Intron A - monotherapy HEPATITIS B

Description
Intron A (interferon alfa-2b)

Background
The interferons are a family of naturally occurring small proteins and glycoproteins that are produced and secreted by cells in response to viral infections and to synthetic or biological inducers. Interferons exert their cellular activities by binding to specific membrane receptors on the cell surface. Once bound to the cell membrane, interferons initiate a complex sequence of intracellular events. In vitro studies demonstrated that these include the induction of certain enzymes, suppression of cell proliferation, immunomodulating activities such as enhancement of the phagocytic activity of macrophages and augmentation of the specific cytotoxicity of lymphocytes for target cells, and inhibition of virus replication in virus-infected cells (1).

Regulatory Status
FDA-approved indications: Intron A is indicated for the treatment of chronic hepatitis B in patients 1 year of age or older with compensated liver disease. Patients who have been serum HBsAg positive for at least 6 months and have evidence of HBV replication (serum HBeAg positive) with elevated serum ALT are candidates for treatment. Studies in these patients demonstrated that Intron A therapy can produce virologic remission of this disease (loss of serum HBeAg) and normalization of serum aminotransferases. Intron A therapy resulted in the loss of serum HBsAg in some responding patients.
Intron A is contraindicated in patients with autoimmune hepatitis and decompensated liver disease. Intron A has a boxed warning that stresses the importance of clinical and laboratory monitoring while on this medication to identify or monitor any possible neuropsychiatric, autoimmune, ischemic, and infectious disorders (1).

Peg Interferon-alfa has the advantages of more convenient administration and more sustained viral suppression. Clinical trials suggest that the efficacy of peg Interferon-alfa is similar to or slightly better than standard Interferon-alfa (2).

Related policies
Actimmune, Alferon N, Infergen, Pegasys, Pegintron

Policy
This policy statement applies to clinical review performed for pre-service (Prior Approval, Precertification, Advanced Benefit Determination, etc.) and/or post-service claims.

Intron-A may be considered medically necessary for the treatment of chronic hepatitis B, in the presence of compensated liver, positive surface antigen (HBsAG) for at least six months, current evidence of hepatitis B viral replication, currently elevated ALT, and without immune-suppression due to transplant. Intron-A is considered investigational for the treatment of hepatitis B, if the previously mentioned conditions are not met.

Prior-Approval Requirements
Age 1 year of age or older

Diagnoses
Patient must have the following:
1. Chronic hepatitis B

AND ALL of the following:
1. Compensated liver disease
2. Been hepatitis B surface antigen (HBsAG) positive for at least 6 months
3. Current evidence of hepatitis B viral replication via either a positive hepatitis
B e antigen (HBeAG) or a positive hepatitis B viral DNA level
4. Currently elevated (2 or more times the upper limit serum alanine aminotransferase (ALT) level
5. NOT an immunosuppressed transplant recipient

Prior – Approval Renewal Requirements
None

Policy Guidelines

Pre - PA Allowance
None

Prior - Approval Limits

Duration  6 months

Rationale

Summary
The interferons are a family of naturally occurring small proteins and glycoproteins, produced and secreted by cells in response to viral infections and to synthetic or biological inducers. FDA-approved indications include hepatitis B. This policy is confined to the indication for hepatitis B.

Prior authorization is required to ensure the safe, clinically appropriate and cost effective use of Intron-A while maintaining optimal therapeutic outcomes.

References
22. Afdhal NH, Freilich B, Black M, et al. National COPILOT investigators. Comparison of therapy with Peg-interon 0.5mcg/kg versus colchicine 0.6mg bid in 250 patients with
cirrhosis and HCV. Interim data from COPILOT study. Hepatology 2002;36; 312A

Policy History

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<tr>
<th>Date</th>
<th>Action</th>
<th>Reason</th>
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<tbody>
<tr>
<td>October 2004</td>
<td>Criteria updated to reflect current guidelines:</td>
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<td>NIH Consensus Statement on Management of Hepatitis C: 2002</td>
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<td>NIH Consensus Statements and State-of-the-Science Statements</td>
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<td>Volume 19, Number 3, June 10-12, 2002</td>
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<td>National Institutes of Health, Office of the Director</td>
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<td>Diagnosis, Management, and Treatment of Hepatitis C</td>
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<td>American Association for the Study of Liver Diseases</td>
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<td>Hepatology, April 2004</td>
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<td>September 2005</td>
<td>Chronic hepatitis B virus (HBV) infection is a growing health problem affecting over a million people in the United States and at least 350 million people worldwide. (3) Patients with chronic hepatitis B are at an increased risk to develop cirrhosis, liver failure, and liver cancer. (4) The goal of chronic hepatitis B therapy is to prevent these complications by decreasing the patient’s hepatitis B viral level and maintaining it at low levels for as long as possible. (4) Despite a common goal, the management of chronic hepatitis B infection remains a controversial issue. Much discussion and analysis has centered around which patients should receive treatment and what that treatment should be composed of. (3-16)</td>
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<td>Hepatitis B e antigen (HBeAg) and Hepatitis B viral DNA (HBV DNA) are both markers of HBV replication and their presence provides a rationale for initiating therapy to stop the progression of liver disease. (4) In the past, the ability to detect HBV DNA in the serum by hybridization assays was a major factor in determining which patients should be treated. This assay is sensitive enough to detect viral DNA when it is present in amounts $\geq 10^5$ copies/ml and consequently this viral level became an important benchmark in treatment algorithms. As improvements in viral detection</td>
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have advanced it has become apparent that it is not possible to designate a single HBV DNA value that can differentiate between inactive hepatitis B carriers and patients suffering from chronic hepatitis B. (4) Recent practice guidelines have recommended that alanine aminotransferase (ALT) levels and liver biopsies can be used to determine which patients with low HBV DNA levels require treatment. (4)

