NDA 20-903/S-006
NDA 20-903/S-007

The Schering Corporation
Attention: Joseph F. Lamendola, Ph.D.
Vice President, U.S. Regulatory Affairs
2000 Galloping Hill Road
Kenilworth, NJ 07033

13 MAR 2001

Dear Dr. Lamendola:

Please refer to your supplemental new drug applications dated May 26, 2000 (S-006) and September 15, 2000 (S-007), received May 27, 2000 and September 18, 2000, respectively, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for REBETRON COMBINATION THERAPY [SCH 30500 - Intron® A (Interferon alfa-2b, recombinant) for Injection/ SCH 18908 - Ribavirin].

We acknowledge receipt of your submissions dated May 26, 2000, September 15, 2000, December 1, 2000, January 29, 2001, and March 1, 2001.

The supplemental new drug application **S-006** provides for revisions to the WARNINGS section of the REBETRON COMBINATION THERAPY™ label, to include a bone marrow toxicity section, as follows:

> **Bone marrow toxicity:**
> INTRON A therapy suppresses bone marrow function and may result in severe cytopenias including very rare events of aplastic anemia. It is advised that complete blood counts (CBC) be obtained pre-treatment and monitored routinely during therapy (see **PRECAUTIONS: Laboratory Tests**). INTRON A therapy should be discontinued in patients who develop severe decreases in neutrophil ($<0.5 \times 10^9$/L) or platelet counts ($<25 \times 10^9$/L) (see **DOSAGE AND ADMINISTRATION: Guidelines for Dose Modifications**).

This supplemental new drug application also provides for revisions to the ADVERSE REACTIONS section, to include vertigo and hearing disorders (b), as follows:

> In addition hearing disorders (tinnitus and hearing loss) and vertigo have occurred in patients treated with combination REBETOL/INTRON A therapy.

The supplemental new drug application **S-007** provides for the inclusion of a Geriatric Use section, pursuant to the requirements of CFR 201.57 (f) (10), as follows:

> **Geriatric Use** Clinical studies of REBETRON Combination Therapy did not include sufficient numbers of subjects aged 65 and over to determine if they respond differently from younger subjects. In clinical trials, elderly subjects had a higher frequency of anemia (67%) than did younger patients (28%) (see **WARNINGS**).
>
> In general, REBETOL (ribavirin) should be administered to elderly patients cautiously, starting at the lower end of the dosing range, reflecting the greater frequency of decreased renal, hepatic and/or cardiac function, and of

concomitant disease or other drug therapy.

REBETOL (ribavirin) is known to be substantially excreted by the kidney, and the risk of adverse reactions to ribavirin may be greater in patients with impaired renal function. Because elderly patients often have decreased renal function, care should be taken in dose selection. Renal function should be monitored and dosage adjustments of ribavirin should be made accordingly (see **DOSAGE AND ADMINISTRATION**: **Guidelines for Dose Modifications**). REBETOL (ribavirin) should be used in elderly patients with creatinine clearance <50 mL/min only if the potential benefit outweighs the risk, and should not be administered to patients with creatinine clearance <30 mL/min (see **WARNINGS**).

REBETRON Combination Therapy should be used very cautiously in elderly patients with a history of psychiatric disorders (see **WARNINGS**).

We have completed the review of these supplemental applications, as amended, and have concluded that adequate information has been presented to demonstrate that the drug product is safe and effective for use as recommended in the agreed upon labeling text. Accordingly, these supplemental applications are approved effective on the date of this letter.

The final printed labeling (FPL) must be identical to the submitted draft labeling (package insert submitted March 1, 2001, patient package insert submitted March 1, 2001).

Please submit the copies of final printed labeling (FPL) electronically to each application according to the guidance for industry titled *Providing Regulatory Submissions in Electronic Format - NDA* (January 1999). Alternatively, you may submit 20 paper copies of the FPL as soon as it is available but no more than 30 days after it is printed. Please individually mount ten of the copies on heavy-weight paper or similar material. For administrative purposes, these submissions should be designated "FPL for approved supplement NDA 20-903/S-006, S-007." Approval of these submissions by FDA is not required before the labeling is used.

In addition, please submit three copies of the introductory promotional materials that you propose to use for this product. All proposed materials should be submitted in draft or mock-up form, not final print. Please submit one copy to this Division and two copies of both the promotional materials and the package insert directly to:

Division of Drug Marketing, Advertising, and Communications, HFD-42
Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857

If a letter communicating important information about this drug product (i.e., a "Dear Health Care Professional" letter) is issued to physicians and others responsible for patient care, we request that you submit a copy of the letter to this NDA and a copy to the following address:

MEDWATCH, HF-2
FDA
5600 Fishers Lane
Rockville, MD 20857

Please submit one market package of the drug product when it is available.

We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 314.80 and 314.81.

If you have any questions, call Destry M. Sillivan, M.S., Regulatory Project Manager, at (301) 827-2335.

Sincerely,

Debra Birnkrant, M.D.
Acting Director
Division of Antiviral Drug Products
Office of Drug Evaluation IV
Center for Drug Evaluation and Research