

Prior Authorization DRUG Guidelines

REBETRON®
(Interferon alfa/2b and ribavirin combination pack)

Effective Date: 07/28/05

Date Developed: 07/28/05 by C. Wilhelmy MD

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Rebetron is an antiviral agent and interferon. Alpha interferons are a family of proteins, produced by nucleated cells, that have antiviral, antiproliferative, and immune-regulating activity. There are 16 known subtypes of alpha interferons. Interferons interact with cells through high affinity cell surface receptors. Following activation, multiple effects can be detected including induction of gene transcription. Inhibits cellular growth, alters the state of cellular differentiation, interferes with oncogene expression, alters cell surface antigen expression, increases phagocytic activity of macrophages, and augments cytotoxicity of lymphocytes for target cells. Ribavirin inhibits replication of RNA and DNA viruses; inhibits influenza virus RNA polymerase activity and inhibits the initiation and elongation of RNA fragments resulting in inhibition of viral protein synthesis.

Pre-Authorization Criteria:

Rebetron is used as combination therapy for the treatment of chronic hepatitis C in patients with compensated liver disease previously untreated with alpha interferon or who have relapsed after alpha interferon therapy. It may be prescribed for a maximum of one year.

VCHCP requires that Rebetron be prescribed by a gastroenterologist or Hepatitis C Clinic physician.

MONITORING PARAMETERS -Obtain pretreatment CBC, liver function tests, TSH, and electrolytes and monitor routinely throughout therapy (at 2 weeks and 4 weeks, more frequently if indicated); discontinue if WBC $<1.0 \times 10^9/L$, neutrophils $<0.5 \times 10^9/L$, platelets $<25 \times 10^9/L$, or if hemoglobin $<8.5 \text{ g/dL}$ (in cardiac patients, discontinue if hemoglobin $<12 \text{ g/dL}$ after 4 weeks of dosage reduction). Pretreatment and monthly pregnancy test for women of childbearing age. Baseline chest x-ray, ECG, weight; patients with pre-existing cardiac abnormalities, or in advanced stages of cancer should have ECGs taken before and during treatment; reticulocyte count, serum HCV RNA levels.

DOSING: ADULTS

Chronic hepatitis C: Recommended dosage of combination therapy: Intron® A: SubQ: 3 million int. units 3 times/week and Rebetol® capsule:

Oral:

- 75 kg (165 pounds): 1000 mg/day (two 200 mg capsules in the morning and three 200 mg capsules in the evening)
- >75 kg: 1200 mg/day (three 200 mg capsules in the morning and three 200 mg capsules in the evening)

DOSING: PEDIATRIC-Chronic hepatitis C: See [Lexi-Comp Online™](#) for details.

DOSING: ELDERLY-Refer to adult dosing.

DOSING: RENAL IMPAIRMENT-Patients with $Cl_{cr} < 50$ mL/minutes should not receive ribavirin.

ADMINISTRATION-Capsule should not be opened, crushed, chewed, or broken. Capsules are not for use in children <5 years of age. Use oral solution for children 3-5 years, those 25 kg, or those who cannot swallow capsules.

CONTRAINDICATIONS-Hypersensitivity to interferon alfa-2b, ribavirin, or any component of the formulation; autoimmune hepatitis; males with a pregnant female partner; pregnancy.

WARNINGS / PRECAUTIONS

Interferon alfa-2b: Suicidal ideation or attempts may occur more frequently in pediatric patients when compared to adults. May cause severe psychiatric adverse events (psychosis, mania, depression, suicidal behavior/ideation) in patients with and without previous psychiatric symptoms, avoid use in severe psychiatric disorders or in patients with a history of depression; careful neuropsychiatric monitoring is required during therapy. Use with caution in patients with a history of seizures, brain metastases, multiple sclerosis, cardiac disease (ischemic or thromboembolic), arrhythmias, myelosuppression, hepatic impairment, or renal dysfunction (use is not recommended if $Cl_{cr} < 50$ mL/minute). Use caution in patients with a history of pulmonary disease, coagulopathy, thyroid disease (monitor thyroid function), hypertension, or diabetes mellitus (particularly if prone to DKA). Caution in patients receiving drugs that may cause lactic acidosis (eg, nucleoside analogues). Avoid use in patients with autoimmune disorders; worsening of psoriasis and/or development of autoimmune disorders has been associated with alpha interferons. Higher doses in elderly patients, or diseases other than hairy cell leukemia, may result in increased CNS toxicity. Treatment should be discontinued in patients who develop severe pulmonary symptoms with chest x-ray changes, autoimmune disorders, worsening of hepatic function, psychiatric symptoms (including depression and/or suicidal thoughts/behaviors), ischemic and/or infectious disorders. Ophthalmologic disorders (including retinal hemorrhages, cotton wool spots and retinal artery or vein obstruction) have occurred in patients receiving alpha interferons. Hypertriglyceridemia has been reported (discontinue if severe).

