BlueCross BlueShield Federal Employee Program

INTRON-A
(interferon alfa-2b)

SECTION 1: Hepatitis B Monotherapy
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RATIONALE FOR INCLUSION IN PA PROGRAM

SECTION 1: Hepatitis B Monotherapy

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 Patients with persistently severe or worsening signs or symptoms of these conditions should be withdrawn from therapy.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

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]. Rahway, NJ: Merck Sharp & Dohme Corp.; March 2023.

SECTION 2: Hepatitis C Monotherapy

Intron A (interferon alfa-2b)

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 protease inhibitor. 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 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 (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 (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).

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).

Non-pegylated interferons, such as Intron A are generally considered inferior to pegylated interferons, such as Pegasys and Pegintron (2).

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 (1-2).

Prior authorization is required to ensure the safe, clinically appropriate and cost-effective use of Intron A 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]. Rahway, NJ: Merck Sharp & Dohme Corp.; March 2023.

SECTION 3: Hepatitis C – Intron A with RIBAVIRIN

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).

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]. Rahway, NJ: Merck & Co., Inc.; March 2023..
3. Rebetol [package insert]. Whitehouse Station, NJ: Merck & Co., Inc.; October 2017.
4. Ribasphere [package insert]. Warrendale, PA: Kadmon Pharmaceuticals, LLC.; September 2017.

SECTION 4: Intron A as Interferon Therapy

Intron A (interferon alfa-2b)

Background

Interferons are a family of naturally-occurring proteins that are made and secreted by cells of the immune system (for example, white blood cells, natural killer cells, fibroblasts, and epithelial cells). Three classes of interferons have been identified: alpha, beta, and gamma (1).

Each class has many effects, though their effects overlap. Commercially available interferons are human interferons manufactured using recombinant DNA technology. The mechanism of action of interferon is complex and is not well understood. Interferons modulate the response of the immune system to viruses, bacteria, cancer, and other foreign substances that invade the body. Interferons do not directly kill viral or cancerous cells; they boost the immune system response and reduce the growth of cancer cells by regulating the action of several genes that control the secretion of numerous cellular proteins that affect growth (1).

Regulatory Status

FDA-approved indications: Intron A is an alpha interferon indicated for:

1. **Hairy Cell Leukemia:** Intron A is indicated for the treatment of patients 18 years of age or older with hairy cell leukemia (2).
2. **Malignant Melanoma:** Intron A is indicated as adjuvant to surgical treatment in patients 18 years of age or older with malignant melanoma who are free of disease but at high risk for systemic recurrence, within 56 days of surgery (2).
3. **Follicular Lymphoma:** Intron A is indicated for the initial treatment of clinically aggressive follicular Non-Hodgkin's Lymphoma in conjunction with anthracycline-containing combination chemotherapy in patients 18 years of age or older. Efficacy of Intron A therapy in patients with low-grade, low tumor burden follicular Non-Hodgkin's Lymphoma has not been demonstrated (2).
4. **Condylomata Acuminata:** Intron A is indicated for intralesional treatment of selected patients 18 years of age or older with condylomata acuminata involving external surfaces of the genital and perianal areas. The use of this product in adolescents has not been studied (2).
5. **AIDS-Related Kaposi's Sarcoma:** Intron A is indicated for the treatment of selected patients 18 years of age or older with AIDS-Related Kaposi's Sarcoma. The likelihood of response to Intron A therapy is greater in patients who are without systemic symptoms, who have limited lymphadenopathy and who have a relatively intact immune system as indicated by total CD4 count (2).

Off-Label Uses: (3 - 7)

1. Carcinoid tumor
2. Polycythemia vera
3. T-Cell Lymphomas - Mycosis Fungoides/Sézary Syndrome
4. Renal cell cancer

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Summary

Interferons are naturally occurring proteins with antiviral, antiproliferative and immunoregulatory properties. They are produced and secreted in response to viral infections and to a variety of other synthetic and biological inducers. Three types of interferons have been identified: alpha, beta, and gamma. Binding of interferon to membrane receptors initiates a series of events including induction of protein synthesis. These actions are followed by a variety of cellular responses, including inhibition of virus replication and suppression of cell proliferation (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. Interferon drug monograph; Drug facts. MedicineNet.com.
2. Intron A [package insert]. Rahway, NJ: Merck Sharp & Dohme Corporation; March 2023.
3. NCCN Clinical Practice Guidelines in Oncology® Neuroendocrine and Adrenal tumors (Version 1.2023). National Comprehensive Cancer Network, Inc. August 2023. Accessed on May 2, 2024.
4. NCCN Clinical Practice Guidelines in Oncology® Myeloproliferative Neoplasms (Version 1.2024). National Comprehensive Cancer Network, Inc. December 2023. Accessed on May 2, 2024.
5. NCCN Clinical Practice Guidelines in Oncology® T-Cell Lymphomas (Version 3.2024). National Comprehensive Cancer Network, Inc. April 2024. Accessed on May 2, 2024.
6. NCCN Clinical Practice Guidelines in Oncology® Kidney Cancer (Version 3.2024). National Comprehensive Cancer Network, Inc. March 2024. Accessed on May 2, 2024.
7. NCCN Drugs and Biologics Compendium®. No Longer Recommended Uses. Accessed on May 2, 2024.