



CIGNA PHARMACY COVERAGE POLICY

The following Coverage Policy applies to all plans administered by CIGNA Companies including plans administered by Great-West Healthcare, which is now a part of CIGNA.

**Subject [Rebetol[®] (ribavirin) and
Intron[®] A (interferon alfa-2b)
Combination Therapy] –
(Rebetron[®])**

**Effective Date 1/15/2011
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Coverage Policy Number 6005**

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Hyperlink to Related Coverage Policies

Alferon N[®]
 Infergen[®]
 Intron A[®]
 PegaSys[®]
 PEG Intron[®]

INSTRUCTIONS FOR USE

Coverage Policies are intended to provide guidance in interpreting certain **standard** CIGNA HealthCare benefit plans as well as benefit plans formerly administered by Great-West Healthcare. Please note, the terms of a participant's particular benefit plan document [Group Service Agreement (GSA), Evidence of Coverage, Certificate of Coverage, Summary Plan Description (SPD) or similar plan document] may differ significantly from the standard benefit plans upon which these Coverage Policies are based. For example, a participant's benefit plan document may contain a specific exclusion related to a topic addressed in a Coverage Policy. In the event of a conflict, a participant's benefit plan document **always supercedes** the information in the Coverage Policies. In the absence of a controlling federal or state coverage mandate, benefits are ultimately determined by the terms of the applicable benefit plan document. Coverage determinations in each specific instance require consideration of 1) the terms of the applicable group benefit plan document in effect on the date of service; 2) any applicable laws/regulations; 3) any relevant collateral source materials including Coverage Policies and; 4) the specific facts of the particular situation. Coverage Policies relate exclusively to the administration of health benefit plans. Coverage Policies are not recommendations for treatment and should never be used as treatment guidelines. Proprietary information of CIGNA. Copyright ©2011 CIGNA

Coverage Policy

CIGNA covers a combination of ribavirin and interferon alfa-2b (Rebetron[®]) as medically necessary for the treatment of Hepatitis C in an individual with compensated liver disease who is intolerant to peginterferon alfa therapy (i.e., injection-site reaction) OR are classified as a non-responder/relapser after treatment with a peginterferon alfa therapy (PegaSys[®], Peg Intron[®]) as follows:

Diagnosis	Treatment Authorization
Genotype 1	<ul style="list-style-type: none"> • Initial authorization - 16 weeks • Subsequent authorization(s) contingent on clinical response of at least a 2 log (100 fold decrease in quantitative HCV RNA by week 16 as follows: <ul style="list-style-type: none"> • If HCV RNA is undetectable (< 50 IU/ml), an additional 32 weeks (total 48 weeks) will be authorized. • If HCV RNA is detectable (> 50 IU/ml), an addition 8 weeks will be authorized and HCV RNA re-evaluated at 24 weeks. An additional 56 weeks (total 72 weeks) will be authorized if there is no detectable virus at 24 weeks (<50IU/ml).

Genotype 2 or 3	Standard treatment authorization - 24 weeks ➤ Genotype 3 with steatosis and initial high viral loads (HCV RNA >600,000 IU/mL) - authorize for 48 weeks
Genotype 4, 5, or 6	48 weeks
Bridging fibrosis or cirrhosis	48 weeks regardless of HCV genotype and changes in HCV RNA levels at week 12
Coinfection with human immunodeficiency virus (HIV)	48 weeks

When coverage is available and medically necessary, the dosage, frequency, site of administration, and duration of therapy should be reasonable, clinically appropriate, and supported by evidence-based literature and adjusted based upon severity, alternative available treatments, and previous response to Rebetron[®] [Rebetol[®] (ribavirin) and Intron[®] A (interferon alfa-2b) Combination Therapy].

FDA Approved Indications

Rebetron is a combination of Rebetol (ribavirin) capsules and Intron A (interferon alfa-2b, recombinant) injection for the treatment of chronic hepatitis C in patients with compensated liver disease who have relapsed following alfa interferon therapy and in patients who have not previously been treated with interferon therapy. Compensated liver disease is defined as when the disease exists but there are either few symptoms, or the symptoms are mild and stable. Intron A injection and Rebetol capsules are packaged together as Rebetron combination therapy.

FDA Recommended Dosing

Interferon alfa-2b (Intron A) is administered subcutaneously three times per week and 1000 or 1200 mg of ribavirin administered orally twice or three times daily, depending on patient's weight.

