Clinical Policy: ribavirin (Rebetol, Ribaspere)

Reference Number: NM.CP.PPA.09
Effective Date: 1/1/19
Last Review Date: 1/11/23
Revision Log

Description & FDA Approved Indication(s)
Ribavirin (Rebetol, and Ribasphere) is a nucleoside analogues.

Ribasphere is indicated for:

- treatment of chronic hepatitis C (CHC) virus infection in combination with Pegasys (peginterferon alfa-2a) in patients 5 years of age and older with compensated liver disease not previously treated with interferon alpha
- treatment of CHC in adult patients co-infected with HIV

Rebetol is indicated for:

- treatment of CHC in combination with interferon alfa-2b (pegylated and non-pegylated) for the treatment of CHC in patients 3 years of age or older with compensated liver disease

Limitation(s) of use: Patients with the following characteristics are less likely to benefit from re-treatment after failing a course of therapy: previous nonresponse, previous pegylated interferon treatment, significant bridging fibrosis or cirrhosis, and genotype 1 infection.

Black Box Warnings

- Teratogenicity: **Ribavirin is contraindicated in women who are pregnant and in male partners of women who are pregnant**. Two forms of contraception recommended during therapy with ribavirin and for 6 months after completion of treatment in both female patients and in female partners of male patients who are taking ribavirin.
- Ribavirin monotherapy is ineffective for treatment of chronic hepatitis C virus infection.
- Hemolytic anemia, which may result in worsening of cardiac disease and fatal and nonfatal myocardial infarctions.
- Avoid use in patients with significant or unstable cardiac disease.

Product Availability
Generic ribavirin
Oral capsule: 200 mg
Oral tablet: 200 mg
Brand: RibaTab *(All other brands have been discontinued)*
Oral tablet: 400 mg, 600 mg

Policy/Criteria

It is the policy of Western Sky Community Care (WSCC) that **ribavirin** for treatment of Hepatitis C **(Rebetol, and Ribasphere)** are **medically necessary** when the following criteria are met:

I. Initial Approval Criteria

A. Chronic Hepatitis C Infection (must meet all)**:**

1. Diagnosis of chronic hepatitis C virus (HCV) infection as evidenced by detectable serum HCV RNA levels by quantitative assay in the last 6 months;
2. Member must meet prior authorization criteria for Mavyret, Epclusa, Harvoni, Sovaldi, Zepatier, or Vosevi for combination use;
3. No current contraindications to ribavirin. See appendix F.
4. For brand Rebetol or Ribasphere requests, member must use generic ribavirin, unless contraindicated or clinically significant adverse effects are experienced
5. Member meets one of the following (a or b):
   a. For , Ribasphere: age ≥ 5 years;
   b. For Rebetol: age ≥ 3 years;
6. ****Dose does not exceed:
   a. ****, Ribasphere: 1,200 mg per day
   b. ****Rebetol: 1,400 mg per day.

Approval duration: Coincides with duration for Mavyret, Epclusa, Harvoni, Sovaldi, Zepatier, or Vosevi Authorization *(see appendix C and D for dosing)*
******If treatment regimen varies in dosing or interval from FDA or AASLD-IDSA guideline recommendations but it is documented on PA request/office chart notes that requested regimen is in consultation with Project ECHO—please approve regimen.**

B. Other diagnoses/indications

1. Refer to the off-label use policy CP.PMN.53 for Medicaid.
2. **If denial is likely please make attempt to prescriber's office for peer-to-peer.**

II. Continued Therapy

A. Chronic Hepatitis C Infection (must meet all)**:**

1. Currently receiving medication or member has previously met initial approval criteria;
2. Documentation of positive response to therapy;
3. No current contraindications to continued therapy with ribavirin. See appendix F.
4. ****If request is for a dose increase, new dose does not exceed:
   a. ****Copegus, Moderiba, Ribasphere: 1,200 mg per day
   b. ****Rebetol: 1,400 mg per day.

