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Section:	Prescription Drugs	**Effective Date:**	July 1, 2022
Subsection:	Anti-Infective Agents	**Original Policy Date:**	September 1, 2011
Subject:	Intron A Ribavirin	**Page:**	1 of 6

Last Review Date: June 16, 2022

Intron A Ribavirin

Description

Intron A (interferon alfa-2b) with ribavirin, (Copegus, Moderiba, Rebetol, Ribapak, 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).

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).

Ribavirin is nucleoside analogue 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).

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 Patients with persistently severe or worsening signs or symptoms of these conditions should be withdrawn from therapy.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 (2).

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 (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. 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. 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).

Ribavirin carries boxed warnings: monotherapy is not effective for the treatment of chronic hepatitis C, hemolytic anemia associated with ribavirin therapy may result in worsening of cardiac disease that has led to fatal and nonfatal myocardial infarctions. Patients with a history of significant or unstable cardiac disease should not be treated with ribavirin, and significant teratogenic and embryocidal effects have been demonstrated in all animal species exposed to ribavirin. Therefore, ribavirin therapy is contraindicated in women who are pregnant and in the male partners of women who are pregnant. Extreme care must be taken to avoid pregnancy during therapy and for 6 months after completion of treatment in both female patients and in female partners of male patients who are taking ribavirin therapy (3-4).

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 and ribavirin may be considered **medically necessary** for the treatment of hepatitis C and if the conditions indicated below are met.

Intron A and ribavirin may be considered **investigational** in patients less than 3 years of age and for all other indications.

Prior-Approval Requirements

Age 3 years of age or older

Diagnosis

Patient must have the following:

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
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

Same as above

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 a protease inhibitor. 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

1. Ghany MG, Strader DB, Thomas DL, Seeff LB. Diagnosis, management, and treatment of hepatitis C: an update. Hepatology. 2009; 49(4):1335-1374.
2. Intron A [package insert]. Whitehouse Station, NJ: Merck & Co., Inc.; August 2019.
3. Rebetol [package insert]. Whitehouse Station, NJ: Merck & Co., Inc.; October 2017.
4. Ribasphere [package insert]. Warrendale, PA: Kadmon Pharmaceuticals, LLC.; September 2017.

Policy History

Date	Action
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
December 2017	Annual editorial review and reference update
November 2018	Annual editorial review and reference update. Removal of examples of protease inhibitors
December 2019	Annual review and reference update
December 2020	Annual review
June 2021	Annual review
June 2022	Annual review

Keywords

This policy was approved by the FEP® Pharmacy and Medical Policy Committee on June 16, 2022 and is effective on July 1, 2022.