



# 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-2b (Intron® A)**

**Effective Date** ..... 1/15/2011  
**Next Review Date** ..... 1/15/2012  
**Coverage Policy Number** ..... 6012

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## Hyperlink to Related Coverage Policies

- Alferon N®
- Infergen®
- PegaSys®
- PEG Intron®
- Rebetron®

### 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-2b (Intron® A) 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 are classified as a non-responder/relapser after treatment with a peginterferon alfa therapy (PegaSys®, Peg Intron®) as follows:**

(Note: Peg Intron is considered a Non-Preferred Brand on Great-West Healthcare Drug List)

Diagnosis	Treatment Authorization
Genotype 1	<ul style="list-style-type: none"> <li>• Initial authorization - 16 weeks</li> <li>• 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"> <li>• If HCV RNA is undetectable (&lt; 50 IU/ml), an additional 32 weeks (total 48 weeks) will be authorized.</li> <li>• If HCV RNA is detectable (&gt; 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 (&lt;50IU/ml).</li> </ul> </li> </ul>
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
Non-responder or relapser after treatment with a non-pegylated interferon	Duration of treatment will be based upon the genotype
Coinfection with human immunodeficiency virus (HIV)	48 weeks

**CIGNA covers interferon alfa-2b (Intron® A) as medically necessary for ANY of the following indications:**

- chronic hepatitis B in individuals 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-2b (Intron® A) therapy.**

### **FDA Approved Indications**

Interferon alfa-2b is approved for the following indications:

- Hairy Cell Leukemia in patients 18 years of age or older
- as adjuvant to surgical treatment in patients 18 years of age or older with malignant melanoma who are free of disease but at high risk for systemic recurrence, within 56 days of surgery
- initial treatment of clinically aggressive follicular Non-Hodgkin's Lymphoma in conjunction with anthracycline-containing combination chemotherapy in patients 18 years of age or older
- intralesional treatment of selected patients 18 years of age or older with condylomata acuminata involving external surfaces of the genital and perianal areas
- AIDS-Related Kaposi's Sarcoma patients 18 years of age or older
- chronic hepatitis C in patients 18 years of age or older with compensated liver disease who have a history of blood or blood-product exposure and/or are HCV antibody positive
- chronic hepatitis B in patients 1 year of age or older with compensated liver disease

### **FDA Recommended Dosing**

- **Hairy Cell Leukemia:** Intramuscular or subcutaneous, two million units per square meter of body surface area three times per week.

- **Malignant Melanoma:** Intravenous infusion, 20 million units per square meter of body surface area for five consecutive days per week for four weeks.
- **Follicular Non-Hodgkin's Lymphoma:** Subcutaneous, five million units three times per week for up to 18 months in conjunction with anthracycline-containing chemotherapy regimen and following completion of chemotherapy regimen.
- **Condyloma Acuminatum:** Intralesional, one million units (using only the 10-million-units-per-mL strength) per wart (up to five warts) three times a week on alternate days for three weeks. If response is not satisfactory 12 to 16 weeks after the initial treatment course, a second course may be given. Patients with six to 10 warts may be given a second (sequential) course of treatment at the same dose to treat up to five additional warts per course; for patients with more than 10 warts, additional courses may be given as needed with up to five additional warts per course.
- **AIDS-Associated Kaposi's Sarcoma:** Intramuscular or subcutaneous, 30 million units (using 50-million-units-per-mL strength) per square meter of body surface area three times a week.
- **Chronic Hepatitis C:** Intramuscular or subcutaneous, three million units three times per week. Patients who relapse may be re-treated with the same dose to which they had previously responded. The approved dose of interferon alfa-2b for pediatric use is 3 MU/m<sup>2</sup>, and ribavirin is also available as a pediatric liquid (40mg/mL).
- **Chronic Hepatitis B:** Subcutaneous, 30 to 35 million units per week, either as five million units per day or 10 million units three times per week, for 16 weeks.

## Black Box Warnings

**Alpha interferons, including Intron A, 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 signs or symptoms of these conditions should be withdrawn from therapy. In many but not all cases these disorders resolve after stopping Intron A therapy**

## Drug Availability

### Intron A Powder for Injection

Intron A Powder for Injection - 10 million IU per vial 1 mL per vial; 18 million IU per vial; and 50 million IU per vial.