Black Box Warnings

Combination Rebetol/Intron A therapy is contraindicated in females who are pregnant and in the male partners of females who are pregnant. Extreme care must be taken to avoid pregnancy during therapy and for 6 months after completion of treatment in female patients, and in female partners of male patients who are taking combination Rebetol/Intron A therapy. Females of childbearing potential and males must use two reliable forms of effective contraception during treatment and during the 6-month posttreatment follow-up period.

Drug Availability

Each Rebetron combination package consists of a box containing vials of Intron A Injection and one bottle containing Rebetol capsules.

General Background

Pharmacology/Pharmacokinetics

The mechanism of action for the inhibition of hepatitis C virus ribonucleic acid (RNA) by ribavirin and recombinant interferon alfa-2b combination therapy is unknown. Ribavirin may apply immunomodulatory effects rather than antiviral effects in the treatment of chronic hepatitis C. Time to peak serum concentration is seven hours for interferon alfa-2b, and the mean half-life values following single- and multiple-dose administrations were 6.8 hours and 6.5 hours, respectively. In clinical studies, ribavirin was rapidly and extensively absorbed following oral administration. Rebetron, a combination of interferon alfa-2b and ribavirin, is indicated for the treatment of chronic hepatitis C in patients with compensated liver disease previously untreated with alfa interferon or who have relapsed following alfa interferon therapy. Compensated liver disease is defined as the presence of liver disease with either few symptoms or symptoms that are classified as mild and stable. In pediatric patients, the general principles of management are the same as those for adults, and the duration of therapy is determined by genotype. The response rates to interferon and ribavirin combination therapy are similar to those reported in adults. The approved dose of interferon alfa-2b for pediatric use is 3 MU/m².

Several types of interferon (IFN) are utilized in the treatment of Hepatitis C (HCV). These include interferon alfa-2a, interferon alfa-2b, interferon alfacon, interferon alfa n3, and two forms of pegylated interferon alfa. There is no data to indicate any clinical difference between the various alfa interferons as monotherapy. However, the addition of ribavirin to interferon was a major breakthrough in the treatment of HCV infection. Studies have shown that the combination therapy with interferon and ribavirin is more effective than interferon alone. There is a significant clinical difference between the interferon alfa and pegylated interferon therapies.

Guidelines

The American Gastroenterological Association and American Association for the Study of Liver Disease (AASLD) Practice Guidelines recommend antiviral therapy in patients with compensated liver disease and laboratory parameters including: total bilirubin level < 1.5 mg/100 mL; prothrombin time < 15 seconds [international normalized ratio (INR), ≤ 1.7]; albumin level > 3.4 g/100 mL; with no history of ascites, bleeding esophagogastric varices, or hepatic encephalopathy. Patients presenting with ascites, bleeding varices or hepatic encephalopathy should be referred for consideration of liver transplantation. Per the manufacturer labels of these products approved by the FDA, the use of interferon therapies is contraindicated in patients who demonstrate hepatic decompensation (Child-Pugh score > 6; class B and C) prior to or during treatment. The Child-Pugh classification is used to assess the prognosis of chronic liver disease. Although it was originally used to predict mortality during surgery, it is now used to determine the prognosis, as well as the required strength of treatment and the necessity of liver transplantation. The score employs five clinical measures of liver disease: total bilirubin level, INR, serum albumin, ascites, and hepatic encephalopathy. Each measure is scored 1–3, with 3 indicating the most severe derangement. Chronic liver disease is classified into Child-Pugh class A, B, and C, as class B (Child-Pugh score: 7–9) and class C (Child-Pugh score: 10–15) are indicators of decompensated liver disease.

The following statements and recommendations are based on practice guidelines (Strader, et al., 2004) supported by the AASLD, the Infectious Diseases Society of America, the American College of Gastroenterology, and the American Gastroenterological Association Technical Review on the Management of Hepatitis C (2006). However, these recommendations are designed to be flexible rather than rigidly inflexible and are intended to guide physicians and other health care workers to make logical patient care decisions. These recommendations should be followed in most cases; however, management decisions for individual patients are left to physicians and health care workers. Recommendations regarding the duration of therapy based on the HCV genotype and the management of special patient population are similar for the standard interferon and pegylated interferon therapies.