There are currently five FDA-approved treatments for chronic HBV infection in the United States, these include interferon alfa-2b (INTRON-A), peginterferon alpha-2a (Pegasys), lamivudine (Epivir-HBV), entecavir (Baraclude) and adefovir dipivoxil (Hepsera). Peginterferon alpha-2a (Pegasys) is the most recent agent to receive FDA approval for the treatment of chronic hepatitis B (Approved 5/13/2005). It works by both stimulating the immune system and inhibiting viral replication. (5) It also has a longer half-life than conventional interferon which allows for once-weekly dosing. (17) Pegasys has been shown to produce superior clinical outcomes in patients with HBeAg-positive chronic HBV and significantly higher response rates in chronic HBV patients that are HBeAg-negative. (5) Another agent that can be used to treat HBV is peginterferon alpha-2b (PEG-INTRON). Although it currently has not received FDA-approval for this indication, it has been shown to be active against HBV in clinical trials. (15)

In the treatment of HBV there are several patient populations that include special consideration. These include patient coinfected with HIV, patients with liver transplants, and patients with cirrhosis. In the United States approximately 10% of all HIV patients are coinfected with HBV. (4) Although no evidence-based practice guidelines exist for the treatment of HBV-HIV coinfection, HIV is known to accelerate the natural course of HBV infection. Consequently, some experts have suggested applying the same criteria for treating non-HIV infected HBV patients to coinfected patients. (12) When treating coinfected patients an effort should be made to avoid the emergence of HIV resistance. (13) Therefore, since interferon therapy does not induce antiretroviral resistance, it could play an important role in treatment of patients not currently requiring HIV therapy. (7) In patients undergoing liver transplantation long-term suppression of HBV is very important to ensure organ survival and some practice guidelines suggest that this treatment should be continued for life. (7,13) Based on this information, a history of liver transplantation has been added to FEP PA criteria as an acceptable diagnosis for renewal of Hepatitis B therapy. The goal for treating HBV-cirrhosis depends upon the patient’s stage of
cirrhosis. For patients with compensated cirrhosis the goal is to prevent the progression to decompensated cirrhosis and to prevent the development of liver cancer. For patients with decompensated cirrhosis the goal is to improve liver function in order to avoid the need for liver transplantation. (11) Limited data suggests that interferon therapy is effective in the treatment of compensated cirrhosis. (4,11) Interferon therapy is not recommended in patients with decompensated cirrhosis because it increases their risk for developing bacterial infections and it can potentially worsen their condition. (11)

There are several compelling reasons to include interferon agents used to treat chronic hepatitis B in the FEP Prior Approval Program. The first reason is to make sure that the decision to begin treatment is justified by the patient’s current stage of disease. Patients with mild chronic hepatitis B and inactive carriers of the disease should generally be monitored closely instead of treated. (4,14) Another reason is to promote the safe use of interferon therapy. Patients with certain liver conditions such as decompensated cirrhosis may actually have their liver function deteriorate if they are treated with interferon therapy. (11) Finally, the appropriate role of interferon therapy in the treatment of hepatitis B continues to evolve as ongoing clinical trials are completed and reviewed. Inclusion in the FEP Prior Approval Program secures continued close monitoring of this data to provide continued safe and optimal use of these products.

January 2006

Criteria updated to reflect a process change to allow patients on Hepatitis C Combination Therapy to switch between ribavirin products during their authorization period without needing a new prior authorization record being set.

August 2007

The interferons are a family of naturally occurring small proteins and glycoprotein produced and secreted by cells in response to viral infections and to synthetic or biological inducers. They exert their cellular activities by binding to specific membrane receptors on the cell surface. Once bound to the cell membrane, interferon’s initiate a complex sequence of intracellular events including the following: induction of certain enzymes, suppression of cell proliferation, immunomodulating activities such as enhancement of the phagocytic activity of macrophages and augmentation of the specific cytotoxicity of lymphocytes for target cells, and inhibition of virus replication in virus-infected cells.

The interferon products are included in the PA program for many reasons,
including the following: the potential to cause or aggravate fatal or life-threatening neuropsychiatric, autoimmune, ischemic, and infectious disorders, the need for frequent lab monitoring including CBC and platelet counts, and serum ALT, and the strict preparation and IV administration guidelines.

Potential concerns with therapy include the following:

CNS effects: Depression and suicidal behavior including suicidal ideation, suicidal attempts, and completed suicides have been reported in association with treatment with interferon. Patients with a preexisting psychiatric condition, especially depression, or a history of severe psychiatric disorder should not be treated with the interferon products.