### Intron A Solution for Injection in Multidose Pens

Intron A Solution for Injection - 6 doses of 3million IU (18million IU) Multidose Pen (22.5 million IU per 1.5 mL per pen); 6 doses of 5million IU (30million IU) Multidose Pen (37.5 million IU per 1.5 mL per pen); 6 doses of 10 million IU (60 million IU) Multidose Pen (75 million IU per 1.5 mL per pen).

### Intron A Solution for Injection in Vials

Intron A Solution for Injection - 18million IU multidose vial (22.8million IU per 3.8mL per vial); 25 million IU multidose vial (32 million IU per 3.2 mL per vial).

## General Background

### Pharmacology/Pharmacokinetics

Interferon alfa is a family of proteins that possess antiviral, antitumor and immunomodulating effects. Interferon alfa-2b is a purified sterile recombinant interferon product. It is administered subcutaneously (SC) or intramuscularly (IM). Following both intramuscular and subcutaneous interferon alfa-2b injections, the maximum serum concentrations were approximately 18–116 IU/ml which occurred 3–12 hours after administration, and the elimination half-life was approximately two to three hours. Serum concentrations were undetectable by 16 hours after the injections.

### 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 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. To date, there is no clinical evidence that shows interferon therapies are effective in relapsers or non-responders 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  $\geq 2$  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**

### **Hairy Cell Leukemia**

In clinical trials in patients with hairy cell leukemia, Interferon alfa-2b treatment resulted in a decrease in bone marrow hypercellularity and hairy cell infiltrates. The hairy cell index (HCI), which represents the percent of bone marrow cellularity times the percent of hairy cell infiltrate, was  $\approx$  50% at the beginning of the study in 87% of patients. The percentage of patients with such an HCI decreased to 25% after six months and to 14% after one year. The percentage of patients with hairy cell leukemia who required red blood cell or platelet transfusions decreased significantly during treatment, and the percentage of patients with confirmed and serious infections declined as granulocyte counts improved. Reversal of splenomegaly and of clinically significant hypersplenism was demonstrated in some patients.

### **Malignant Melanoma**

In a randomized controlled study, the safety and efficacy of interferon alfa-2b was evaluated as adjuvant to surgical treatment in 280 patients with melanoma who were free of disease but at high risk for systemic recurrence. A significant increase in relapse-free and overall survival was observed in the interferon alfa-2b treatment group. Median time to relapse for the interferon alfa-2b treated patients versus observation patients was 1.72 years versus 0.98 years ( $p \leq 0.01$ ). Using the Kaplan-Meier method, the estimated five-year relapse-free survival (RFS) rate, was 37% for interferon alfa-2b versus 26% for observation patients, and the estimated five-year overall survival rate was 46% for interferon alfa-2b versus 37% for observation patients. Median overall survival time for interferon alfa-2b-treated patients was 3.82 years versus 2.78 years with observation patients ( $p=0.047$ ).

In another randomized study, a total of 642 resected high-risk melanoma patients were randomized to high-dose interferon alfa-2b therapy for one year, low-dose interferon alfa-2b therapy for two years (3 MU/d three times per week [tiw] SC), or observation. High-dose interferon alfa-2b therapy demonstrated an improvement in relapse-

free survival (three-year estimated RFS 48% vs. 41%; median RFS 2.4 vs. 1.6 years). Similar relapse-free survival rates were observed in the low-dose interferon alfa-2b arm and in the observation arm.

### **Follicular Non-Hodgkin's Lymphoma**

In a randomized controlled study, the safety and efficacy of interferon alfa-2b in conjunction with a combination chemotherapy regimen (cyclophosphamide 600, doxorubicin, and teniposide, and prednisone [CHVP]) was evaluated as initial treatment in 265 patients with clinically aggressive, Stage III/IV follicular Non-Hodgkin's Lymphoma. A total of 130 patients received CHVP therapy, and 135 patients received CHVP therapy plus interferon alfa-2b. Treatment consisted of six CHVP cycles administered monthly, followed by an additional six cycles administered every two months for one year. Results showed that the combination of interferon alfa-2b plus CHVP treatment arm had a significantly longer progression-free survival (2.9 vs. 1.5 years,  $p=0.0001$ ) than the CHVP treatment arm. After a median follow-up of 6.1 years, the median survival for patients treated with CHVP alone was 5.5 years, while median survival for patients treated with CHVP plus interferon alfa-2b had not been reached ( $p=0.004$ ). In three additional published, randomized controlled studies of the addition of interferon alfa to anthracycline-containing combination chemotherapy regimens, the addition of interferon alfa was associated with significantly prolonged progression-free survival.