Safety and efficacy in children <3 years of age have not been established. Do not treat patients with visceral AIDS-related Kaposi's sarcoma associated with rapidly- progressing or life-

threatening disease. A transient increase in SGOT (>2x baseline) is common in patients treated with interferon alfa-2b for chronic hepatitis. Therapy generally may continue, however, functional indicators (albumin, prothrombin time, bilirubin) should be monitored at 2-week intervals. Due to differences in dosage, patients should not change brands of interferons.

Intron® A may cause bone marrow suppression, including very rarely, aplastic anemia. Hemolytic anemia (hemoglobin <10 g/dL) was observed in 10% of treated patients in clinical trials; anemia occurred within 1-2 weeks of initiation of therapy.

Ribavirin: Oral: Anemia has been observed in patients receiving the interferon/ribavirin combination. Severe psychiatric events have also occurred including depression and suicidal behavior during combination therapy; avoid use in patients with a psychiatric history. Hemolytic anemia is a significant toxicity; usually occurring within 1-2 weeks. Assess cardiac disease before initiation. Anemia may worsen underlying cardiac disease; use caution. If any deterioration in cardiovascular status occurs, discontinue therapy. Use caution in pulmonary disease; pulmonary symptoms have been associated with administration. Use caution in patients with sarcoidosis (exacerbation reported). Negative pregnancy test is required before initiation and monthly thereafter. Avoid pregnancy in female patients and female partners of patients during therapy. Discontinue therapy in suspected/confirmed pancreatitis. Use caution in elderly patients; higher frequency of anemia; take renal function into consideration before initiating. Safety and efficacy have not been established in organ transplant patients, decompensated liver disease, concurrent hepatitis B virus or HIV exposure, or pediatric patients <3 years of age. Use caution in patients receiving concurrent medications which may cause lactic acidosis (eg, nucleoside analogues).

DRUG INTERACTIONS-Interferon Alfa-2b: Inhibits CYP1A2 (weak) ACE inhibitors: Interferons may increase the adverse/toxic effects of ACE inhibitors, specifically the development of granulocytopenia. Risk: Monitor

Antiretroviral (nucleoside): Concomitant use of ribavirin and nucleoside analogues may increase the risk of developing lactic acidosis (includes adefovir, didanosine, lamivudine, stavudine, zalcitabine, zidovudine).

Clozapine: A case report of agranulocytosis with concurrent use. Erythropoietin: Case reports of decreased hematopoietic effect.

Fluorouracil: Possible toxicity with doubling of concentrations in patients with gastrointestinal carcinoma. Monitor and adjust fluorouracil dose if necessary.

Melphalan: Interferon alpha may decrease the serum concentrations of melphalan; this may or may not decrease the potential toxicity of melphalan. Risk: Monitor
Prednisone: Prednisone may decrease the therapeutic effects of Interferon alpha. Risk: Moderate
Stavudine: Ribavirin may decrease the activity of stavudine; avoid concurrent use.

Theophylline: Interferon alpha may decrease the P450 isoenzyme metabolism of theophylline. Risk: Moderate

Thyroid hormone: Thyroid dysfunction has been reported with interferon/ribavirin therapy; monitor.

Warfarin: Interferons may increase the anticoagulant effects of warfarin. Risk: Monitor

Zidovudine: Interferons may decrease the metabolism of zidovudine. Ribavirin may decrease the activity of zidovudine. Avoid concurrent use.

PREGNANCY RISK FACTOR-X

PREGNANCY IMPLICATIONS -Abortifacient and teratogenic effects have been reported with ribavirin. Negative pregnancy test is required before initiation and monthly thereafter. Avoid pregnancy in female patients and female partners of patients during therapy by using two effective forms of contraception; continue contraceptive measures for at least 6 months after completion of therapy. If patient or female partner becomes pregnant during treatment, she should be counseled about potential risks of exposure. Pregnancies that occur during use, or within 6 months after treatment, should be reported to the manufacturer (800-593-2214).

LACTATION-Excretion in breast milk unknown/not recommended.

BREAST-FEEDING CONSIDERATIONS-Women with hepatitis C should be instructed that there is a theoretical risk the virus may be transmitted in breast milk.

DIETARY CONSIDERATIONS-Take oral formulation without regard to food, but always in a consistent manner with respect to food intake (ie, always take with food or always take on an empty stomach).

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