Clinical Policy: Ribavirin (Rebetol, Ribasphere RibaPak)

Reference Number: CP.PHAR.141
Effective Date: 11.16.16
Last Review Date: 11.23
Line of Business: Commercial, HIM, Medicaid

Revision Log

See Important Reminder at the end of this policy for important regulatory and legal information.

Description

Ribavirin (Rebetol® and Ribasphere® RibaPak®) is a nucleoside analogue.

FDA Approved Indication(s)

Ribasphere Ribapak is indicated for the 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, and in adult CHC patients coinfected with HIV.

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

The following points should be considered when initiating Rebetol combination therapy with PegIntron® or Intron A®:

- Combination therapy with Rebetol/PegIntron is preferred over Rebetol/Intron A as this combination provides substantially better response rates.
- 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.
- No safety and efficacy data are available for treatment duration lasting longer than one year.

Policy/Criteria

Provider must submit documentation (such as office chart notes, lab results or other clinical information) supporting that member has met all approval criteria.

It is the policy of health plans affiliated with Centene Corporation® that Rebetol and Ribasphere Ribapak 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. Prescribed by or in consultation with a gastroenterologist, hepatologist, infectious disease specialist, or provider who has expertise in treating HCV based on a certified training program (*see Appendix E*);

3. Member meets prior authorization criteria for Epclusa®, Harvoni®, Mavyret®, Sovaldi®, Zepatier®, Viekira Pak®, or Vosevi® for combination use;
4. For brand Rebetol or Ribasphere Ribapak 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. Ribasphere Ribapak: Age ≥ 5 years;
   b. Rebetol: Age ≥ 3 years;
6. Dose does not exceed:
   a. Ribasphere Ribapak: 1,200 mg per day;
   b. Rebetol: 1,400 mg per day.

Approval duration: Coincides with duration for Epclusa, Harvoni, Mavyret, Sovaldi, Zepatier, Viekira Pak, or Vosevi authorization

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

1. If this drug has recently (within the last 6 months) undergone a label change (e.g., newly approved indication, age expansion, new dosing regimen) that is not yet reflected in this policy, refer to one of the following policies (a or b):
   a. For drugs on the formulary (commercial, health insurance marketplace) or PDL (Medicaid), the no coverage criteria policy for the relevant line of business: CP.CPA.190 for commercial, HIM.PA.33 for health insurance marketplace, and CP.PMN.255 for Medicaid; or
   b. For drugs NOT on the formulary (commercial, health insurance marketplace) or PDL (Medicaid), the non-formulary policy for the relevant line of business: CP.CPA.190 for commercial, HIM.PA.103 for health insurance marketplace, and CP.PMN.16 for Medicaid; or
2. If the requested use (e.g., diagnosis, age, dosing regimen) is NOT specifically listed under section III (Diagnoses/Indications for which coverage is NOT authorized) AND criterion 1 above does not apply, refer to the off-label use policy for the relevant line of business: CP.CPA.09 for commercial, HIM.PA.154 for health insurance marketplace, and CP.PMN.53 for Medicaid.

II. Continued Therapy

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

1. Member meets one of the following (a or b):
   a. Currently receiving medication via Centene benefit or member has previously met initial approval criteria;
   b. Member is currently receiving medication and is enrolled in a state and product with continuity of care regulations (*refer to state specific addendums for CC.PHARM.03A and CC.PHARM.03B);*
2. Member is responding positively to therapy;
3. For brand Rebetol or Ribasphere Ribapak requests, member must use generic ribavirin, unless contraindicated or clinically significant adverse effects are experienced;
4. If request is for a dose increase, new dose does not exceed:
   a. Ribasphere Ribapak: 1,200 mg per day;

b. Rebetol: 1,400 mg per day.

Approval duration: Coincides with duration for Epclusa, Harvoni, Mavyret, Sovaldi, Zepatier, Viekira Pak, or Vosevi authorization

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

1. If this drug has recently (within the last 6 months) undergone a label change (e.g., newly approved indication, age expansion, new dosing regimen) that is not yet reflected in this policy, refer to one of the following policies (a or b):
   a. For drugs on the formulary (commercial, health insurance marketplace) or PDL (Medicaid), the no coverage criteria policy for the relevant line of business: CP.CPA.190 for commercial, HIM.PA.33 for health insurance marketplace, and CP.PMN.255 for Medicaid; or
   b. For drugs NOT on the formulary (commercial, health insurance marketplace) or PDL (Medicaid), the non-formulary policy for the relevant line of business: CP.CPA.190 for commercial, HIM.PA.103 for health insurance marketplace, and CP.PMN.16 for Medicaid; or
2. If the requested use (e.g., diagnosis, age, dosing regimen) is NOT specifically listed under section III (Diagnoses/Indications for which coverage is NOT authorized) AND criterion 1 above does not apply, refer to the off-label use policy for the relevant line of business: CP.CPA.09 for commercial, HIM.PA.154 for health insurance marketplace, and CP.PMN.53 for Medicaid.

