



Horizon BCBSNJ
Medical Necessity Guideline

Section
Policy Number
Effective Date
Review Date

Drugs

6/25/04
5/27/05, 10/27/05, 4/27/06,
10/4/07, 9/26/08

Subject:

BRAND NAME **Rebetol**
(Generic) **(ribavirin capsule and oral solution)**

Copegus
(ribavirin oral tablet)

Ribasphere
(ribavirin capsules)

IMPORTANT NOTE:

*The purpose of this policy is to provide general information applicable to the administration of outpatient prescription drug benefits that Horizon Blue Cross Blue Shield of New Jersey and Horizon Healthcare of New Jersey, Inc. (collectively "Horizon BCBSNJ") insures or administers. **Outpatient prescription drugs are not covered under all Horizon benefit plans.** If the member's contract benefits differ from the pharmacy guideline, the contract prevails. Although a service, supply drug or procedure may be medically necessary, it may be subject to limitations and/or exclusions under a member's benefit plan. If a service, supply drug or procedure is not covered and the member proceeds to obtain the service, supply drug or procedure, the member may be responsible for the cost. Decisions regarding treatment and treatment plans are the responsibility of the physician. This policy is not intended to direct the course of clinical care a physician provides to a member, and it does not replace a physician's or pharmacist's independent professional clinical judgment or duty to exercise special knowledge and skill in the treatment of Horizon BCBSNJ members. Horizon BCBSNJ is not responsible for, does not provide, and does not hold itself out as a provider of medical care. The physician remains responsible for the quality and type of health care services provided to a Horizon BCBSNJ member.*

Horizon BCBSNJ pharmacy guidelines do not constitute medical advice, authorization, certification, approval, explanation of benefits, offer of coverage, contract or guarantee of payment.

BLACK BOX WARNINGS

Rebetol/Copegus monotherapy is not effective for the treatment of chronic hepatitis C virus (HCV) infection and should not be used alone for this indication.

The primary toxicity of ribavirin is hemolytic anemia. The anemia associated with ribavirin therapy may result in the worsening of cardiac disease that has led to fatal and nonfatal myocardial infarctions. Patients with a history of significant or unstable cardiac disease should not be treated with ribavirin.

Significant teratogenic and/or embryocidal effects have been demonstrated in all animal species exposed to ribavirin. In addition, ribavirin has a multiple dose half-life of 12 days, so it may persist in nonplasma compartments for as long as six months. Therefore, ribavirin therapy is contraindicated in women who are pregnant and in the male partners of women who are pregnant. Extreme care must be taken to avoid pregnancy during therapy and for six months after completion of treatment in both female patients and in female partners of male patients who are taking ribavirin therapy. At least two reliable forms of effective contraception must be utilized during treatment and during the six-month post-treatment follow-up period.

FDA-APPROVED INDICATION

- Rebetol Capsules and Oral Solution are indicated for use only in combination with Intron A (interferon alfa-2b, recombinant) Injection for the treatment of chronic hepatitis C in patients 3 years of age and older with compensated liver disease previously untreated with alpha interferon or in patients 18 years of age and older who have relapsed following alpha interferon therapy.
- Rebetol Capsules are indicated in combination with Peg-Intron injection for the treatment of chronic hepatitis C in patients with compensated liver disease who have not been previously treated with interferon alpha and are at least 18 years of age.
- The safety and efficacy of Rebetol Capsules or Oral Solution with interferons other than Intron A or Peg-Intron products have not been established.
- Pediatric Use:
Evidence of disease progression, such as hepatic inflammation and fibrosis, as well as prognostic factors for response, HCV genotype and viral load, should be considered when deciding to treat a pediatric patient. The benefits of treatment should be weighed against the safety findings observed for pediatric subjects in the clinical trials.
- Copegus in combination with Pegasys (Peginterferon alfa-2a) is indicated for the treatment of adults with chronic hepatitis C virus infection who have compensated liver disease and have not been previously treated with interferon alpha. Patients in whom efficacy was demonstrated include patients with compensated liver disease and histological evidence of cirrhosis (Child-Pugh Class A).

