DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

JUL 15 1999

TRANSMITTED VIA FACSIMILE

Mary Jane Nehring
Director, Marketed Products Support
Worldwide Regulatory Affairs
Schering Corporation
2000 Galloping Hill Road
Kenilworth, NJ 07033

RE: **NDA 20-903**
REBETRON Combination Therapy
Rebetol® (Ribavirin, USP) Capsules
Intron® A (Interferon alfa-2b, recombinant) Injection
MACMIS #8097

Dear Ms. Nehring:

This letter concerns Schering's promotional materials for Rebetron Combination Therapy. The Division of Drug Marketing, Advertising, and Communications (DDMAC) has reviewed these promotional materials as part of its routine monitoring and surveillance program. From its review, DDMAC has concluded that Schering Corporation (Schering) has distributed materials that are false and/or misleading, in violation of the Federal Food, Drug, and Cosmetic Act (Act) and its implementing regulations.

Lacking in Fair Balance

In its promotional materials, Schering fails to present information relating to contraindications, warnings, and other risk information with a prominence and readability reasonably comparable to the presentation of information relating to the effectiveness of the drug.[1] For example, Schering presents risk information and the boxed warning in a block paragraph format, with very little white space, printed on the inside cover of a ½ page flap, with headings that either lack prominence or are nonexistent. In contrast to the presentation of risks, efficacy claims are presented on at least two full pages, in a bulleted format, with white space and prominent headings. Another example is in the promotional

[1] IH0479B, IH0580, IH0631, IH0675, IH0660D, IH0665, IH0699, IH0708, IH0714, IH0713, IH0708, IH0661, IH0660, IH0642, IH0732A

video, wherein Schering presents warnings and contraindications concurrently as a VOICEOVER and as a SUPER with competing messages.[2] Such presentation interferes with the viewer's ability to simultaneously read, listen, and process important risk information. Promotional materials are therefore lacking in fair balance because risk information is not presented in a manner comparable to the claims regarding efficacy.

Misleading Safety Claims

Schering claims that Rebetron Combination Therapy (Rebetol/Intron A) is "Well Accepted" and "Well tolerated-minimal differences in side effects compared with INTRON A monotherapy."[3] These claims are misleading because they minimize the risks associated with the product and are inconsistent with the product's safety profile as described in the labeling. Examples of risk information from the approved product labeling include the following:

a) The primary toxicity of Rebetol is hemolytic anemia. Cardiac and pulmonary events associated with anemia occurred in approximately 10% of patients treated with Rebetol/Intron A therapy.

b) With 24 weeks of treatment, 32% and 23% of previously untreated and relapsed patients, respectively, reported depression in the Rebetol/Intron A arms compared to 25% and 14% in the INTRON A arms.

c) Overall, 19% and 6% of previously untreated and relapsed patients, respectively, discontinued therapy due to adverse events in the Rebetol/Intron A arms compared to 13% and 3% in the Intron A arms.

d) 26% of patients required modification of their dose of Rebetol capsules, INTRON A Injection, or both agents due to adverse events.

e) Significant teratogenic and/or embryocidal effects have been demonstrated for Rebetol in all animal species studied. These effects occurred at doses as low as one twentieth of the recommended human dose of Rebetol Capsules. Rebetron Combination Therapy (Rebetol/Intron A) is contraindicated in women who are pregnant and in male partners of women who are pregnant.

Thus, to suggest that the product is "well accepted" and "well tolerated-minimal differences..." is misleading because it overstates the safety of Rebetron Combination Therapy, undermines important risk information, and is not consistent with the product labeling.

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[2] IH0631
[3] IH0680, IH0684, IH0708, IH0712, IH0708

Misleading Efficacy Claims

In promotional materials, Schering overstates Rebetron's efficacy by claiming that patient responders were "HCV-RNA negative."[4] The phrase "HCV-RNA negative" is misleading because it suggests complete eradication of the HCV, and such has not been demonstrated. We note the disclaimer in small font size located on a separate page (under a flap) defining HCV-RNA negative as HCV-RNA below limits of detection using a research-based RT-PCR assay; however, this disclaimer is insufficient to overcome the more prominent misleading claim. In other promotional materials, Schering goes even farther to misleadingly assert that "Patients were considered virologic sustained responders only if they demonstrated eradication of serum HCV-RNA."[5] These claims are false and misleading because eradication of serum HCV-RNA has not been demonstrated.

Misleading Superiority Claims

In its promotional materials, Schering makes misleading superiority claims such as, "In Well-Controlled Clinical Trials Efficacy Proven Superior to Monotherapy in Treatment-Naïve" and "In Well-Controlled Clinical Trials Efficacy Proven Superior to Monotherapy in Relapsers."[6] These claims are misleading because it implies that Rebetron Combination Therapy is superior to all monotherapies, which has not been demonstrated. In well controlled trials of Rebetron Combination Therapy, efficacy for Rebetron was proven superior only to INTRON A monotherapy. Thus, claims that imply superiority over other monotherapies is misleading because it is unsupported by substantial evidence.

Schering should immediately cease publication or dissemination of promotional materials or activities that contain these or similar claims. Schering should respond in writing no later than July 29, 1999, describing its plan to comply. Schering should also include a list of all similarly violative materials being discontinued, as well as the date of discontinuation.

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[4] IH0732A
[5] IH0579
[6] IH0632, IH0633

Your response should be directed to Ele Ibarra-Pratt by fax at (301) 594-6771, or at the Food and Drug Administration, Division of Drug Marketing, Advertising and Communications, HFD-40, 17B-20, 5600 Fishers Lane, Rockville, MD 20857. We remind Schering that only written communications are considered official.

In all future correspondence regarding this particular matter, please refer to MACMIS ID # 8097 in addition to the NDA number.

Sincerely,

/S/

Ele Ibarra-Pratt, R.N., M.P.H.
Regulatory Review Officer
Division of Drug Marketing,
Advertising, and Communications