III. Diagnoses/Indications for which coverage is NOT authorized:

A. Non-FDA approved indications, which are not addressed in this policy, unless there is sufficient documentation of efficacy and safety according to the off label use policies – CP.CPA.09 for commercial, HIM.PA.154 for health insurance marketplace, and CP.PMN.53 for Medicaid, or evidence of coverage documents.

IV. Appendices/General Information

Appendix A: Abbreviation/Acronym Key

CHC: chronic hepatitis C	HCV: hepatitis C virus
FDA: Food and Drug Administration	HIV: human immunodeficiency virus

Appendix B: Therapeutic Alternatives

Not applicable

Appendix C: Contraindications/Boxed Warnings

- Rebetol and Ribasphere Ribapak are contraindicated in:
  - Women who are pregnant
  - Men whose female partners are pregnant
  - Patients with hemoglobinopathies (e.g., thalassemia major, sickle-cell anemia)
  - Coadministration with didanosine
  - Patients with autoimmune hepatitis (when in combination with Pegasys)
  - When used in combination with Pegasys: Ribasphere Ribapak is additionally contraindicated in patients with hepatic decompensation (Child-Pugh B or C) in cirrhotic CHC patients.

- Rebetol only:
  - Patients with known hypersensitivity reactions such as Stevens-Johnson syndrome, toxic, epidermal necrolysis, and erythema multiforme to ribavirin or any component of the product
  - Creatinine clearance less than 50 mL/min
- Boxed warning(s):
  - Ribasphere Ribapak: risk of serious disorders and ribavirin-associated effects
  - Rebetol: embryo-fetal toxicity, hemolytic anemia, and monotherapy not recommended

Appendix D: General Information

- Ribasphere brands are no longer commercially being manufactured.

Appendix E: Healthcare Provider HCV Training

- Acceptable HCV training programs and/or online courses include, but are not limited to the following:
- Hepatitis C online course (https://www.hepatitisc.uw.edu/): University of Washington is funded by the Division of Viral Hepatitis to develop a comprehensive, online self-study course for medical providers on diagnosis, monitoring, and management of hepatitis C virus infection. Free CME and CNE credit available.
- Fundamentals of Liver Disease (https://liverlearning.aasld.org/fundamentals-of-liverdisease): The AASLD, in collaboration with ECHO, the American College of Physicians (ACP), CDC, and the Department of Veterans Affairs, has developed Fundamentals of Liver Disease, a free, online CME course to improve providers' knowledge and clinical skills in hepatology.
- Clinical Care Options: http://www.clinicaloptions.com/hepatitis.aspx
- CDC training resources: https://www.cdc.gov/hepatitis/resources/professionals/trainingresources.htm

V. Dosage and Administration

<table>
<tr><th>Indication</th><th>Dosing Regimen</th><th>Maximum Dose</th></tr>
<tr><td>CHC</td><td>The daily dose of administered orally in two divided doses. The dose should be individualized to the patient depending on baseline disease characteristics (e.g., genotype), response to therapy, and tolerability of the regimen.
<table>
<tr><th>Body Weight kg (lbs)</th><th>Rebetol Daily Dose</th><th>Rebetol Number of Capsules</th></tr>
<tr><td>< 66 (< 144)</td><td>800 mg/day</td><td>2 x 200-mg capsules A.M.
2 x 200-mg capsules P.M.</td></tr>
<tr><td>66-80 (145-177)</td><td>1000 mg/day</td><td>2 x 200-mg capsules A.M.
3 x 200-mg capsules P.M.</td></tr>
</table></td><td>1,400 mg/day</td></tr>
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Indication	Dosing Regimen			Maximum Dose
	81-105 (178-231)	1,200 mg/day	3 x 200-mg capsules A.M. 3 x 200-mg capsules P.M.	
	> 105 (231)	1,400 mg/day	3 x 200-mg capsules A.M. 4 x 200-mg capsules P.M.	

