# PEG-Intron® and PEG-Intron®/Rebetol®

## Prior Authorization Criteria

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## FDA Approved Indications

### PEG-Intron

PEG-Intron (peginterferon alfa-2b), is indicated for use alone or in combination with Rebetol for the treatment of chronic hepatitis C in patients with compensated liver disease who have not been previously treated with interferon alpha and who are 18 years of age or older.

### Rebetol

Rebetol capsules are indicated in combination with Intron A for the treatment of chronic hepatitis C virus infection in patients with compensated liver disease previously untreated with alpha interferon or who have relapsed following alpha interferon therapy.

Rebetol capsules are indicated for combination therapy with PEG-Intron for treatment of chronic hepatitis C virus infection in patients with compensated liver disease who have not been previously treated with alpha interferon.

The safety and efficacy Rebetol capsules administered in combination with interferons other than Intron A or PEG-Intron has not been established.

## Black Box Warnings

### PEG-Intron

Alpha interferons, including PEG-Intron, 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 Patients with persistently severe or worsening signs or symptoms of these conditions should be withdrawn from therapy.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 PEG-Intron therapy.

Use with ribavirin: Ribavirin may cause birth defects and/or death of the unborn child. Extreme care must be taken to avoid pregnancy in female patients and in female partners of male patients. Ribavirin causes hemolytic anemia. The anemia associated with Rebetol therapy may result in a worsening of cardiac disease. Ribavirin is genotoxic and mutagenic and should be considered a potential carcinogen.
Rebetol

Rebetol monotherapy is not effective for the treatment of chronic hepatitis C virus infection and should not be used alone for this indication.

The primary toxicity of ribavirin is hemolytic anemia. The anemia associated with Rebetol 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 Rebetol.

Significant teratogenic and/or embryocidal effects have been demonstrated in all animal species exposed to ribavirin. In addition, ribavirin has a multiple-dose half-life of 12 days, and so it may persist in nonplasma compartments for as long as 6 months. Therefore, Rebetol 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 Rebetol therapy. At least two reliable forms of effective contraception must be utilized during treatment and during the 6 month post-treatment follow-up period.

Rationale

The intent of the Prior Authorization (PA) criteria for PEG-Intron and PEG-Intron/Rebetol is to ensure that patients are appropriately selected and treated for an appropriate duration of therapy according to parameters defined in product labeling and/or clinical evidence and/or guidelines.

Therapy Duration Limitations

Major side effects of combination interferon/ribavirin therapy include influenza-like symptoms, hematologic abnormalities, and neuropsychiatric symptoms. In registration trials of pegylated interferon and ribavirin, significant side effects resulted in discontinuation of treatment in 10 to 14 percent of patients. The PA criteria for the interferons will limit the total quantity dispensed to 24 months. There will be no duration or therapy limits for the treatment of a cancerous or precancerous diagnosis. Patients will be approved for a full six- to twelve-month initial course of therapy and another six- to twelve-month course for patients who have relapsed or not responded.

Initial and Renewal Evaluation Hepatitis B Virus infection

Therapy for chronic hepatitis B is recommended for patients who are one year of age or older with compensated liver disease. Treatment is indicated for patients with persistent elevations in serum aminotransferase (ALT) concentrations, detectable levels of HBsAg (hepatitis B surface antigen), HBeAg (hepatitis B e antigen), and HVB DNA in serum. A liver biopsy is recommended to establish the diagnosis of chronic hepatitis and to evaluate the extent of liver damage but will not be required before initiation of therapy. Patients with normal ALT values are not candidates for treatment. Response to therapy is considered beneficial if the patient is negative for both HBV DNA and HBeAg and has normal or nearly normal ALT values six months after completion of therapy. A small proportion of patients may have an atypical serologic pattern with HBV DNA in the serum, but no HBeAg. These patients have a variant strain containing a mutation that blocks secretion of HBeAg. They respond less favorably to therapy than HBeAg-positive patients and often relapse after therapy is terminated. A twelve-month course of therapy may benefit these patients. Peginterferon alfa-2a (Pegasys) has been approved by the FDA for the treatment of Hepatitis B virus infection and use of PEG-Intron for this indication will also be approved through the prior authorization process. Patients with the diagnosis of Hepatitis B virus infection will be approved for six months for initial treatment and for renewal.

Initial and Renewal Evaluation for Hepatitis C virus infection

All patients with chronic hepatitis C (HCV) are candidates for antiviral therapy. Treatment is recommended only for those patients with an increased risk of developing cirrhosis. At risk patients are characterized by detectable HCV RNA levels higher than 50 IU/mL and a liver biopsy.
indicating portal or bridging fibrosis, and at least moderate hepatic inflammation and necrosis. The majority of these patients also have persistently elevated ALT values. However, approximately thirty percent of patients with chronic HCV infection have persistently normal ALT levels and some of these patients may progress to cirrhosis or hepatocellular cancer (HCC). Genotyping of the hepatitis C virus will be required in order to define the dose and duration of treatment of combination therapy.

