Kadmon

<Date>

<Name>
<Address line 1>
<Address line 2>
<City, State, Zip>

Dear <Healthcare Provider>,

As an expert in the treatment of Hepatitis C, you understand first-hand the complexity of chronic HCV treatment. Patients with HCV require extensive education about how to take their medication and the importance of taking all medication as prescribed. In addition, the significant pill burden and side effects of HCV therapy can quickly lead to non-adherence.[1]

Ribasphere® RibaPak® (ribavirin, USP) Tablets may help improve patient adherence to HCV medication[2], leading to improved rates of SVR.

- The only 2 pill/day ribavirin at all doses
  - Reduces ribavirin pill burden by up to 66%*
  - Reduces pill fatigue
- Unique compliance pack
  - Pills are clearly labeled for 7 days of AM and PM dosing
  - Patients can easily recognize missed doses
  - Finishing a weekly pack serves as a reminder to administer the peginterferon injection

Enclosed Are Materials to Get Started

Enclosed in this package are materials on Ribasphere RibaPak and the services we offer to you and your patients. Should you be interested in more information, please feel free to contact me directly or call Kadmon Pharmaceuticals at 724-778-6100.

Please see accompanying Important Safety Information, including Black Box Warning, and enclosed full prescribing information for Ribasphere® RibaPak® (ribavirin, USP) Tablets.

Sincerely,

<Name>

<xxx-xxx-xxxx>

Sales Specialist, Hepatology

1. Agency for Healthcare Research and Quality. US Department of Health & Human Services. Adherence to Hepatitis C Treatment Interventions: A Comparative Effectiveness Review. AHRQ Publication 2012.
2. Alam I, Stainbrook T, Cecil B, Kistler KD. Enhanced adherence to HCV therapy with higher dose ribavirin formulation: final analyses from the ADHERE registry. *Aliment Pharmacol Ther* 2010;32(4):535-542.

*Ribavirin pill burden based on a patient receiving a 1200mg daily dose of either Ribaspher 600mg or ribavirin 200 mg tablets for 48 weeks

450 East 29th Street
New York, NY 10016
212.308.6000

Important Safety Information about Ribasphere RibaPak (ribavirin, USP) Tablets

INDICATION

Ribasphere (ribavirin, USP) in combination with peginterferon alfa-2a is indicated for the treatment of adults with chronic hepatitis C virus infection who have compensated liver disease and have not been previously treated with interferon alpha.

Ribasphere (ribavirin, USP) monotherapy is not effective for the treatment of chronic hepatitis C virus infection and should not be used alone for this indication (see WARNINGS).

The primary clinical toxicity of ribavirin is hemolytic anemia. The 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.

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 it may persist in non-plasma compartments for as long as 6 months. 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 therapy in both female patients and in female partners of male patients who are taking ribavirin therapy. At least two reliable forms of effective contraception must be utilized during treatment and during the 6-month posttreatment follow-up period.

CONTRAINDICATIONS

Ribasphere (ribavirin, USP) is contraindicated in:

- Patients with known hypersensitivity to Ribasphere (ribavirin, USP) or to any component of the tablet.
- Women who are pregnant.
- Men whose female partners are pregnant, plan to become pregnant, or are not using contraception.
- Patients with hemoglobinopathies (e.g., thalassemia major or sickle-cell anemia).
- In combination with didanosine. Reports of fatal hepatic failure, as well as peripheral neuropathy, pancreatitis, and symptomatic hyperlactatemia/lactic acidosis have been reported in clinical trials.

Ribasphere (ribavirin, USP) and peginterferon alfa-2a combination therapy is contraindicated in patients with:

- Autoimmune hepatitis.
- Hepatic decompensation (Child-Pugh score greater than 6; class B and C) in cirrhotic CHC monoinfected patients before or during treatment.
- Hepatic decompensation with Child-Pugh score greater than or equal to 6 in cirrhotic CHC patients coinfected with HIV before or during treatment.

WARNINGS AND PRECAUTIONS

Treatment with Ribasphere (ribavirin, USP) and peginterferon alfa-2a should be administered under the guidance of a qualified physician and may lead to moderate to severe adverse experiences requiring dose reduction, temporary dose cessation or discontinuation of therapy.