Approval duration: Coincides with duration for Mavyret, Epclusa, Harvoni, Sovaldi, Zepatier, or Vosevi Authorization *(see appendix C and D for dosing)*

******If treatment regimen varies in dosing or interval from FDA or AASLD-IDSA guideline recommendations but it is documented on PA request/office chart notes that requested regimen in consultation with Project ECHO—please approve regimen.**

B. Other diagnoses/indications (must meet 1 or 2)**:**

1. Currently receiving medication and documentation supports positive response to therapy.
   Approval duration: Duration of request or 12 months (whichever is less); or
2. Refer to the off-label use policy CP.PMN.53 for Medicaid.
   ***If denial is likely please make attempt to prescriber's office for peer-to-peer.**

Appendices

Appendix A: Abbreviation/Acronym Key

AASLD: American Association for the Study of Liver Diseases
APRI: AST to platelet ratio
FDA: Food and Drug Administration
FIB-4: Fibrosis-4 index
HBV: hepatitis B virus
HCC: hepatocellular carcinoma
HCV: hepatitis C virus
HIV: human immunodeficiency virus
IDSA: Infectious Diseases Society of America
IQR: interquartile range
MRE: magnetic resonance elastography
NS3/4A, NS5A/B: nonstructural protein
PegIFN: pegylated interferon
RBV: ribavirin
RNA: ribonucleic acid

***Serologic tests:**

FibroTest (available through Quest as FibroTest or LabCorp as FibroSure)
FIBROSpect II (available through Prometheus Laboratory)
APRI (AST to platelet ratio index)
FIB-4 (Fibrosis-4 index: includes age, AST level, platelet count)

†Radiologic tests:

FibroScan (transient elastography)
MRE (magnetic resonance elastography)

‡Liver biopsy (histologic scoring systems):

METAVIR F3/F4 is equivalent to Knodell, Scheuer, and Batts-Ludwig F3/F4 and Ishak F4-5/F5-6
METAVIR fibrosis stages: F0 = no fibrosis; F1 = portal fibrosis without septa; F2 = few septa; F3 = numerous septa without cirrhosis; F4 = cirrhosis

Appendix B: Direct-Acting Antivirals for Treatment of HCV Infection

Brand Name	Drug Class				
	NS5A Inhibitor	Nucleotide Analog NS5B Polymerase Inhibitor	Non-Nucleoside NS5B Palm Polymerase Inhibitor	NS3/4A Protease Inhibitor (PI)	CYP3A Inhibitor
Daklinza**	Daclatasvir				
Epclusa*	Velpatasvir	Sofosbuvir			
Harvoni*	Ledipasvir	Sofosbuvir			
Mavyret*	Pibrentasvir			Glecaprevir	
Olysio				Simeprevir	
Sovaldi		Sofosbuvir			
Technivie**	Ombitasvir			Paritaprevir	Ritonavir
Viekira XR/Pak**	Ombitasvir		Dasabuvir	Paritaprevir	Ritonavir
Vosevi*	Velpatasvir	Sofosbuvir		Voxilaprevir	
Zepatier*	Elbasvir			Grazoprevir	

*Combination drugs ***Additional PIs no longer recommended that have been discontinued*

Appendix C:
Dosing of ribavirin for Hepatitis C
The daily dose of administered orally in two divided doses and generally weight-based. The dose should be individualized to the patient depending on baseline disease characteristics (e.g., genotype), response to therapy, and tolerability of the regimen. *Low initial dose of ribavirin (600 mg) is recommended for patients with CTP class C cirrhosis; increase as tolerated.*

Body Weight (kg)	Rebetol Daily Dose	Rebetol Number of Capsules
< 66	800 mg/day	2 x 200-mg capsules A.M. 2 x 200-mg capsules P.M.
66-80	1000 mg/day	2 x 200-mg capsules A.M. 3 x 200-mg capsules P.M.
81-105	1,200 mg/day	3 x 200-mg capsules A.M. 3 x 200-mg capsules P.M.
> 105	1,400 mg/day **(MAX dose)**	3 x 200-mg capsules A.M. 4 x 200-mg capsules P.M.