### **Condylomata Acuminata**

Three controlled, double-blind clinical trials evaluated the safety and efficacy of interferon alfa-2b for the treatment of condylomata acuminata. In these studies, interferon alfa-2b doses of one million international units (IU)/lesion were administered intralesionally three times a week (tiw), in  $\square$  five lesions per patient for three weeks. The patients were observed for up to 16 weeks after completion of the full treatment course. Results showed that Interferon alfa-2b was significantly more effective than placebo, as measured by disappearance of lesions, decreases in lesion size, and by an overall change in disease status. Of 192 interferon alfa-2b treated patients and 206 placebo treated patients, 42% of interferon alfa-2b patients versus 17% of placebo patients experienced clearing of all treated lesions. Likewise, 24% of interferon alfa-2b patients versus 8% of placebo patients experienced marked ( $\square$  75% to  $\square$  100%) reduction in lesion size; 18% vs. 9% experienced moderate ( $\square$  50% to  $\square$  75%) reduction in lesion size; 10% vs. 42% had a slight ( $\square$  50%) reduction in lesion size; 5% vs. 24% had no change in lesion size; and 0% vs. 1% experienced exacerbation ( $p \leq 0.001$ ). During the second course of treatment in patients who had not achieved total clearing of all their treated lesions, 38–67% of patients had clearing of all treated lesions. After two courses of treatment, the overall percentage of patients who had cleared all their treated lesions ranged from 57–85%. Maximal response to interferon alfa-2b therapy was noted four to eight weeks after initiation of treatment.

### **Acquired Immune Deficiency Syndrome (AIDS)-Related Kaposi's Sarcoma (KS)**

The safety and efficacy of interferon alfa-2b for the treatment of Kaposi's Sarcoma were evaluated in clinical trials in 144 patients. About 44% of asymptomatic patients versus 7% of symptomatic patients responded to the therapy. The median time to response was approximately two months and one month for asymptomatic and symptomatic patients, respectively. The median duration of response was three months for the asymptomatic and one month for symptomatic patients.

Another study evaluated the maintenance dose of interferon alfa-2b administered subcutaneously every other day for up to one year in patients achieving antitumor and antiviral responses. The median time of response was two months, and the median duration of response was five months in the asymptomatic patients.

### **Chronic Hepatitis**

The FDA has approved the interferon alfa 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 (INR) ratio,  $\leq 1.7$ ]; 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.

### **Chronic Hepatitis C**

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

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 ages 3–17, and the approved dose of interferon alfa-2b for pediatric use is 3 MU/m<sup>2</sup>. 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 ages 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, larger studies are needed evaluating the efficacy and safety of peginterferon alfa as monotherapy as well as in combination with ribavirin in pediatric patients with chronic hepatitis C.

Five randomized clinical trials evaluated the safety and efficacy of interferon alfa-2b three million IU three times per week in the treatment of chronic hepatitis C. The initial three studies were placebo-controlled trials that evaluated a six-month course of therapy. In each study, interferon alfa-2b therapy resulted in a reduction in serum alanine aminotransferase (ALT) in a greater proportion of patients versus control patients at the end of six months of dosing. During the six months of follow-up, approximately 50% of the patients who responded maintained their ALT response. A combined analysis comparing pretreatment and post-treatment liver biopsies revealed histological improvement in a statistically significantly greater proportion of interferon alfa-2b, recombinant treated patients compared to controls.

