

## 5.01.01

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<b>Subsection:</b>	Anti-Infective Agents	<b>Original Policy Date:</b>	October 1, 2004
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**Last Review Date:** November 30, 2018

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## Intron A Hepatitis B

### Description

#### Intron A (interferon alfa-2b)

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#### 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 (1).

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,

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autoimmune, ischemic, and infectious disorders. Alpha interferons, including Intron A, cause or aggravate fatal or life-threatening neuropsychiatric, autoimmune, ischemic, and infectious disorders. Patients with persistently severe or worsening signs or symptoms of these conditions should be withdrawn from therapy.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 (1).

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## Related policies

Actimmune, Alferon N, 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 patients 1 year of age and older, 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** in patients that are less than 1 years of age and for all other indications.

## 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 Be antigen (HBeAG) or a positive hepatitis B viral DNA level
4. Currently elevated (2 or more times the upper limit serum alanine

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- aminotransferase) ALT level
5. **NOT** an immunosuppressed transplant recipient

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## 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 (1).

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

#### References

1. Intron A [package insert]. Whitehouse Station, NJ: Merck Sharp & Dohme Corp.; May 2018

### Policy History

Date	Action
October 2004	Criteria updated to reflect current guidelines: NIH Consensus Statement on Management of Hepatitis C: 2002 NIH Consensus Statements and State-of-the-Science Statements Volume 19, Number 3, June 10-12, 2002 National Institutes of Health, Office of the Director Diagnosis, Management, and Treatment of Hepatitis C American Association for the Study of Liver Diseases Hepatology, April 2004

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September 2005      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)

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 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)

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In the treatment of HBV there are several patient populations that include special consideration. These include patient coinfecting with HIV, patients with liver transplants, and patients with cirrhosis. In the United States approximately 10% of all HIV patients are coinfecting 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 coinfecting patients. (12) When treating coinfecting 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)

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.

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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 Therapy)* as they are currently addressed in the criteria document entitled Interferon Therapy Criteria, which addresses Actimmune and Alferon-N.
- September 2011

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**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.

September 2012	Annual editorial and reference update
June 2014	Annual review and reference update
September 2015	Annual editorial review and reference update
March 2016	Annual editorial review and reference update Policy number changed from 5.03.01 to 5.01.01
December 2017	Annual editorial review and reference update
November 2018	Annual editorial review and reference update

## Keywords

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**This policy was approved by the FEP<sup>®</sup> Pharmacy and Medical Policy Committee on November 30, 2018 and is effective January 1, 2019.**