



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 Interferon Alfacon-1 (Infergen®)

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Hyperlink to Related Coverage Policies

Alferon N®
 Intron A®
 PegaSys®
 PEG Intron®
 Rebetrone®

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 interferon alfacon-1 (Infergen®) as medically necessary for the treatment of Hepatitis C, as monotherapy or in combination with ribavirin, in an individual with compensated liver disease who is intolerant to peginterferon alfa therapy (i.e., injection-site reaction) OR is 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

Note: When medical necessity criteria have been met, CIGNA covers interferon alfacon-1 (Infergen®) on a 3 times per week dosing schedule. Daily dosing may be indicated in select populations including liver transplantation candidates and non-responders to pegylated interferon treatment.

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 interferon alfacon-1 (Infergen®) therapy.

FDA Approved Indications

Interferon alfacon-1 is indicated for the treatment of chronic HCV infection in patients 18 years of age or older with compensated liver disease who have anti-HCV serum antibodies and/or the presence of HCV RNA.

FDA Recommended Dosing

Interferon alfacon-1 is dosed at 9 mcg subcutaneously (SC) three times a week (TIW) for the treatment of chronic HCV infection. At least 48 hours should elapse between doses of interferon alfacon-1. Patients who tolerated previous interferon therapy and did not respond or relapsed following its discontinuation may be subsequently treated with 15 mcg of interferon alfacon-1 TIW administered SC as a single injection for up to 48 weeks.

Black Box Warnings

Alpha interferons, including Infergen, cause or aggravate fatal or life-threatening neuropsychiatric, autoimmune, ischemic, and infectious disorders. Patients should be monitored closely with periodic clinical and laboratory evaluations. Patients with persistently severe or worsening symptoms of these conditions should be withdrawn from therapy. In many but not all cases, these disorders resolve after stopping interferon alfacon-1 therapy.

Drug Availability

Interferon alfacon-1 is available in single-dose vials containing 9mcg or 15 mcg of interferon alfacon-1 in dispensing packs of 6 vials.

General Background

Disease Overview/Pharmacology

The FDA has approved several types of interferon therapies including interferon alfa-2a, interferon alfa-2b, interferon alfacon, interferon alfa N, and two forms of pegylated interferon alfa indicated for the treatment of chronic hepatitis C in patients with compensated liver disease. Compensated liver disease is defined as the presence of liver disease with either few symptoms or symptoms that are classified as mild and stable. Interferons occur naturally in the body and stimulate up-regulation of gene products that provide the antiviral, antiproliferative and immunomodulatory effects. There is no convincing data to indicate a significant clinical difference between the various alpha interferons.

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 are 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 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. 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. Currently, 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 to interferon alfa alone in interferon-naïve patients.

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A valuable clinical milestone for monitoring the response to antiviral therapy in patients with genotype 1 is an 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.

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

Clinical Studies

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 also a significant clinical difference between the interferon alfa and pegylated interferon therapies.

To date, there is no published clinical study to support the use of interferon alfacon-1 as monotherapy or in combination with ribavirin for previous nonresponders to HCV therapy. However, there are some promising data on interferon alfacon-1 [consensus interferon (CIFN)] for retreatment of nonresponders to pegylated interferon plus ribavirin therapy. A randomized, open-label, multicenter, (Daily-Dose Consensus Interferon and Ribavirin: Efficacy of Combined Therapy - DIRECT Trial) is a study evaluating SVR rate of combination therapy with daily CIFN plus RBV compared with no treatment in HCV-infected patients who were nonresponsive and were compliant to previous pegylated interferon plus ribavirin therapy. Patients randomly received either 9 mcg

(n=245) or 15 mcg (n=242) CIFN daily plus ribavirin or no treatment (n=172). In November 2007, the results were presented at the 58th annual meeting of the American Association for the Study of Liver Diseases (AASLD) in Boston, MA. Results showed that patients with lower fibrosis stages experienced improved responses with CIFN. Non-cirrhotic patients who were sensitive to peginterferon/ribavirin therapy had the best response. Overall patients treated with 15 mcg group consistently experienced a better response than the 9 mcg group. Daily CIFN in combination with RBV was well tolerated at doses up to 15 mcg. The authors concluded that patients who received CIFN 15 mcg plus RBV achieved up to a 17% SVR (p<0.001). Approximately 33% of non-cirrhotic patients (15 mcg group) who were sensitive to PegIFN/RBV and did not modify their CIFN/RBV dosages achieved an SVR.

Interferon-naïve studies showed significantly greater improvement of HCV RNA and amino alanine transferase (ALT) outcomes for IFN alfacon-1 patients than for those receiving placebo. The proportions of patients with undetectable HCV RNA plasma levels at the end of the treatment and observation periods (24 weeks each) for the IFN alfacon-1 group were 11.5% for the 3 mcg group, 40% for the 9 mcg group and 0% for the placebo group. Interferon alfacon-1 resulted in similar or greater improvement of HCV RNA and ALT outcomes than IFN alfa-2a and 2b did. After the treatment and observation periods, compared to IFN alfa-2b, IFN alfacon-1 showed greater improvement in HCV RNA concentration reductions for genotype 1 patients but similar proportions of patients with undetectable HCV RNA plasma levels. The proportions of patients with undetectable HCV RNA plasma levels at the end of the treatment and observation periods (24 weeks each) for the IFN alfacon-1 group were 66.2% for the 9 mcg group, 67.2% for the 15 mcg group and 54.1% for the IFN alfa-2a group. IFN alfacon-1 showed similar improvement of HCV RNA and ALT outcomes, whether administered alone or in combination with ribavirin. In a few case series, IFN alfacon-1 showed potential improvement in outcomes in patients with no response or relapse to previous IFN therapy.

Based on American Hospital Formulary Service (AHFS) compendia, treatment of chronic hepatitis B in patients with compensated liver disease is an accepted indication for interferon alfacon-1. However, interferon therapies are no longer used for this indication as peginterferon alfa 2a is the drug of choice for the treatment of chronic hepatitis B.

Adverse Reactions

The most common adverse events associated with IFN alfacon-1 therapy include: flu-like symptoms, psychiatric disorders (e.g., depression) and hematologic changes (e.g. leukopenia). In clinical studies, there were no significant differences in adverse events between IFN alfacon-1 and IFN alfa-2a and 2b. The drug interactions with IFN alfacon-1 are similar to those with the other alfa IFNs.

Coding/Billing Information

Note: This section is not in use.

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Policy History

Pre-Merger Organizations	Last Review Date	Policy Number	Title
CIGNA HealthCare Great-West Healthcare	1/15/2009	5011	Interferon alfacon-1 (Infergen)

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