Two additional studies assessed longer treatment durations, up to 24 months in patients who had hepatitis with or without cirrhosis in the absence of decompensated liver disease. Complete response to treatment was defined as normalization of the final two serum ALT levels during the treatment period. A sustained response was defined as a complete response at the end of the treatment period with sustained normal ALT values lasting at least six months following discontinuation of therapy. Results showed that longer durations of interferon alfa-2b therapy improved the sustained response rate. In patients with complete responses (CR) to interferon alfa-2b therapy after six months of treatment (42%), responses were less often sustained if the drug was discontinued (30%) than if it was continued for 18–24 months (56%). In both trials, the sustained response rate in the patients receiving 18 or 24 months of therapy was 22% and 26%, respectively. Additional therapy did not result in significantly more responses in patients who did not have a CR by six months, since almost all patients responded to therapy within the first 16 weeks of treatment.

### **Chronic Hepatitis B**

Interferon alfa-2b is indicated for the treatment of hepatitis B in patients one year of age or older with compensated liver disease. Three clinical studies evaluated the safety and efficacy of interferon alfa-2b in adult patients with chronic hepatitis B and compensated liver disease. Two of these three studies were randomized controlled studies, and a significantly greater proportion of interferon alfa-2b treated patients exhibited a

virologic response compared with untreated control patients. In a third study without a concurrent control group, a similar response rate to interferon alfa-2b therapy was observed. Hepatitis B surface antigen (HBsAg) was lost in 27% of patients who responded to interferon alfa-2b therapy at a dose of five million IU every day (qd), and 35% of patients who responded to 10 million IU tiw. No untreated control patient lost HBsAg in these studies. In both controlled studies, interferon alfa-2b resulted in normalization of serum ALT in a significantly greater proportion of treated patients compared to untreated patients. In a third study without a concurrent control group, normalization of serum ALT was observed in 50% of patients receiving interferon alfa-2b therapy. Virologic response was associated with a reduction in serum ALT to normal or near normal in 87% of patients responding to interferon alfa-2b therapy at five million IU qd and 100% of patients responding to 10 million IU three times per week.

### Off-Label Indications

Based on American Hospital Formulary Service (AHFS) the treatment of renal carcinoma, chronic myelocytic leukemia, multiple myeloma, mycosis fungoides, carcinoid tumors, skin carcinoma, essential thrombocytosis, and superficial bladder cancer are accepted indications for interferon alfa-2b.

Published clinical studies have evaluated the intravesical administration of interferon alfa-2b in the treatment of superficial bladder carcinoma. Final results from a national multicenter phase II trial of combination bacillus Calmette-Guerin (BCG) plus interferon alfa-2b for treatment of superficial bladder cancer in 1007 patients showed that patients who were naïve to BCG (59%) and those having BCG failure (45%), respectively, remained disease-free at the 24-month median follow-up. A prospective, randomized, phase II/III study evaluated the efficacy of two different doses of intravesical mitoxantrone and interferon alfa-2b in 208 patients with superficial bladder cancer. Results showed that patients with interferon alfa-2b therapy experienced lower rates of recurrence with tumor progression than patients in the other treatment group. Time to first disease recurrence was significantly shorter in the two mitoxantrone treatment groups compared to the interferon alfa-2b arm ( $p < 0.05$ ). The recurrence rate per 100 patient-months was significantly higher in the control group versus the treatment groups ( $p < 0.05$ ), with the lowest recurrence seen in the interferon alfa-2b group.

### Adverse Drug Reactions/Drug Interactions/Precautions

There are cases of cerebrovascular complications due to stroke in patients with few or no expected risk factors for stroke. Patients with persistently severe or worsening signs or symptoms of these conditions should be withdrawn from therapy. In many, but not all, cases, these disorders resolve after stopping interferon alfa-2b therapy.

There are a number of possible side effects associated with interferon alfa-2b therapy injections. 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, suicidal thoughts and behavior), alopecia, injection-site discomfort, and blood disorders. These side effects typically start in the first few weeks of treatment and become less bothersome over time, although reactions can vary in both duration and intensity from person to person.

## 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
070.22-	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 neoplasm 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 breast and genitourinary system
238.4	Polycythemia vera
238.71	Essential thrombocythemia

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## Policy History

Pre-Merger Organizations	Last Review Date	Policy Number	Title
CIGNA HealthCare Great-West Healthcare	1/15/2009	6012	Interferon alfa-2b (Intron® A)

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