Intron A Ribavirin

**Description**

Intron A (interferon alfa-2b) with ribavirin, (Moderiba, Rebetol, Ribasphere, RibaTab, ribavirin tablets/capsules - all strengths)

**Background**

Hepatitis C is a viral disease caused by the hepatitis C virus (HCV) that leads to inflammation of the liver. Most people who were recently infected with hepatitis C do not have symptoms, but most people infected with hepatitis C develop a chronic infection. Untreated, chronic infection can lead to liver cirrhosis and/or liver cancer. Six genotypes of the hepatitis C virus exist and genotyping is essential to effective treatment. Hepatitis C infection may be detected in the blood by the HCV RNA assay. Disease status may be monitored by assays of biochemical liver tests or liver biopsy (1).

The goals of HCV treatment are to remove the virus from the blood and reduce the risk of cirrhosis and liver cancer that can result from long-term HCV infection. The most common treatment regimens are based on combinations of pegylated interferon alfa, ribavirin, and a direct acting agent. In some cases, treatment with a single agent or two agents is most appropriate (1).

**Regulatory Status (limited to hepatitis C)**

FDA-approved indication: Intron A is indicated for the treatment of 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. Studies in these patients demonstrated that
Intron A therapy can produce clinically meaningful effects on this disease, manifested by normalization of serum alanine aminotransferase (ALT) and reduction in liver necrosis and degeneration (2).

All alpha interferons, including Intron A, carry a boxed warning that they can 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 Patients with persistently severe or worsening signs or symptoms of these conditions should be withdrawn from therapy.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 (2).

A liver biopsy should be performed to establish the diagnosis of chronic hepatitis. Patients should be tested for the presence of antibody to HCV. Patients with other causes of chronic hepatitis, including autoimmune hepatitis, should be excluded. Prior to initiation of Intron A therapy, the physician should establish that the patient has compensated liver disease. The following patient entrance criteria for compensated liver disease were used in the clinical studies and should be considered before Intron A treatment of patients with chronic hepatitis C (2):

- No history of hepatic encephalopathy, variceal bleeding, ascites, or other clinical signs of decompensation
- Bilirubin Less than or equal to 2 mg/dL
- Albumin Stable and within normal limits
- Prothrombin Time Less than 3 seconds prolonged
- WBC Greater than or equal to 3000/mm$^3$
- Platelets Greater than or equal to 70,000/mm$^3$
- Serum creatinine should be normal or near normal.

Prior to initiation of Intron A therapy, CBC and platelet counts should be evaluated in order to establish baselines for monitoring potential toxicity. These tests should be repeated at Weeks 1 and 2 following initiation of Intron A therapy, and monthly thereafter. Serum ALT should be evaluated at approximately 3-month intervals to assess response to treatment (1).

Patients with preexisting thyroid abnormalities may be treated if thyroid stimulating hormone (TSH) levels can be maintained in the normal range by medication. TSH levels must be within normal limits upon initiation of Intron A treatment and TSH testing should be repeated at 3 and 6 months (2).
Intron A in combination with Rebetol is indicated for the treatment of chronic hepatitis C in patients 3 years of age and older with compensated liver disease previously untreated with alpha interferon therapy and in patients 18 years of age and older who have relapsed following alpha interferon therapy. See Rebetol package insert for additional information (2,3)

Patients with causes of chronic hepatitis other than chronic hepatitis B or chronic hepatitis C should not be treated with Intron A. CBC and platelet counts should be evaluated prior to initiation of Intron A therapy in order to establish baselines for monitoring potential toxicity. These tests should be repeated at treatment Weeks 1, 2, 4, 8, 12, and 16. Liver function tests, including serum ALT, albumin, and bilirubin, should be evaluated at treatment Weeks 1, 2, 4, 8, 12, and 16. HBeAg, HBsAg, and ALT should be evaluated at the end of therapy, as well as 3- and 6-months posttherapy, since patients may become virologic responders during the 6-month period following the end of treatment (2).