The goal of HCV treatment is to eradicate the virus and prevent progression to end-stage liver disease. Treatment responses are characterized by the results of HCV ribonucleic acid (RNA) testing. Infection is considered eradicated when there is a sustained virologic response (SVR), defined as the absence of HCV RNA in serum at the end of treatment and six months later. In randomized clinical trials, the highest overall SVR rates have been achieved with the combination of weekly subcutaneous injections of long-acting peginterferon alfa and oral ribavirin. Ribavirin is a synthetic nucleoside analogue with broad antiviral activity against both RNA and deoxyribonucleic acid (DNA) viruses. Ribavirin alone is not effective for the treatment of HCV.

Prior to treatment, HCV genotype should be determined in all persons by serologic immunoassay or molecular determination. The HCV genotype will determine the duration of therapy and likelihood of response. There are currently six known HCV genotypes. The majority of patients within the United States have genotype 1 (70%–80%), with the remainder presenting with genotypes 2 and 3 (20%–30%). Patients with genotype 4, 5 and 6 are uncommonly encountered in the United States. Peginterferon alfa drugs (PEG-IFN alfa-2a and PEG-IFN alfa-2b) are the only currently FDA-approved pegylated interferon products on the market. The combination therapy with oral ribavirin and pegylated-interferon is the standard of care for the treatment of chronic hepatitis C. Combination therapy of pegylated-interferon and ribavirin has demonstrated superior effectiveness compared with interferon alfa alone in interferon-naïve patients. There is no clinical evidence that shows interferon therapies are effective in nonresponders to peginterferon therapies.

A valuable clinical milestone for monitoring the response to antiviral therapy in patients with genotype 1 is an early virologic response (EVR), which is defined as ≥ 2 log (100-fold) decrease in quantitative HCV RNA levels during the first 12 weeks of therapy. Therefore, baseline and 12-week monitoring of HCV RNA levels should be performed on all patients diagnosed with HCV genotype 1.

Genotype 1 patients are generally more treatment-refractory (SVR \leq 40–50%); therefore, a full 48 weeks of therapy in combination with maximum doses of ribavirin (1000–1200 mg/day) is recommended. Quantitative serum HCV RNA should be performed at the initiation of, or shortly before, treatment and at week 12 of therapy. If patients do not achieve an EVR at 12 weeks, the treatment may be discontinued, since 97% of patients who do not achieve an EVR will fail to develop an SVR. However, in order to obtain the lab value, CIGNA HealthCare allows an approval of 16 weeks' initial authorization. An additional 32 weeks (total 48 weeks) will be authorized if there is at least a 2 log (100-fold) decrease in quantitative HCV RNA, which is usually drawn on week 12 but no later than week 16. There will be no additional authorization past the initial 16 weeks if there is less than a 2 log decrease in HCV RNA. Patients whose treatment continues through 48 weeks and whose qualitative measurement of HCV RNA at that time is negative should be retested for HCV RNA 24 weeks later to document an SVR. An additional 56 weeks (total 72 weeks) will be authorized if patient is identified as slow virologic responder who has an EVR with a 2 log drop but detectable virus (>50 IU/ml) at 12 weeks and has no detectable virus at 24 weeks (<50 IU/ml).

For genotype 2 and 3 patients who demonstrate a more treatment-favorable response to therapy (SVR \geq 80%), 24 weeks of therapy with interferon plus ribavirin should be administered. Patients whose treatment continues for the full 24 weeks, and whose qualitative measurement of HCV RNA at that time is negative, should be retested for HCV RNA 24 weeks later to document an SVR.

Studies have shown that there is a direct viral mechanism involved in the development of steatosis in people infected with HCV genotype 3. Steatosis, known as fatty liver, is a condition characterized by the accumulation of fat in the liver. Steatosis appears to increase the rate of HCV disease progression. Recent studies have shown that higher grades of steatosis correlate with higher grades of fibrosis, and with more rapid development of fibrosis and cirrhosis. On the basis of available evidence, genotype 3 patients with steatosis and high viral loads (HCV RNA $>600,000$ IU/mL) may need longer duration of treatment, and therapy should be continued for the full 48 weeks.

There is insufficient experience to provide recommendations for treatment of persons with genotypes 4, 5, and 6. In the absence of any clinical trial including a sufficient number of patients, the likelihood of an SVR and the optimal treatment schedule remain unknown for patients infected with HCV genotypes 4, 5 or 6. It is thus recommended to treat them like those infected with HCV genotype 1. In the absence of published data, no stopping rules have been defined, and it is recommended these patients be treated for a total of 48 weeks.

