DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

FOI

JUN 12 1998

TRANSMITTED BY FACSIMILE

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

Re: **NDA 20-903**
Rebetron Combination Therapy containing Rebetol (ribavirin, USP) Capsules and Intron A (interferon alfa-2b, recombinant) Injection
MACMIS ID#6748

Dear Ms. Nehring:

This letter concerns promotional materials distributed by Schering Corporation (Schering) for its product Rebetron Combination Therapy. The Division of Drug Marketing, Advertising, and Communications (DDMAC) has determined that Schering disseminated promotional materials prior to clearance for marketing of Rebetron Combination Therapy and then, subsequent to approval, disseminated a misleading press release in violation of the Federal Food, Drug, and Cosmetic Act (Act) and regulations promulgated thereunder.

Pre-approval Promotion

Specifically, at Digestive Diseases Week in New Orleans held May 16-22, 1998, Schering distributed information resembling a package insert for the combination therapy of Intron A and Rebetol. Based on a review of these materials, DDMAC has concluded that Schering made promotional representations concerning the efficacy and safety of Rebetron Combination Therapy prior to marketing clearance. The regulations promulgated pursuant to the Federal Food, Drug, and Cosmetic Act (Act), at 21 CFR §312.7 state, among other things, that an investigational new drug may not be promoted as being safe and effective for the uses under investigation. Schering did not receive approval for marketing until June 5, 1998. Therefore, these representations constitute pre-approval promotion and are in violation of the Act.

Lacking in Fair Balance

The disseminated press release fails to adequately convey the serious risks associated with the use of Rebetron. DDMAC notes that the press release contains some information concerning the risks associated with the use of the product. However, Schering omits any mention of the bolded warning related to the incidence and severity of anemia associated with Rebetron Combination Therapy. Specifically, this warning states that 10% of patients experienced anemia during the clinical trials and that the anemia occurs rapidly, i.e., in the first one or two weeks of therapy. Because of the risk of anemia, the healthcare professional must complete blood counts prior to therapy and at weeks 2 and 4 of therapy. None of this risk information was disclosed. Finally, Schering failed to disclose that patients with underlying cardiovascular disease should be assessed prior to initiation of Rebetron Combination Therapy.

Similarly, Schering's statement that "[p]sychiatric disorders have been reported during REBETRON combination therapy, ..." does not convey that severe psychiatric adverse events have occurred during combination therapy in patients with and without a previous psychiatric illness. Moreover, Schering fails to disclose that suicides have occurred while patients were on combination therapy.

In addition, Schering fails to adequately convey sufficient information regarding the boxed warning about the use of the combination therapy in women who are pregnant. The tone of the language used to convey the risk information minimizes the seriousness of these risks. Schering's paraphrasing of the language from the approved product labeling does not sufficiently convey that Rebetron combination therapy must not be used by women who are or may become pregnant anytime during treatment and up to six months following treatment with the drug.

Thus, this press release is lacking in fair balance concerning the risks associated with the use of Rebetron combination therapy and is misleading.

Misleading Statements

Schering states that during the Phase III studies, therapy with the combination "resulted in a tenfold increase in the number of patients showing eradication of detectable [HCV-RNA (qPCR)-negative] hepatitis C virus as compared to patients receiving INTRON A alone." However, the approved product labeling for Rebetron discloses both the virologic rates noted by Schering in the press release as well as the histological response which was also a primary endpoint. Schering's use of only the virologic data suggests greater efficacy than was demonstrated in clinical trials. Moreover, Schering's press release suggests that use of Rebetron cures hepatitis C, when in fact, the impact of this drug on the course of the disease is unknown.

We remind Schering that under 21 CFR § 314.81(b)(3), Schering must submit specimens of labeling or advertising devised for promotion of the drug product at the time of initial dissemination of the labeling and at the time of initial publication of the advertisement for a prescription drug product.

Schering should acknowledge receipt of this letter and its plans to discontinue similar violative promotional activities by June 26, 1998. Schering should direct its response to the undersigned at the Food and Drug Administration, Division of Drug Marketing, Advertising and Communications, HFD-40, Rm 17B-20, 5600 Fishers Lane, Rockville, MD, 20857. DDMAC reminds Schering that only written communications are considered official.

In all future correspondence regarding this matter, please refer to MACMIS ID #6748, in addition to the NDA number.

Sincerely,

/S/

Stephen Sherman, JD, MBA
Regulatory Review Officer
Division of Drug Marketing,
Advertising and Communications