Hepatotoxicity: Hepatotoxicity, including fatality, has been observed in interferon treated patients. Any patient developing liver function abnormalities during treatment should be monitored closely and if appropriate, treatment should be discontinued.

Pulmonary effects: Pulmonary infiltrates, pneumonitis and pneumonia, including fatality, have been observed in interferon treated patients. The cause is not yet known. Any patient developing fever, cough, dyspnea, or other respiratory symptoms should have a chest X-ray taken. If the chest X-ray shows pulmonary infiltrates or there is evidence of pulmonary function impairment, the patient should be closely monitored, and, if appropriate, interferon treatment should be discontinued.

Autoimmune disease: Rare cases of autoimmune diseases including thrombocytopenia, vasculitis, Raynaud's phenomenon, rheumatoid arthritis, lupus erythematosus, and rhabdomyolysis have been observed in patients treated with interferon. In very rare cases the event resulted in fatality. The mechanism by which these events develop and their relationship to interferon alfa therapy is not clear. Any patient developing an autoimmune disorder during treatment should be closely monitored and, if appropriate, treatment should be discontinued.

Interchangeability: Variations in dosage, routes of administration, and adverse reactions exist among different brands of interferon. Therefore, do not use different brands of interferon in any single treatment regimen.
### Prescription Drugs

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<th>Prescription Drugs</th>
<th>Effective Date:</th>
<th>July 1, 2014</th>
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<tbody>
<tr>
<td>Subsection:</td>
<td>Anti-Infective Agents</td>
<td>Original Policy Date:</td>
<td>October 1, 2004</td>
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**December 2008**

FDA grants clearance to market a regimen that combines ribavirin with peginterferon alpha-2b to treat chronic hepatitis C in previously untreated children ages 3 to 17. The two-drug therapy offers extended effectiveness with the aid of pegylation, a technology that allows the medication to remain in the blood longer. The only previously approved therapy in the US for treating pediatric hepatitis C is interferon alfa-2b in combination with ribavirin.

**June 2009**

Follicular lymphoma maintenance therapy added as a new indication for interferon therapy. (18) The use of aggressive chemotherapy and maintenance therapy with interferon alpha-2b in follicular lymphoma improved outcome; more than 60% of patients remain alive, free of disease at longer follow-up. (19)

**July 2009**

Criteria updated to remove Roferon, which has been discontinued by manufacturer. Recommend renewal limits of 1 year based on three large randomized controlled trials of maintenance therapy in patients with HCV infection who failed to achieve SVR following previous therapy with conventional treatment (combination therapy of pegylated interferon and ribavirin). (20-23) The Hepatitis C Antiviral long-term Treatment against Cirrhosis (HALT-C) trial, sponsored by the National Institutes of Health, is the largest and most well recognized of these studies. These trials have been evaluating the efficacy of low dose Interferon maintenance therapy and reduced dose pegylated interferon in prior non-responders to prevent further progression of fibrosis in this subset of patients who already have advanced fibrosis/cirrhosis. (20-22) The Shiffman et al. study showed this prevention of progression of Hepatitis C damage in patients on low dose Intron-A therapy at 24 months. (22) Such a strategy can prevent these patients from developing complications such as decompensated cirrhosis and Hepatocellular carcinoma.

**March 2010**

Intron A removed from the Interferon Therapy Criteria document and made into its own criteria document. Criteria documents reorganized by drug, rather than disease state, to improve functionality and prior authorization work flow.

Diagnoses of hepatitis B and hepatitis C removed from Section 4 (Interferon Therapy) as they are now addressed in Section 1 (Hepatitis B), Section 2 (Hepatitis B Monotherapy) and Section 3 (Hepatitis C Combination Therapy CHILD) of this document. References to Actimmune and the diagnosis of osteopetrosis removed from Section 4 (Interferon
Section 1 (Hepatitis B) reviewed and revised to follow the current Intron A package insert, as follows: Intron A is indicated for the treatment of chronic hepatitis B in patients 1 year of age or older with compensated liver disease. Patients who have been serum hepatitis B surface antigen (HBsAG) positive for at least 6 months and have evidence of hepatitis B viral replication with elevated serum alanine aminotransferase (ALT) are candidates for treatment. (1) Indicators of viral replication are generally accepted to be either a positive hepatitis B e antigen (HBeAG) or a positive hepatitis B virus DNA level. (1,2) An elevated ALT is commonly accepted as being 2 or more times the upper limit of normal. (2)

Currently approved therapies do not eradicate the hepatitis B virus; thus, the short-term goal of treatment is sustained suppression of the hepatitis B virus and remission of liver disease. (1) The ultimate goal is to prevent cirrhosis and hepatic failure. The package insert does not discuss treatment beyond 24 weeks. Patients who are immunosuppressed transplant recipients should not be treated with Intron A. There are reports of worsening liver disease, including jaundice, hepatic encephalopathy, hepatic failure, and death following Intron A therapy in such patients. (1) Liver transplant removed from criteria and renewal will not be allowed.