Ribasphere (ribavirin, USP) must not be used alone because ribavirin monotherapy is not effective for the treatment of chronic hepatitis C virus infection.

Ribasphere (ribavirin, USP) and peginterferon alfa-2a should be discontinued in patients who develop evidence of hepatic decompensation during treatment.

There are significant adverse events caused by ribavirin/peginterferon alfa-2a therapy, including severe depression and suicidal ideation, hemolytic anemia, suppression of bone marrow function, autoimmune and infectious disorders, ophthalmologic disorders, cerebrovascular disorders, pulmonary dysfunction, colitis, pancreatitis, and diabetes. The peginterferon alfa-2a package insert and medication guide should be reviewed in their entirety prior to initiation of combination treatment for additional safety information.

Pregnancy: Ribavirin may cause birth defects and/or death of the exposed fetus. Extreme care must be taken to avoid pregnancy in female patients and in female partners of male patients.

Anemia: The primary toxicity of ribavirin is hemolytic anemia (hemoglobin <10 g/dL), which was observed in approximately 13% of all ribavirin and peginterferon alfa-2a treated patients in clinical trials.

Hepatic Failure: Chronic hepatitis C (CHC) patients with cirrhosis may be at risk of hepatic decompensation and death when treated with alpha interferons, including peginterferon alfa-2a. Cirrhotic CHC patients coinfected with HIV receiving highly active antiretroviral therapy (HAART) and interferon alfa-2a with or without ribavirin appear to be at increased risk for the development of hepatic decompensation compared to patients not receiving HAART.

Hypersensitivity: Severe acute hypersensitivity reactions (e.g., urticaria, angioedema, bronchoconstriction, and anaphylaxis) have been observed during alpha interferon and ribavirin therapy.

Renal Impairment: Ribasphere (ribavirin, USP) should not be used in patients with creatinine clearance <50 mL/min.

Pulmonary: Pulmonary symptoms, including dyspnea, pulmonary infiltrates, pneumonitis, pulmonary hypertension, pneumonia, and occasional cases of fatal pneumonia, have been reported during therapy with ribavirin and interferon. In addition, sarcoidosis or the exacerbation of sarcoidosis has been reported.

Bone Marrow Suppression: Pancytopenia (marked decreases in RBCs, neutrophils and platelets) and bone marrow suppression have been reported in the literature to occur within 3 to 7 weeks after the concomitant administration of pegylated interferon/ribavirin and azathioprine.

Pancreatitis: Ribasphere (ribavirin, USP) and peginterferon alfa-2a therapy should be suspended in patients with signs and symptoms of pancreatitis, and discontinued in patients with confirmed pancreatitis.

Laboratory Tests: Before beginning peginterferon alfa-2a/Ribasphere (ribavirin, USP) combination therapy, standard hematological and biochemical laboratory tests are recommended for all patients.

Drug Interactions: Nucleoside Analogues: NRTIs: In clinical trials, cases of hepatic decompensation (some fatal) were observed among the CHC/HIV coinfected cirrhotic patients receiving NRTIs. Patients receiving peginterferon alfa-2a/ribavirin and NRTIs should be closely monitored for treatment associated toxicities.

ADVERSE REACTIONS

Peginterferon alfa-2a in combination with ribavirin causes a broad variet y of serious adverse reactions. The most common serious or life-threatening adverse reactions induced or aggravated by peginterferon alfa-2a and ribavirin include depression, suicide, relapse of drug abuse/overdose, and bacterial infections, each occurring at a frequency of <1%. Hepatic decompensation occurred in 2% of CHC/HIV patients. Nearly all patients in clinical trials experienced one or more adverse events.

For more information please see the accompanying Ribasphere RibaPak (ribavirin, USP) Tablets Full Prescribing Information. The peginterferon alfa-2a Package Insert should be reviewed in its entirety for additional safety information prior to initiation of combination treatment.

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Please see Important Safety Information, including Black Box Warning, as well as accompanying complete Prescribing Information and Medication Guide.

Kadmon PHARMACEUTICALS, LLC