Appendix D: AASLD-IDSA Recommended Regimens and Treatment Durations
https://www.hcvguidelines.org/

Appendix E:
Any of the following meet the definition for cirrhosis per NM state directives:

- APRI >= 1.0
- Fib-4 >= 3.25
- Transient Elastography Score >= 12.5 dP3 (F4 equivalent)
- Fibrotest >= 0.73 (f4 equivalent) OR Fibrometer with F4 predominance
- Radiographic imaging or physical exam findings consistent with cirrhosis
- Liver biopsy confirming a METAVIR score of F4

Child-Pugh Score:

	1 Point	2 Points	3 Points
Bilirubin	Less than 2 mg/dL Less than 34 umol/L	2-3 mg/dL 34-50 umol/L	Over 3 mg/dL Over 50 umol/L
Albumin	Over 3.5 g/dL Over 35 g/L	2.8-3.5 g/dL 28-35 g/L	Less than 2.8 g/dL Less than 28 g/L
INR	Less than 1.7	1.7 - 2.2	Over 2.2
Ascites	None	Mild / medically controlled	Moderate-severe / poorly controlled
Encephalopathy	None	Mild / medically controlled Grade I-II	Moderate-severe / poorly controlled. Grade III-IV

Child-Pugh class is determined by the total number of points: A = 5-6 points; B = 7-9 points; C = 10-15 points

Appendix F: Contraindications and Black Box Warnings
Copegus and Rebetol are contraindicated in:

- Women who are pregnant
  - For women of child-bearing age must be on at least two forms of effective contraception during treatment and for 6 months after treatment has been stopped. Pregnancy testing recommended monthly.
- Men whose female partners are pregnant
- Patients with known hypersensitivity reactions such as Stevens-Johnson syndrome, toxic, epidermal necrolysis, and erythema multiforme to ribavirin or any component of the product
- Patients with autoimmune hepatitis (when in combination with Pegasys for Copegus)
- Patients with hemoglobinopathies (e.g., thalassemia major, sickle-cell anemia)
- Co-administration with didanosine
- Copegus in combination with Pegasys is additionally contraindicated in patients with hepatic decompensation (Child-Pugh B or C) in cirrhotic CHC patients.

Boxed warning(s): risk of serious disorders and ribavirin-associated effects

References

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4. American Association for the Study of Liver Diseases/ Infectious Disease Society of America (AASLD-IDSA). HCV guidance: recommendations for testing, managing, and treating hepatitis C. Last updated October 24, 2022. Available at: https://www.hcvguidelines.org/. Accessed January 9, 2023.
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6. NM Human Services Department, Medical Assistance Division. Supplement 20-13. Uniform New Mexico Hepatitis C Virus Checklist- Repeal and Replace MAD 634 Form. Available at: https://www.hsd.state.nm.us/wp-content/uploads/2020/12/20-13-uniform-new-mexico-hepatitis-c-virus-checklist-repeal-and-replace-634.pdf Accessed January 9, 2023.
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Revision Log

Reviews, Revisions, and Approvals	Date	Approval Date
New clinical policy created for WSCC based on New Mexico requirements	11/18	11/18
Added provision for approval of drug dosing and interval (despite not meeting AASLD and IDSA recommended guidelines) if regimen is recommended/requested after consultation with Project ECHO; added Project ECHO to references	1/25/19	1/25/19
Renamed clinical policy per corporate guidelines; Changed from NM.CP.PHAR.09 to NM.CP.PPA.09; Name presented at WSCC P&T Committee	3/20/19	3/20/19
Annual Review. References updated. Reviewed and approved by WSCC P&T Committee.	1/29/20	1/29/20

Reviews, Revisions, and Approvals	Date	Approval Date
Edited criteria to match updated directive from NM HSD, MAD Supplement 20-13 to include updated forms. Updated references to reflect this change in NM Medicaid direction. Edited product availability.	1/15/21	
Annual review. Reviewed and approved by WSCC P&T Committee.		1/20/21
Removed Daklinza, Olysio, Vikiera Pak & Technivie from combination sue criteria as they are no longer commercially available; added Mavyret and Vosevi. Edited references and links to NM HCV Uniform HCV checklist.	1/7/22	
Annual review. Reviewed and approved by WSCC P&T Committee.		1/12/22
Annual Review. Updated References. Copegus, Moderiba removed from policy as they are no longer being manufactured. Added redirection to generic ribavirin. Removed requirement for Drug Authorization Form and Uniform New Mexico HCV Checklist. Reviewed and approved by WSCC P&T Committee.	1/9/23	1/11/23