



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 alfa-n3 (Alferon® N)

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Hyperlink to Related Coverage Policies

Infergen®
 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 alfa-n3 (Alferon® N) 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"> 16 weeks - Initial authorization 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	24 weeks
Genotype 3	<ul style="list-style-type: none"> 24 weeks - standard treatment authorization

	<ul style="list-style-type: none"> 48 weeks - if steatosis and initial high viral loads (HCV RNA >600,000 IU/mL)
Genotype 4, 5, or 6	48 weeks
Bridging fibrosis or cirrhosis	48 weeks - regardless of HCV genotype and/or changes in HCV RNA levels at week 12
Non-responder or relapser after treatment with a non-pegylated interferon	Duration of treatment based upon the genotype

CIGNA covers interferon alfa-n3 (Alferon® N) as medically necessary for ANY of the following indications:

- chronic hepatitis B in patients with compensated liver disease who have failure, contraindication, or intolerance to peginterferon alfa therapy
- acquired immune deficiency syndrome (AIDS)-associated Kaposi's sarcoma
- hairy cell leukemia
- malignant melanoma
- non-Hodgkin's lymphoma
- condylomata acuminata, intralesional only
- renal carcinoma (kidney cancer)
- chronic myelocytic leukemia
- laryngeal papillomatosis
- multiple myeloma
- cutaneous T-cell lymphomas (e.g. mycosis fungoides, Sezary syndrome)
- carcinoid tumors
- epithelial ovarian carcinoma
- skin carcinoma
- polycythemia vera
- essential thrombocytosis
- superficial bladder carcinoma

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 alfa-n3 (Alferon® N) therapy.

FDA Approved Indication

Interferon alfa-n3 is indicated for the treatment of condyloma acuminatum.

FDA Recommended Dosing

Intralesional, 0.05 ml (250,000 International Unit [IU]) per wart administered twice weekly for up to eight weeks. The maximum recommended dose per treatment session is 0.5 ml (2.5 million IU).

Black Box Warnings

Patients treated with alpha interferons, including interferon alfa-n3 (Alferon® N), should be monitored closely with periodic clinical and laboratory evaluations, since it may cause or aggravate fatal or life-threatening neuropsychiatric, autoimmune, ischemic, and infectious disorders. Therapy should be withdrawn in patients with persistently severe or worsening signs or symptoms of these conditions.

Drug Availability

It is available in injectable solution with each vial containing 1 ml of interferon alfa-n3 injection.

General Background

Pharmacology

Interferon alfa-n3 is a natural, human interferon alpha protein with both antiviral and antiproliferative properties for use by injection. Generally, interferons exert their cellular activities by binding to specific membrane receptors on the cell surface. Plasma concentrations of interferon below the detection limit of the assay, i.e., less than or equal to 3 IU/ml were observed in a study of intralesional use of interferon alfa-n3 for the treatment of condylomata acuminata.

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 alpha 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 alpha and pegylated interferon therapies. Peginterferons are produced by binding of the inert polyethylene glycol (PEG) moiety to interferon molecules, which results in decreasing renal clearance, altering metabolism, and increasing the half-life of the peginterferon molecule. These pharmacokinetic characteristics of pegylated interferon allow for once-weekly administration of peginterferon therapies.

Guidelines

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 deoxy-ribonucleic 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 ribonucleic acid (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 co-infected 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 alpha 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 co-infection. 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 end points 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-alpha 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 a multicenter, randomized, double-blind, placebo-controlled clinical trial, the safety and efficacy of interferon alfa-n3 was evaluated on 156 patients for the treatment of condylomata acuminata. Patients had a mean of five warts (range was 2–14), and all warts were treated. Patients, 81 in treatment group and 75 in placebo group, were injected intralesionally with a mean of 225,000 IU of interferon alfa-n3 per wart two times a week for up to eight weeks. Compared to placebo-treated patients 44% (33/75), 80% (65/81) of patients treated with interferon alfa-n3 had a complete or partial resolution of warts ($p < 0.001$). Interferon alfa-n3 was significantly more effective than placebo in producing a complete resolution of warts ($p < 0.001$). Approximately half (21/44) the patients who had a complete resolution of warts had complete resolution by the end of treatment, and half (23/44) had complete resolution of warts during the three months after the cessation of treatment. About 76% (31/41) of interferon alfa-n3-treated patients who achieved complete resolution of warts remained clear of all treated lesions during follow-up, while 79% (11/14) of the placebo-treated patients remained clear of all treated lesions during follow-up. Overall, interferon alfa-n3 therapy was effective in treating lesions of all sizes, and there was no difference in resolution for perianal, penile, or vulvar lesions. No difference in resolution was observed in patients who had received prior treatment of their warts and for those who had not. Among patients with warts that were refractory to previous treatment or recurring, 82% of the evaluable patients had complete or partial resolution of warts due to intralesional administration of interferon alfa-n3 as compared to 43% of placebo patients ($p < 0.001$). After injections of interferon alfa-n3, side effects were minor and transient.