A transient increase in ALT greater than or equal to 2 times baseline value (flare) can occur during Intron A therapy for chronic hepatitis B. When ALT flare occurs, in general, Intron A therapy should be continued unless signs and symptoms of liver failure are observed. During ALT flare, clinical symptomatology and liver function tests including ALT, prothrombin time, alkaline phosphatase, albumin, and bilirubin, should be monitored at approximately 2-week intervals (2).

Rebetol and Ribasphere capsules are nucleoside analogues indicated in combination with interferon alfa-2b (pegylated and nonpegylated) for the treatment of Chronic Hepatitis C (CHC) in patients 3 years of age or older with compensated liver disease (3,4).

Patients with the following characteristics are less likely to benefit from retreatment after failing a course of therapy: previous nonresponse, previous pegylated interferon treatment, significant bridging fibrosis or cirrhosis, and genotype 1 infection (3,4,5)

Ribavirin capsules are a nucleoside analogue indicated in combination with interferon alfa-2b (nonpegylated) for the treatment of Chronic Hepatitis C (CHC) in patients 3 years of age or older with compensated liver disease (5).

Non-pegylated interferons, such as Intron-A, are generally considered inferior to pegylated interferons, such as Pegasys and Pegintron (2).
Intron A and ribavirin may be considered **medically necessary** for the treatment of hepatitis C in patients with compensated liver disease who are previously untreated with alpha interferon or who relapsed following alpha interferon therapy (relapsers must be 18 years of age or older) and who are not candidates for treatment with a pegylated interferon in combination with ribavirin and a protease inhibitor, who are not pregnant or the partner of a pregnant woman, who have been instructed to practice birth control during therapy and for six months after stopping therapy, who have not been diagnosed with renal failure and who are not immunosuppressed transplant recipients.

Intron A and ribavirin may be considered **investigational** in patients with hepatitis C who are less than 3 years of age or who do not meet the criteria for medical necessity.

**Prior-Approval Requirements**

**Age**  3 years of age or older

**Diagnosis**

Patient must have the following:

1. Chronic hepatitis C

AND ALL of the following:

1. Compensated liver disease
2. Previously untreated with alpha interferon **OR** relapsed following alpha interferon therapy (relapsers must be 18 years of age or greater)
3. Must **NOT** be an appropriate candidate for treatment with a pegylated interferon in combination with ribavirin and a protease inhibitor (such as Victrelis, Incivek, or Olysio)
4. The patient or the partner of the patient is not pregnant
5. Patients of child bearing age have been or will be instructed to practice effective contraception during therapy and for 6 months after stopping ribavirin therapy
6. **NOT** diagnosed with renal failure
7. **NOT** an immunosuppressed transplant recipient

### Prior – Approval *Renewal* Requirements

Same as above

#### Policy Guidelines

**Pre - PA Allowance**

None

**Prior - Approval Limits**

Duration 6 months

**Prior – Approval *Renewal* Limits**

Duration 6 months

### Rationale

**Summary**

Hepatitis C is a viral disease caused by the hepatitis C virus (HCV) that leads to inflammation of the liver. Untreated, chronic infection can lead to liver cirrhosis and/or liver cancer. The most common treatment regimens are based on combinations of pegylated interferon alfa, ribavirin, and the protease inhibitors, telaprevir and boceprevir. In some cases, treatment with a single agent or two agents is most appropriate (1-4).

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

**References**

September 2011  Section 3 title changed from Hepatitis C Combination Therapy CHILD to Hepatitis C with RIBAVIRIN. Intron A in combination with ribavirin is indicated for the treatment of chronic hepatitis C in patients 3 years of age and older with compensated liver disease previously untreated with alpha interferon therapy and in patients 18 years of age and older who have relapsed following alpha interferon therapy. A patient is said to have experienced a virologic relapse if hep C virus becomes undetectable during treatment but becomes detectable after cessation of treatment. 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.

September 2012  Annual editorial and reference update
March 2014  Annual editorial review and reference update
December 2014  Annual editorial review and reference update. Addition of Moderiba
March 2016  Annual editorial review and reference update
Policy number changed from 5.03.06 to 5.01.06

Keywords

This policy was approved by the FEP® Pharmacy and Medical Policy Committee on March 18, 2016 and is effective April 1, 2016.

Deborah M. Smith, MD, MPH