontinue treatment.
Platelets <50 x 10^9/L: Children: Oral capsules, solution: Permanently discontinue treatment.
Platelets <25 x 10^9/L: Adults: Oral capsules, solution: Permanently discontinue treatment.
Creatinine (serum) >2 mg/dL: Children: Oral capsules, solution: Permanently discontinue treatment.

Patient with cardiac history:
Hemoglobin has decreased ≥2 g/dL during any 4-week period of treatment:
Children: Oral capsules, solution: Weekly evaluation and hematologic testing
Children ≥5 years: Oral tablets (Copegus®):
23-33 kg: Decrease dose to 200 mg daily (in the morning)
34-59 kg: Decrease dose to 400 mg daily (200 mg in the morning and evening)
≥60 kg: 600 mg daily (200 mg in the morning, 400 mg in the evening)
Hemoglobin has decreased >2 g/dL during any 4-week period of treatment: Adults:
Oral capsules, solution: Decrease dose by 200 mg daily
Oral tablets: 600 mg (200 mg in the morning, 400 mg in the evening)
Hemoglobin <12 g/dL after 4 weeks of reduced dose: Children and Adults: Oral capsules, solution, tablets: Permanently discontinue treatment.
Hemoglobin <8.5 g/dL: Children and Adults: Oral capsules, solution, tablets: Permanently discontinue treatment.
WBC <1000 mm^3, neutrophils <500 mm^3: Children and Adults: Oral capsules, solution: Permanently discontinue treatment.
Platelets <50 x 10^9/L: Children: Oral capsules, solution: Permanently discontinue treatment.

Platelets <25 x 10^9/L: Adults: Oral capsules, solution: Permanently discontinue treatment.
Creatinine (serum) >2 mg/dL at any time during therapy: Children: Oral capsules, solution: Permanently discontinue treatment.

Dosage Forms: U.S.:
Excipient information presented when available (limited, particularly for generics); consult specific product labeling.
Capsule, oral: 200 mg
Rebetol®: 200 mg
Ribasphere®: 200 mg
Powder for solution, for nebulization:
Virazole®: 6 g [reconstituted product contains ribavirin 20 mg/mL]
Solution, oral:
Rebetol®: 40 mg/mL (100 mL) [contains propylene glycol, sodium benzoate; bubblegum flavor]
Tablet, oral: 200 mg
Copegus®: 200 mg
Ribasphere®: 200 mg, 400 mg, 600 mg
Tablet, oral [dose-pack]:
Ribasphere® RibaPak® 600: 200 mg AM dose, 400 mg PM dose (14s, 56s)
Ribasphere® RibaPak® 800: 400 mg AM dose, 400 mg PM dose (14s, 56s)
Ribasphere® RibaPak® 1000: 600 mg AM dose, 400 mg PM dose (14s, 56s)
Ribasphere® RibaPak® 1200: 600 mg AM dose, 600 mg PM dose (14s, 56s)

Generic Equivalent Available: U.S.-Yes: Capsule, tablet

Administration:
Inhalation: Ribavirin should be administered in well-ventilated rooms (at least 6 air changes/hour). In mechanically-ventilated patients, ribavirin can potentially be deposited in the ventilator delivery system depending on temperature, humidity, and electrostatic forces; this deposition can lead to malfunction or obstruction of the expiratory valve, resulting in inadvertently high positive end-expiratory pressures. The use of one-way valves in the inspiratory lines, a breathing circuit filter in the expiratory line, and frequent monitoring and filter replacement have been effective in preventing these problems. Solutions in SPAG-2 unit should be discarded at least every 24 hours and when the liquid level is low before adding newly reconstituted solution. Should not be mixed with other aerosolized medication.
Oral: Administer concurrently with interferon alfa injection. Capsule should not be opened, crushed, chewed, or broken. Use oral solution for children <47 kg, or those who cannot swallow capsules.
Capsule, solution, tablet: Administer with food.

Hazardous agent; use appropriate precautions for handling and disposal (NIOSH, 2012).

Compatibility
Inhalation: Should not be mixed with other aerosolized medication.

Exceptions:
Ribavirin is not to be used as monotherapy in the treatment of chronic hepatitis C.

Ribavirin is not covered for use in treatment of RSV in adult hematopoietic stem cell or heart/lung transplant reciepients as this is an unlabeled use.
Ribavirin is not to be used in patients with chronic hepatitis C infection and hepatic decompensation (Child-Pugh class B and C)
Ribavirin is not covered for use in other viral infections including influenza A and B and adenovirus as this is an unlabeled use.
Ribavirin is not to be used in pregnant patient and their male partners.

Adverse Reactions:
>10%: Fatigue, headache, fever, insomnia, depression, irritability, dizziness, impaired concentration, emotional lability, alopecia, pruritus, rash, dry skin, dermatitis, growth suppression, hyperuricemia, nausea, anorexia, weight decrease, vomiting, diarrhea, dyspepsia, abdominal pain, xerostomia, RUQ pain, leukopenia, neutropenia, hemoglobin decreased, anemia, thrombocytopenia, lymphopenia, hemolytic anemia, bilirubin increase, myalgia, rigors, arthralgia, musculoskeletal pain, upper respiratory tract infection, dyspnea, cough, pharyngitis, sinusitis, flu-like syndrome, viral infection, diaphoresis.
Other Serious Less Common Reactions: aplastic anemia, pure red cell aplasia, teratogenicity, embryocidal, severe infection, severe depression, suicidal ideation, autoimmune disorders, pulmonary toxicity, pancreatitis, diabetes mellitus, hypo- or hyperthyroidism, MI, arrhythmias, colitis, retinal hemorrhage, retinal thrombosis, hypersensitivity reactions, dental/periodontal disorders.

U.S. BOXED WARNING:
Monotherapy ineffective for chronic HCV and should be avoided.
Hemolytic anemia primary clinical toxicity; may worsen cardiac disease and lead to fatal and nonfatal MI; avoid use in patients with significant or unstable cardiac disease
Teratogenic/embryocidal effects in all animal species; multiple dose half-life 12 days and may persist in non-plasma compartments <6 months; contraindicated in pregnant women and their male partners; avoid pregnancy during and for 6 months after treatment in female patients and female partners of male patients; use two forms of reliable contraception during and for 6 months after treatment.
Use with caution in patients requiring assisted ventilation because precipitation of the drug in the respiratory equipment may interfere with safe and effective patient ventilation; sudden deterioration of respiratory function has been observed.

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