Medical Necessity Guideline:

1. The following questionnaire may be used to determine medical necessity of Rebetol prescriptions.

1. Does the patient have the diagnosis of chronic hepatitis C virus infection? [If the answer to this question is no, then no further questions are required.]	Yes	No
2. Will the patient be taking interferon alfa (e.g., Intron A, Roferon A, Pegasys, PEG-Intron) concurrently with ribavirin therapy? [If the answer to this question is no, then no further questions are required.]	Yes	No
3. Prior to initiating drug treatment did the patient have detectable levels of Hepatitis C RNA (a viral load) in the serum? [If the answer to this question is no, then no further questions required.]	Yes	No
4. Does the patient have a one of the following: -diagnosis of HIV -liver transplantation [If the answer to this question is yes, then skip to question 9.]	Yes	No
5. Is the patient Genotype-2 or 3? [If the answer to this question is no, then skip to question 7.]	Yes	No
6. Has the patient had 24 weeks total of ribavirin therapy? [If the answer to this question is no, then no skip to question 9.] [If the answer to this question is yes, then no further questions required.]	Yes	No
7. Has the patient received at least 12 weeks of ribavirin therapy in the past 3 months? [If the answer to this question is no, then skip to question 9.]	Yes	No
8. Did the patient experience at least a 2-log decrease in serum Hepatitis C RNA levels (viral load) since the initiation of Hepatitis C therapy? [Skip to question 11.]	Yes	No
9. Does the patient have any of the following: -history of unstable heart disease? (e.g., Coronary Artery Disease-CAD ischemic heart disease, congestive heart failure) -decompensated cirrhosis	Yes	No

-creatinine clearance \geq 50ml/min
 -hemoglobinopathy such as thalassemia major or sickle-cell anemia
 -pregnancy or partner of the patient is pregnant
 [If the answer to this question is yes, then no further questions required.]

10. Has or will the patient (male or female) be instructed to practice effective contraception during therapy and for six months after ribavirin therapy? Yes No
 [If the answer to this question is no, then no further questions required.]

11. Is the ribavirin request for MORE THAN the following dispensing limits: Yes No
 -7 capsules or tablets per day
 -2940 mL every 84 days (12 weeks)?

Guidelines for Approval					
Set 1-Hep C with LT or HIV		Set 2-Genotype-2 or 3 Initial-no soln		Set 3-Genotype-1 or 4 < 12 weeks of therapy w/in past 3 months	
Duration of Approval	48 weeks	Duration of Approval	24 weeks	Duration of Approval	16 Weeks
Yes to question(s)	No to question(s)	Yes to question(s)	No to question(s)	Yes to question(s)	No to question(s)
1	9	1	4	1	4
2	11	2	6	2	5
3		3	9	3	7
4		5	11	10	9
10		10			11
Set 4-Genotype-1 or 4 – at least 12 weeks of therapy w/in past 3 months					
Duration of Approval	32 weeks				
Yes to question(s)	No to question(s)				
1	4				
2	5				
3	9				
7	11				
8					
10					

Horizon BCBSNJ Pharmacy Guideline Development Process: This Horizon BCBSNJ Pharmacy Guideline (the "Pharmacy Guideline") has been developed by Horizon BCBSNJ's Pharmacy Drug Policy Subcommittee, Clinical Issues Subcommittee, and Quality Improvement Committee which include practicing physicians and pharmacists. This guideline is consistent with generally accepted standards of medical and pharmacy practice, and reflects Horizon BCBSNJ's view of the subject health care services, supplies drugs or procedures, and in what circumstances they are deemed to be medically necessary or experimental/ investigational in nature. This Pharmacy Guideline also considers whether and to what degree the subject health care services, supplies or procedures are clinically appropriate, in terms of type, frequency, extent, site and duration and if they are considered effective for the illnesses, injuries or diseases discussed. Where relevant, this Pharmacy Guideline considers whether the subject prescription drugs are being requested primarily for the convenience of the covered person or the health care provider. It may also consider whether the prescription drugs are more costly than alternative prescription drugs that are at least as likely to produce equivalent therapeutic or diagnostic results as to the diagnosis or treatment of the relevant illness, injury or disease. In reaching its conclusion regarding what it considers to be the generally accepted standards of medical and pharmacy practice, Horizon BCBSNJ reviews and considers the following: all credible scientific evidence published in peer-reviewed medical literature generally recognized by the relevant medical community, physician and health care provider specialty society recommendations, the views of physicians

and health care providers practicing in relevant clinical areas (including, but not limited to, the prevailing opinion within the appropriate specialty), the findings and directives of the Food and Drug Administration and any other relevant factor as determined by applicable State and Federal laws and regulations.

RATIONALE

The intent of the criteria is to ensure that patients follow selection elements established by Horizon BCBS New Jersey's medical policies.