Three large, pivotal trials evaluating the efficacy of pegylated interferon plus ribavirin in the treatment of HCV infection have helped define the dose and duration of treatment according to genotype. Twenty-four weeks of treatment with peginterferon and a ribavirin dose of 800 milligrams daily was as effective as a forty-eight week course of therapy in patients with HCV genotype 2 and 3. Treatment of these patients with standard interferon and ribavirin were comparable to those with pegylated interferon and ribavirin. Patients with genotype 1 require forty-eight weeks of treatment with a standard ribavirin dose of 1000 milligrams to 1200 milligrams daily.

The PA criteria will approve combination therapy for HCV genotype 1 for three months of initial therapy and will renew therapy for an additional nine months if early viral response (EVR) is detectable. An EVR is defined as a minimum of 2 log_{10} decrease in viral load during the first twelve weeks of treatment. Patients who do not achieve an EVR at week twelve of treatment have a small chance of achieving a sustained viral response (SVR). Continuation of treatment is not recommended for these patients.

In studies evaluating combination therapy patients with genotypes 2 and 3 were more likely to respond to interferon therapy than patients with genotype 1. The numbers of patients with genotype 5 and 6 were too few to allow for meaningful assessment. In a small study comparing response to interferon/ribavirin therapy between genotype 1 (n=24) and genotype 6 (n=16), genotype 6 demonstrated a better response than genotype 1 (p=0.05). Currently, it is recommended that genotypes other than 2 and 3 be treated the same as genotype 1.

Patients with HCV genotype 2 or 3 have response rates to combination therapy of 73 percent to 76 percent with 24 weeks of therapy and assessment of HCV RNA levels at week twelve will not be required. Initial approval will be for the entire six months of therapy with no renewal.

Antiviral therapy is contraindicated for patients who are or may become pregnant, and patients with hemoglobin-opathies, severe depression, psychosis, autoimmune hepatitis, severe cytopenia, thyroid disease, renal transplant, or decompensated liver disease. The physician must be aware of warnings regarding depression. Labeling recommends that all patients be monitored for evidence of depression and in cases of severe depression therapy should be stopped and psychiatric intervention sought.

Ribavirin may cause birth defects and/or death of the fetus. Ribavirin has a multiple dose half-life of twelve days and may persist in non-plasma compartments for as long as six months. It is extremely important to avoid pregnancy during ribavirin therapy and for six months post therapy for both female patients and in female partners of male patients taking ribavirin. It is recommended that two reliable forms of effective contraception be utilized during treatment and for six months following treatment.

**CRITERIA FOR APPROVAL**

**PEG-Intron**

**Initial Evaluation**

1. Is the patient being currently treated with PEG-Intron or PEG-Intron/ribavirin?
   - If yes, continue to 2. If no, continue to 3.

2. Has the patient been treated continuously for 3 months or more with PEG-Intron or PEG-Intron/ribavirin prior to this request?
If yes reference “renewal criteria.” If no, continue to 3.

3. Does the patient have the diagnosis of a cancerous or pre-cancerous condition (e.g., Hairy Cell Leukemia, Malignant Melanoma, Follicular Lymphoma)?
   If yes, approve for 12 months. If no, continue to 4.

4. Does the patient have the diagnosis of chronic hepatitis C (HCV)?
   If yes, continue to 6. If no, deny.

5. Has the patient been prescribed PEG-Intron/ribavirin combination therapy?
   If yes, continue to 6. If no, (PEG-Intron monotherapy), approve for 3 months if total interferon therapy has not exceeded 24 months.

6. Has the patient’s HCV genotype been determined?
   If yes, approve for 3 months for genotypes 1, 4, 5, or 6 and for 6 months for genotypes 2 or 3 if total interferon treatment has not exceeded 24 months. If no, deny.

RENEWAL EVALUATION

PEG-Intron
1. Is the patient being currently treated with PEG-Intron?
   If yes, continue to 2. If no, reference the Initial Evaluation.

2. Has the patient been treated continuously for 3 months or more with PEG-Intron prior to this request?
   If yes, continue to 3. If no, reference the Initial Evaluation.

3. Does the patient have the diagnosis of a cancerous or pre-cancerous condition?
   If yes, approve for 12 months. If no, continue to 4.

4. Does the patient have the diagnosis of chronic HCV?
   If yes, continue to 5. If no, deny.

5. Is the patient being treated with PEG-Intron monotherapy?
   If yes, continue to 7. If no, continue to 6.

6. Is the patient genotype 2 or 3?
   If yes, approve for the remainder of six months. (12 months, if confirmed cirrhosis-SEE PHARMACIST) If no (genotype 1. 4, 5, 6, or unknown), continue to 7.

7. Is the HCV RNA level after 12 or 24 weeks of therapy negative or decreased by at least two \( \log_{10} \) units (such as from 2 million IU to 20,000 IU or less)?
   If yes, approve for the remainder of 12 months. If no, deny.