In a randomized, double-blind, placebo-controlled, multicenter trial, the activity of interferon alfa-n3 was assessed in the treatment of condylomata acuminata in 158 patients. Interferon alfa-n3 or placebo was injected into lesions twice weekly for up to eight weeks. Eighty-six percent of interferon alfa-n3-treated patients and 89% of placebo-treated patients had received previous therapy for condylomata acuminata. Treatment completely eliminated warts in 62% of interferon alfa-treated patients compared with only 21% of placebo-treated patients. Side effects, usually flu-like symptoms, occurred briefly after the injections; if present, they disappeared before the end of the third week of therapy.

In an open-label study clinical trial, the efficacy of interferon alfa-n3 using a once-a-week treatment schedule for up to 16 weeks was evaluated in 28 patients. A total of 154 warts were treated, with 77% resolved completely. After four weeks of treatment, the frequency of adverse reactions was similar in the interferon alfa-n3 treatment arm and placebo treatment arm. The most frequent side effects were myalgias, fever, and headache.

Off-Label Indications

According to American Hospital Formulary Service (AHFS), the treatment of hairy cell leukemia, chronic hepatitis C, chronic hepatitis B, renal carcinoma, acquired immune deficiency syndrome (AIDS)-associated Kaposi's sarcoma, chronic myelocytic leukemia, superficial bladder carcinoma, multiple myeloma, mycosis fungoides, carcinoid tumors, non-Hodgkin's lymphoma, epithelial ovarian carcinoma, malignant melanoma, essential thrombocytosis, superficial bladder carcinoma are accepted indications for interferon alfa-n3.

Chronic Hepatitis C: The FDA has approved the interferon alpha therapies 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. 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 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.

Adverse Drug Reactions/Drug Interactions/Precautions

Interferon alfa-n3 should be used cautiously in patients with debilitating medical conditions, such as cardiovascular disease (e.g., unstable angina and uncontrolled congestive heart failure), severe pulmonary disease (e.g., chronic obstructive pulmonary disease), or diabetes mellitus with ketoacidosis, in patients with coagulation disorders (e.g., thrombophlebitis, pulmonary embolism and hemophilia), severe myelosuppression, or seizure disorders.

There are a number of possible side effects associated with interferon alfa-n3 therapy injection. They include flu-like symptoms (i.e., fever, chills, headaches, muscle aches), fatigue and low energy levels, digestive discomforts (i.e., nausea, lack of appetite, vomiting, diarrhea), mood disturbances (i.e., depression).

Coding/Billing Information

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

Covered when medically necessary:

HCPCS Codes	Description
J9215	Injection, interferon, alfa-N3, (human leukocyte derived), 250,000 IU

ICD-9-CM Diagnosis Codes	Description
070.22-	Viral hepatitis B with hepatic coma, chronic, without mention of hepatic delta
070.23	Viral hepatitis B with hepatic coma, chronic, with hepatitis delta
070.30-	Viral hepatitis B without hepatic coma, chronic, without mention of hepatic delta
070.33	Viral hepatitis B without hepatic coma, chronic, with hepatitis delta
070.41	Acute hepatitis C with hepatic coma
070.44	Chronic hepatitis C with hepatic coma
070.51	Acute hepatitis C without mention of hepatic coma
070.54	Chronic hepatitis C without mention of hepatic coma
070.70- 070.71	Unspecified viral hepatitis C
078.11	Condyloma acuminatum
172.0-172.9	Malignant melanoma of skin
176.0-176.9	Kaposi's sarcoma
183.0	Malignant neoplasm of ovary
188.0-188.9	Malignant neoplasm of bladder
189.0	Malignant neoplasm of kidney, except pelvis
200.00- 200.88	Lymphosarcoma and reticulosarcoma and other specified malignant tumors of lymphatic tissue
202.00- 202.88	Other malignant neoplasms of lymphoid and histiocytic tissue
203.00- 203.02	Multiple myeloma
205.10- 205.12	Chronic myeloid leukemia
209.24	Malignant carcinoid tumor of kidney
232.0-232.9	Carcinoma in situ of skin
233.7	Carcinoma in situ of bladder
238.4	Neoplasm of uncertain behavior of polycythemia vera
238.71	Essential thrombocytemia

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Policy History

Pre-Merger Organizations	Last Review Date	Policy Number	Title
CIGNA HealthCare Great-West Healthcare	1/15/2009	6014	Interferon alfa-n3 (Alferon [®] N)

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