Patients with compensated cirrhosis or advanced fibrosis who can tolerate and respond to therapy should be considered candidates for therapy. Response rates observed in patients with bridging fibrosis and cirrhosis have increased (approximately 40%) with the introduction of IFN/ribavirin combination regimens.

Patients who are coinfecting with Hepatitis C and HIV should be considered as candidates for therapy, regardless of genotype. Although there are no FDA-approved medications for the treatment of hepatitis C in HIV-infected patients, three large studies compared the efficacy of peginterferon alfa plus ribavirin versus standard interferon alfa 2b plus ribavirin. Data from these trials show that SVR rates are higher in HIV-infected patients who receive peginterferon alfa and ribavirin combination therapy than in those who receive standard interferon alfa and ribavirin. These results support a recommendation of a full 48 weeks of peginterferon and ribavirin combination therapy for patients with HCV/HIV coinfection. Due to potential drug-drug interactions, if didanosine is critical to the HIV regimen, ribavirin should be avoided.

To date, no recommendation can be made regarding maintenance therapy. Several randomized controlled, phase III studies with only low-dose PEG-IFN are in progress to evaluate the effect of maintenance therapy on histologic and clinical endpoints in patients with chronic hepatitis C.

To date, there is no recommendation regarding the extension of treatment duration beyond 48 weeks. However, two open-labeled studies evaluated the potential benefits of extending treatment from 48 to 72 weeks with peginterferon-alfa 2a plus ribavirin. One study found that patients with detectable HCV RNA after four weeks of therapy could benefit from extending therapy from 48 to 72 weeks. The second study found that in patients classified as 'slow viral response' (positive HCV RNA at week 12 with between 50 to 5,000 IU/mL, but negative HCV RNA at week 24), extension of therapy beyond 48 weeks could reduce relapse rates and improve sustained response rates. Currently, several phase IV clinical studies are in progress to evaluate the extension of treatment duration beyond 48 weeks.

Clinical Studies

In pediatric patients, the general principles of management are the same as those for adults, and the duration of therapy is determined by genotype. The response rates to interferon monotherapy and interferon and ribavirin combination therapy are similar to those reported in adults. The combination of interferon alfa 2b and ribavirin is recommended in children age 3–17, and the approved dose of interferon alfa-2b for pediatric use is 3 MU/m². Treatment of children under the age of three years is contraindicated. Several trials of pegylated interferon in combination with ribavirin in pediatrics are in progress since the improved antiviral efficacy of weekly pegylated interferons relative to standard interferons in adults with chronic HCV infection suggests that pegylated interferons may also improve antiviral efficacy in children. In a recent published study (Schwarz, et al., 2006), the pharmacokinetics, efficacy and safety of peginterferon alfa -2a were evaluated in 14 children age 2–8 years with chronic hepatitis C (13 genotype 1, 1 non-1 genotype). All patients received once-weekly subcutaneous injections of peginterferon alfa-2 for 48 weeks. At week 24, the mean trough concentration was about 20% below values obtained from adults treated with peginterferon alfa -2a, and the area under the curve from 0 to 168 hours was about 20% above adult values, suggesting that drug doses calculated from body surface area (BSA) achieved therapeutically adequate concentrations. Six of 14 patients (43%), all infected with genotype 1, achieved a sustained virological response. Based on these findings, the larger studies are needed to evaluate the efficacy and safety of peginterferon alfa as monotherapy, as well as in combination with ribavirin in pediatric patients with chronic hepatitis C.

Two multicenter, double-blind, randomized trials enrolled adults with compensated chronic hepatitis C and detectable hepatitis C (HCV) RNA who were previously untreated with alfa interferon therapy. Patients randomly received Rebetol capsules 1200 mg/day (1000 mg/day for patients weighing 75 kg) plus Intron A injection 3 MIU three times weekly or Intron A injection plus placebo for 24 or 48 weeks followed by 24 weeks of therapy follow-up. Of patients who had not achieved HCV RNA below the limit of detection of the research-based assay by week 24 of Rebetol/Intron A treatment, less than 5% responded to an additional 24 weeks of combination treatment. Among patients with HCV genotype 1 treated with Rebetol/Intron A therapy who achieved HCV RNA below the detection limit of the research-based assay by 24 weeks, those randomized to 48 weeks of treatment had higher virologic responses compared to those in the 24-week treatment group. There was no observed increase in response rates for patients with HCV nongenotype 1 randomized to Rebetol/Intron A therapy for 48 weeks compared to 24 weeks.