VI. Product Availability

Drug	Availability
Ribavirin (Rebetol)	Capsule: 200 mg
Ribavirin (Ribasphere RibaPak)	Tablets: 200 mg, 400 mg, 600 mg (brand version no longer being manufactured) RibaPak compliance pack, tablets: 800 mg/day, 1,000 mg/day, 1,200 mg/day (brand version no longer being manufactured)

VII. References

1. Rebetol Prescribing Information. Whitehouse Station, NJ; Merck and Co; March 2022. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2022/020903s057,021546s013lbl.pdf . Accessed August 6, 2023.
2. Ribasphere Prescribing Information. Warrendale, PA: Kadmon Pharmaceuticals, LLC; September 2017. Available at: https://rsc.niaid.nih.gov/sites/default/files/ribavirin-ribasphere-pi-dated-september-2017.pdf. Accessed June 28, 2023.
3. 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 August 5, 2023.
4. Clinical Pharmacology [database online]. Tampa, FL: Gold Standard, Inc. Updated periodically. Accessed August 6, 2023.

Reviews, Revisions, and Approvals	Date	P&T Approval Date
4Q 2019 annual review: no significant changes; references reviewed and updated.	08.05.19	11.19
4Q 2020 annual review: added Mavyret and Vosevi, removed Olysio & Technivie from combination use criterion as they are no longer commercially available; expanded prescriber requirement to include a "provider who has expertise in treating HCV based on a certified training program"; Appendix E (Healthcare Provider HCV Training) added; references reviewed and updated.	08.09.20	11.20
4Q 2021 annual review: no significant changes; added redirection to generic formulation; removed Daklinza criteria references as Daklinza has been discontinued; references for HIM line of business off-label use revised from HIM.PHAR.21 to HIM.PA.154; references reviewed and updated.	08.05.21	11.21

Reviews, Revisions, and Approvals	Date	P&T Approval Date
4Q 2022 annual review: Copegus, Moderiba and Rebetol oral solution removed from policy as they are no longer being manufactured (per Medispan obsolete dates and Clinical Pharmacology); added template generic redirection verbiage for generic ribavirin use; references reviewed and updated. Template changes applied to other diagnoses/indications and continued therapy section.	08.05.22	11.22
4Q 2023 annual review: removed references to Ribasphere since it's no longer manufactured but retained Ribasphere Ribapak due to availability per Clinical Pharmacology; references reviewed and updated.	08.25.23	11.23

Important Reminder

This clinical policy has been developed by appropriately experienced and licensed health care professionals based on a review and consideration of currently available generally accepted standards of medical practice; peer-reviewed medical literature; government agency/program approval status; evidence-based guidelines and positions of leading national health professional organizations; views of physicians practicing in relevant clinical areas affected by this clinical policy; and other available clinical information. The Health Plan makes no representations and accepts no liability with respect to the content of any external information used or relied upon in developing this clinical policy. This clinical policy is consistent with standards of medical practice current at the time that this clinical policy was approved. "Health Plan" means a health plan that has adopted this clinical policy and that is operated or administered, in whole or in part, by Centene Management Company, LLC, or any of such health plan's affiliates, as applicable.

The purpose of this clinical policy is to provide a guide to medical necessity, which is a component of the guidelines used to assist in making coverage decisions and administering benefits. It does not constitute a contract or guarantee regarding payment or results. Coverage decisions and the administration of benefits are subject to all terms, conditions, exclusions and limitations of the coverage documents (e.g., evidence of coverage, certificate of coverage, policy, contract of insurance, etc.), as well as to state and federal requirements and applicable Health Plan-level administrative policies and procedures.

This clinical policy is effective as of the date determined by the Health Plan. The date of posting may not be the effective date of this clinical policy. This clinical policy may be subject to applicable legal and regulatory requirements relating to provider notification. If there is a discrepancy between the effective date of this clinical policy and any applicable legal or regulatory requirement, the requirements of law and regulation shall govern. The Health Plan retains the right to change, amend or withdraw this clinical policy, and additional clinical policies may be developed and adopted as needed, at any time.

This clinical policy does not constitute medical advice, medical treatment or medical care. It is not intended to dictate to providers how to practice medicine. Providers are expected to exercise professional medical judgment in providing the most appropriate care, and are solely responsible

for the medical advice and treatment of members. This clinical policy is not intended to recommend treatment for members. Members should consult with their treating physician in connection with diagnosis and treatment decisions.

Providers referred to in this clinical policy are independent contractors who exercise independent judgment and over whom the Health Plan has no control or right of control. Providers are not agents or employees of the Health Plan.

This clinical policy is the property of the Health Plan. Unauthorized copying, use, and distribution of this clinical policy or any information contained herein are strictly prohibited. Providers, members and their representatives are bound to the terms and conditions expressed herein through the terms of their contracts. Where no such contract exists, providers, members and their representatives agree to be bound by such terms and conditions by providing services to members and/or submitting claims for payment for such services.

Note:
For Medicaid members, when state Medicaid coverage provisions conflict with the coverage provisions in this clinical policy, state Medicaid coverage provisions take precedence. Please refer to the state Medicaid manual for any coverage provisions pertaining to this clinical policy.