DOSAGE AND ADMINISTRATION

Intron A, PEG-Intron or Pegasys injection should be administered subcutaneously and ribavirin should be administered orally. Dosages are based on weight. For Rebetol use in pediatrics, the recommended dose is 15 mg/kg per day in a divided dose (AM and PM), up to the maximum adult dose of 1200 mg per day. The recommended duration of treatment for pediatric patients with genotype 1 is 48 weeks; for those with genotype 2 or 3 the recommended duration of treatment is 24 weeks. The recommended duration of treatment for adult patients previously untreated with interferon is 24 to 48 weeks. The duration of treatment should be individualized to the patient, depending on baseline disease characteristics, response to therapy, and tolerability of the regimen. In clinical trials, almost 26 percent of patients required modification of their dose of ribavirin, interferon alpha, or both agents. Virologic response should be assessed after 24 weeks of treatment. Treatment discontinuation should be considered in any patient who has not achieved an HCV RNA below the limit of detection of the assay by 24 weeks.

The following laboratory tests are recommended for all patients on ribavirin, prior to beginning treatment and periodically thereafter:

- Standard hematologic tests—including hemoglobin (pretreatment, week two, week four and as clinically appropriate), complete and differential white blood cell counts, and platelet count
- Liver function tests and thyroid stimulating hormone (TSH)
- Pregnancy—including monthly monitoring for women of childbearing potential
- ECG

It is recommended that a patient whose hemoglobin level falls below 10 g/dL have his/her ribavirin dose reduced to 600 mg daily. A patient whose hemoglobin level falls below 8.5 g/dL should be permanently discontinued from ribavirin therapy.

RISK FACTORS/CONTRAINDICATIONS

Warnings

Based on results of clinical trials, ribavirin monotherapy is not effective for the treatment of chronic hepatitis C virus infection; therefore, ribavirin must not be used alone. The safety and efficacy of Rebetol/Copegus have only been established when used together with Intron A, PEG-Intron or Pegasys as combination therapy. [Note: interferon alfa products are not considered interchangeable]

There are significant adverse events caused by Rebetol/Intron A or Copegus/Pegasys, including severe depression and suicidal ideation, hemolytic anemia, suppression of bone marrow function, pulmonary dysfunction, pancreatitis, and diabetes. The Rebetol/Copegus product information should be reviewed in its entirety prior to initiation of combination treatment for additional safety information.

THE PRIMARY TOXICITY OF RIBAVIRIN IS HEMOLYTIC ANEMIA, WHICH WAS OBSERVED IN APPROXIMATELY 10 PERCENT OF RIBAVIRIN / INTERFERON ALPHA —TREATED PATIENTS IN CLINICAL TRIALS. THE ANEMIA ASSOCIATED WITH RIBAVIRIN OCCURS WITHIN ONE TO TWO WEEKS OF INITIATION OF THERAPY. BECAUSE THE INITIAL DROP IN HEMOGLOBIN OR HEMATOCRIT MAY BE SIGNIFICANT, IT IS ADVISED THAT HEMOGLOBIN OR HEMATOCRIT BE OBTAINED PRETREATMENT AND AT WEEK TWO AND WEEK FOUR OF THERAPY, OR MORE FREQUENTLY IF CLINICALLY INDICATED. PATIENTS SHOULD THEN BE FOLLOWED AS CLINICALLY APPROPRIATE.

Fatal and nonfatal myocardial infarctions have been reported in patients with anemia caused by ribavirin. Patients should be assessed for underlying cardiac disease before initiation of ribavirin therapy and should be appropriately monitored during therapy. If there is any deterioration of cardiovascular status, therapy should be suspended or discontinued. Because cardiac disease may be worsened by drug-induced anemia, patients with a history of significant or unstable cardiac disease should not use Rebetol.

REFERENCES

1. Copegus product information. Roche Laboratories Inc., December 2002
2. Rebetol product information. Schering Corporation, March 2003
3. Glue P, Rouzier-Panis R, Raffanel C, for The Hepatitis C Intervention Therapy Group. A dose-ranging study of pegylated interferon alfa-2b ribavirin in chronic hepatitis C. *Hepatology*. 2000;32(3):647-653.
4. Ahmed A, Keeffe E. Treatment strategies for chronic hepatitis C: update since the 1997 National Institutes of Health Consensus Development Conference. *J Gastroenterol Hepatol*. 1999;14(suppl):S12-S18.
5. Boyer N, Marcellin P. Pathogenesis, diagnosis and management of hepatitis C. *J Hepatol*. 2000;32(suppl 1):98-112.
6. National Institutes of Health Consensus Development Conference Panel Statement: Management of Hepatitis C. *Hepatology*. 1997;26(suppl 1):2S-10S.

Pharmacy Guidelines can be highly technical and are designed for use by the Horizon BCBSNJ professional staff in making coverage determinations. Members referring to this policy should discuss it with their treating physician or pharmacist, and should refer to their specific benefit plan for the terms, conditions, limitations and exclusions of their coverage.

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