RATIONALE FOR INCLUSION IN PA PROGRAM

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).

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 (2).

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 protease inhibitor. In some cases, treatment with a single agent or two agents is most appropriate (2).

Regulatory Status (limited to hepatitis C)
FDA-approved indication: Intron A is an alpha interferon 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 (1).

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 (1).

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 (1):

- 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 (1).

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 (1).

Non-pegylated interferons, such as Intron A are generally considered inferior to pegylated
interferons, such as Pegasys and Pegintron (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, 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).

**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).

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.

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