A randomized study compared the effect of interferon alone with that of interferon plus oral ribavirin for relapses of chronic hepatitis C. Results showed that in patients with chronic hepatitis C who relapse after treatment with interferon, therapy with interferon and oral ribavirin results in higher rates of sustained virologic, biochemical, and histologic response than treatment with interferon alone. A total of 345 patients with chronic hepatitis C who relapsed after interferon treatment were enrolled in this study. A total of 173 patients were randomly assigned to receive recombinant interferon alfa-2b concurrently with ribavirin 1000 to 1200 mg orally per day for six months, and 172 patients were assigned to receive interferon and placebo. At the completion of treatment, serum levels of hepatitis C virus (HCV) RNA were undetectable in 141 of the 173 patients who were treated with interferon and ribavirin (82%) and in 80 of the 172 patients who were treated with interferon alone (47%) (p<0.001). Twenty-four weeks post-treatment, serum HCV RNA levels remained undetectable in 84 patients (49%) in the combination-therapy group, but in only eight patients (5%) in the interferon group (p<0.001). Viral genotypes other than type 1 were associated with sustained responses only in the combination-therapy group.

Adverse Drug Reactions/Drug Interactions/Precautions

Combination Rebetol/Intron A therapy cannot be used by women who are pregnant or by men whose female partners are pregnant. Combination Rebetol/Intron A therapy should not be initiated until a report of a negative pregnancy test has been obtained immediately prior to initiation of therapy. Women of childbearing potential and men must use two forms of effective contraception during treatment and during the six months after treatment has been concluded. Patients with autoimmune hepatitis must not be treated with combination Rebetol/Intron A therapy.

The most common side effects associated with therapy containing ribavirin capsules and interferon alfa-2b injection are flu-like symptoms. There are also more serious side effects associated with this therapy, such as headache, fatigue, pain in the muscles (myalgia), and fever, which appear to decrease in severity as treatment continues. Severe psychiatric adverse events, including: depression, psychoses, aggressive behavior, hallucinations, violent behavior (suicidal ideation, suicidal attempts, and suicides), and rare instances of

homicidal ideation have occurred during combination Rebetol/Intron therapy, both in patients with and without a previous psychiatric disorder.

Coding/Billing Information

Note: This list of codes may not be all-inclusive.

Covered when medically necessary:

HCPCS Codes	Description
J9214	Injection, interferon, alfa-2b, recombinant, 1 million units

ICD-9-CM Diagnosis Codes	Description
070.41	Acute hepatitis C with hepatic coma
070.44	Chronic hepatitis C with hepatic coma
070.51	Acute hepatic C without mention of hepatic coma
070.54	Chronic hepatitis C without mention of hepatic coma
070.70	Unspecified viral hepatitis C without hepatic coma
070.71	Unspecified viral hepatitis C with hepatic coma

References

1. American Gastroenterological Association Technical Review on the Management of Hepatitis C. Gastro 2006;130:231-264.
2. Bacon BR and McHutchinson JG. Treatment Issues With Chronic Hepatitis C: Special Populations and Pharmacy Strategies. Am J Managed Care 2005;11:S296-S306.
3. Davis GL, Esteban-Mur R, Rustgi V, et al. Interferon alfa-2b alone or in combination with ribavirin for the treatment of relapse of chronic hepatitis C. International Hepatitis Interventional Therapy Group. N Engl J Med.1998;19,339(21):1493-9.
4. McEvoy GK, ed. AHFS 2010 Drug Information. Bethesda, MD: American Society of Health-Systems Pharmacists, Inc. 2010.
5. Schering Corporation. Combination Therapy containing Rebetol[®] (ribavirin, USP) Capsules and Intron[®] A (interferon alfa-2b, recombinant) Injection – (Rebetron[®]) Product Information. Kenilworth, NJ: Schering Corporation.October 2003.
6. Strader DB, Wright T, Thomas DL, Seeff LB. Diagnosis, Management, and Treatment of Hepatitis C. Hepatology 2004;39(4): 1147-1171.

Policy History

Pre-Merger Organizations	Last Review Date	Policy Number	Title
CIGNA HealthCare	1/15/2009	6005	[Rebetol [®] (ribavirin) and Intron [®] A (interferon alfa-2b) Combination Therapy] – (Rebetron [®])

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