DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Silver Spring, MD 20993

TRANSMITTED BY FACSIMILE

Samuel D. Waksal, Ph.D.
Chairman and Chief Executive Officer
Kadmon Pharmaceuticals, LLC
119 Commonwealth Drive
Warrendale, PA 15086

RE: ANDA 077456
Ribasphere® RibaPak® (ribavirin, USP) Tablets
MA #72

WARNING LETTER

Dear Dr. Waksal:

The Office of Prescription Drug Promotion (OPDP) of the U.S. Food and Drug Administration (FDA) has reviewed a RibaPak Intro Letter (2013.011/C130.00043) (letter) for Ribasphere® RibaPak® (ribavirin, USP) Tablets (Ribasphere) submitted by Kadmon Pharmaceuticals, LLC (Kadmon), under cover of Form FDA 2253. The letter is false or misleading because it omits important risk information for Ribasphere, suggests that the drug is useful in a broader range of patients or conditions than has been substantiated, omits material facts, and makes unsubstantiated efficacy claims. Thus, the letter misbrands Ribasphere within the meaning of the Federal Food, Drug, and Cosmetic Act (FD&C Act) and makes its distribution violative of the FD&C Act. 21 U.S.C. 352(a); 321(n); 331(a); and FDA implementing regulation 21 CFR 1.21(a). *Cf*. 21 CFR 202.1(e)(5); (e)(6)(i), (x). The letter also provides evidence that Ribasphere is intended for a new use for which it lacks approval, and for which its labeling does not provide adequate directions for use, which also renders Ribasphere misbranded or otherwise makes its distribution violative. See 21 USC 355(a); 331(a) & 331(d); 352(f); 21 CFR 201.5, 201.100, 201.115. These violations are concerning from a public health perspective because they suggest that Ribasphere, a drug associated with a number of serious and potentially fatal risks, is safer and more effective than has been demonstrated.

Background

Below are the indication and summary of the most serious and most common risks associated with the use of Ribasphere.[1] According to its FDA-approved product labeling (PI):

[1] This information is for background purposes only and does not necessarily represent the risk information that should be included in the promotional piece(s) cited in this letter.

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

The following points should be considered when initiating Ribasphere combination therapy with peginterferon alfa-2a:

- This indication is based on clinical trials of combination therapy in patients with CHC and compensated liver disease, some of whom had histological evidence of cirrhosis (Child-Pugh class A), and in patients with clinically stable HIV disease and CD4 count > 100 cells/mm^2.
- This indication is based on achieving undetectable HCV-RNA after treatment for 24 or 48 weeks, based on HCV genotype, and maintaining a Sustained Viral Response (SVR) 24 weeks after the last dose.
- Safety and efficacy data are not available for treatment longer than 48 weeks.
- The safety and efficacy of ribavirin and peginterferon alfa-2a therapy have not been established in liver or other organ transplant recipients, patients with decompensated liver disease, or previous non-responders to interferon therapy.
- The safety and efficacy of ribavirin therapy for the treatment of adenovirus, RSV, parainfluenza, or influenza infections have not been established. Ribasphere should not be used for these indications. Ribavirin for inhalation has a separate package insert, which should be consulted if ribavirin inhalation therapy is being considered.

Ribasphere is associated with a number of serious risks. According to the PI, Ribasphere has Boxed Warnings regarding the lack of efficacy of Ribasphere monotherapy for the treatment of chronic hepatitis C virus infection, the risk of hemolytic anemia, the contraindication in women who are pregnant and in the male partners of women who are pregnant, and the extreme care that must be taken to avoid pregnancy during therapy and for six months after completion of therapy in female patients and female partners of male patients. In addition, Ribasphere is contraindicated in patients with hemoglobinopathies and in combination with didanosine. Ribasphere and peginterferon alfa-2a combination therapy is contraindicated in patients with autoimmune hepatitis, and in cirrhotic patients with hepatic decompensation before treatment.

Furthermore, the PI includes Warnings and Precautions regarding hepatic failure, hypersensitivity, renal impairment, pulmonary disorders, bone marrow suppression, pancreatitis, and laboratory testing The most common serious or life-threatening adverse reactions induced or aggravated by ribavirin/peginterferon alfa-2a include depression, suicide, relapse of drug abuse/overdose, and bacterial infections. The most common adverse reactions associated with Ribasphere therapy in adults receiving combination therapy are fatigue/asthenia, pyrexia, myalgia, and headache.

Prior Communications

False or misleading presentations by Kadmon are particularly troubling considering OPDP expressed concerns regarding similar violative promotional activities in March 2011. On March 21, 2011, OPDP sent Kadmon a warning letter for INFERGEN® (interferon alfacon-1) injection for subcutaneous use (Infergen). The letter concerned a STATgram which omitted

and minimized important risk information for Infergen, broadened and omitted material facts about Infergen's approved indication, overstated its efficacy, and made an unsubstantiated claim. OPDP is concerned that Kadmon is continuing to promote its prescription products in a violative manner.

Omission of Risk Information

Promotional materials are misleading if they fail to reveal facts that are material in light of the representations made or with respect to consequences that may result from the use of the drug as recommended or suggested in the materials.

The letter is misleading because it includes numerous claims regarding the benefits of Ribasphere, but fails to include any risk information associated with the drug in the body of the letter. We note that there is a statement at the end of the letter which reads, "Please see accompanying Important Safety Information, including Black Box Warning, and enclosed full prescribing information for Ribasphere® RibaPak® (ribavirin, USP) Tablets," and that "Important Safety Information about Ribasphere RibaPak (ribavirin, USP) Tablets" was provided with the letter. However, this statement and the inclusion of a separate document with the safety information do not mitigate the misleading representations within the body of the letter.

Broadening of Patient Population or Condition

Promotional materials are misleading if they suggest that a drug is useful in a broader range of conditions or patients than has been demonstrated by substantial evidence or substantial clinical experience.

The letter discusses the use of Ribasphere for the treatment of hepatitis C, but fails to present the drug's full indication. For example, the letter states, **"Ribasphere® RibaPak® (ribavirin, USP) Tablets may help improve patient adherence to HCV medication, leading to improved rates of SVR**" (emphasis original). This presentation misleadingly broadens Ribasphere's patient population or condition. As described in the Background section, Ribasphere is only indicated in combination with peginterferon alfa-2a 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. Therefore, the letter misleadingly broadens the patient population or condition of Ribasphere by implying that it is approved as monotherapy to treat all patients with hepatitis C, when this has not been demonstrated by substantial evidence or substantial clinical experience. We acknowledge that the statement, "Finishing a weekly pack serves as a reminder to administer the peginterferon injection" appears as the last bullet point in the body of the letter. However, this statement does not correct the overwhelming misleading impression conveyed by the letter that Ribasphere can be used as monotherapy. This violation is particularly egregious because as stated in the Boxed Warning, "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."

Information sufficient to support use in the broader patient population or condition suggested in this letter has not been submitted to FDA in an application, nor are we otherwise aware of

substantial evidence or substantial clinical experience that would support it. The presentation in the letter also provides evidence that Ribasphere is intended for a new use for which it lacks approval, and for which its labeling does not provide adequate directions for use.

Omission of Material Fact

Promotional materials are misleading if they fail to reveal facts that are material in light of the representations made by the materials or with respect to consequences that may result from the use of the drug as recommended or suggested in the materials. The letter omits material information from the INDICATIONS AND USAGE section of the PI concerning the points to consider when initiating Ribasphere. Specifically, the letter omits that the indication is based on clinical trials of combination therapy in patients with CHC and compensated liver disease, some of whom had histological evidence of cirrhosis (Child-Pugh class A), and in patients with clinically stable HIV disease and CD4 count more than 100 cells/mm^2; and that the indication is based on achieving undetectable HCV-RNA after treatment for 24 or 48 weeks, and maintaining an SVR 24 weeks after the last dose. Moreover, the letter also omits that no safety and efficacy data are available for treatment longer than 48 weeks, and that the safety and efficacy of ribavirin and peginterferon alfa-2a therapy have not been established in liver or other organ transplant recipients, patients with decompensated liver disease, or previous non-responders to interferon therapy.

Unsubstantiated Efficacy Claims

Promotional materials are misleading if they contain a representation or suggestion that a drug is more effective than has been demonstrated by substantial evidence or substantial clinical experience.

The letter includes the following claims (emphasis original):

> 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.[2]
>
> **Ribasphere® RibaPak® (ribavirin, USP) Tablets may help improve patient adherence to HCV medication[3], 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

[2] 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.
[3] Alam I, Stainbrook T, Cecil B, et al. Enhanced adherence to HCV therapy with higher dose ribavirin formulation: final analysis from the ADHERE registry. Aliment Pharmacol Ther. 2010;32(4):535-542.

- Patients can easily recognize missed doses
- Finishing a weekly pack serves as a reminder to administer the peginterferon injection

The totality of the above claims misleadingly suggests that a medication regimen with the Ribasphere RibaPak for the treatment of HCV will have a positive impact on patient adherence to ribavirin therapy as well as HCV treatment overall, thereby improving rates of SVR, when these outcomes have not been demonstrated by substantial evidence or substantial clinical experience. The references cited[2,3] describe a report based on a literature review and an observational registry. These references do not describe adequate and well-controlled studies assessing adherence endpoints or clinical outcomes that specifically examined Ribasphere RibaPak. While we acknowledge that some of the claims are factually correct (e.g., "Pills are clearly labeled for 7 days of AM and PM dosing"), the overall impression is misleading. We are not aware of any evidence to suggest that Ribasphere's packaging characteristic (i.e., Ribasphere Ribapak) or availability in multiple dose strengths will improve patient adherence to ribavirin treatment or HCV treatment overall, leading to improved rates of SVR. In the absence of substantial evidence or substantial clinical experience, the above claims do not support the implication that Ribasphere RibaPak for the treatment of HCV will have a positive impact on patient adherence to ribavirin therapy leading to improved rates of SVR.

Conclusion and Requested Action

For the reasons discussed above, the letter misbrands Ribasphere within the meaning of the FD&C Act and makes its distribution violative. 21 U.S.C. 352(a); 321(n); 331(a); and FDA implementing regulation 21 CFR 1.21(a). *Cf*. 21 CFR 202.1(e)(5); (e)(6)(i), (x). The letter also provides evidence that Ribasphere is intended for a new use for which it lacks approval, and for which its labeling does not provide adequate directions for use, which also renders Ribasphere misbranded or otherwise makes its distribution violative. See 21 USC 355(a), 331(a) & 331(d); 352(f); 21 CFR 201.5, 201.100, 201.115.

OPDP requests that Kadmon immediately cease misbranding Ribasphere and/or cease introducing the misbranded drug into interstate commerce. Please submit a written response to this letter on or before December 2, 2013, stating whether you intend to comply with this request, listing all promotional materials (with the 2253 submission date) for Ribasphere that contain statements such as those described above, and explaining your plan for discontinuing use of such materials or, in the alternative, for ceasing distribution of Ribasphere. Because the violations described above are serious, we request, further, that your submission include a comprehensive plan of action to disseminate truthful, non-misleading, and complete corrective messages about the issues discussed in this letter to the audience(s) that received the violative promotional materials. In order to clearly identify the violative promotional piece(s) and/or activity and focus on the corrective message(s), OPDP recommends that corrective piece(s) include a description of the violative promotional piece(s) and/or activity, include a summary of the violative message(s), provide information to correct each of the violative message(s), and be free of promotional claims and presentations. To the extent possible, corrective messaging should be distributed using the same media, and generally for the same duration of time and with the same frequency that the violative promotional material was disseminated.

Please direct your response to the undersigned at the **Food and Drug Administration, Center for Drug Evaluation and Research, Office of Prescription Drug Promotion, 5901-B Ammendale Road, Beltsville, Maryland 20705-1266** or by facsimile at (301) 847-8444. To ensure timely delivery of your submissions, please use the full address above and include a prominent directional notation (e.g. a sticker) to indicate that the submission is intended for OPDP. Please refer to the MA #72 in addition to the ANDA number in all future correspondence relating to this particular matter. All correspondence should include a subject line that clearly identifies the submission as a Response to Warning Letter. OPDP reminds you that only written communications are considered official.

The violations discussed in this letter do not necessarily constitute an exhaustive list. It is your responsibility to ensure that your distribution of Ribasphere complies with each applicable requirement of the FD&C Act and FDA implementing regulations.

Failure to correct the violations discussed above may result in FDA regulatory action, including seizure or injunction, without further notice.

Sincerely,

{See appended electronic signature page}

Andrew S.T. Haffer, Pharm.D.
Division Director
Office of Prescription Drug Promotion

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

ANDREW S HAFFER
11/18/2013