NDA 20-903/S-013

Schering Corporation
Attention: Joseph F. Lamendola
Senior Director, Marketed Products, Support and Training
2000 Galloping Hill Road
Kenilworth, NJ 07033

Dear Dr. Lamendola,

Please refer to your supplemental new drug application dated February 28, 2001, received March 1, 2001, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for REBETOL® (ribavirin) capsules for use in combination with the approved biologic product Intron®A (interferon alfa 2b) (Rebetron Combination Therapy™).

We also acknowledge receipt of your submissions dated July, 9, 2001, July 13, 2001, July 17, 2001, November 1, 2001, November 8, 2001, November 19, 2001 and December 21, 2001.

This supplemental new drug application provides for the inclusion of new pediatric pharmacokinetic information in a table format, as found in the **CLINICAL PHARMACOLOGY**, **Pharmacokinetics,** ***Special Populations, Pediatric Patients*** section of the **Rebetron Combination Therapy™** label, as follows:

> Multiple-dose pharmacokinetic properties for ribavirin in pediatric patients with chronic hepatitis C between 5 and 16 years of age are summarized in **TABLE 2**.

TABLE 2. Mean (% CV) Pharmacokinetic Parameters for REBETOL When Administered to Pediatric Patients with Chronic Hepatitis C

Parameter	12 mg/kg/day as 2 divided doses (n=19)	15 mg/kg/day as 2 divided doses (n=19)
T_{max} (hr)	1.4 (60)	1.9 (81)
C_{max} (ng/mL)	2705 (17)	3243 (24)
AUC_{12} (ng*hr/mL)	25049 (16)	29620 (25)
Apparent Clearance (L/hr/kg)	0.25 (16)	0.27 (25)

This supplemental new drug application also provides for the inclusion of updated information in the **PRECAUTIONS, Pediatric use** section of the **Rebetron Combination Therapy™** label, as follows:

> One hundred twenty-five pediatric patients between three and sixteen years of age with chronic hepatitis C virus infection (median duration 10.7 years) received REBETOL Capsules with INTRON A for up to 48 weeks. The overall sustained response rate cannot be calculated since all patients have not yet completed 24-weeks of off-therapy follow-up.

Suicidal ideation or attempts occurred more frequently among pediatric patients compared to adult patients (2.4% versus 1%) during treatment and off therapy follow-up (see WARNINGS). As in adult patients, pediatric patients experienced other psychiatric adverse events (e.g., depression, emotional lability, somnolence), anemia, and neutropenia (see **WARNINGS**). During a 48 week course of therapy there was a decrease in the rate of linear growth (mean percentile assignment decrease of 7%) and a decrease in the rate of weight gain (mean percentile assignment decrease of 9%). A general reversal of these trends was noted during the 24 week post treatment period.

Injection site disorders, fever, anorexia, vomiting, and emotional lability occurred more frequently in pediatric patients compared to adult patients. Conversely, pediatric patients experienced less fatigue, dyspepsia, arthralgia, insomnia, irritability, impaired concentration, dyspnea, and pruritis compared to adult patients.

This supplemental new drug application also provides for the inclusion of new dosing recommendations for REBETOL capsules with respect to administration with food, and for pediatric patients with chronic hepatitis C virus (HCV) infection, as found in the **DOSAGE AND ADMINISTRATION** section of the **Rebetron Combination Therapy™** label, as follows:

DOSAGE AND ADMINISTRATION

REBETOL may be administered without regard to food, but should be administered in a consistent manner. (See **CLINICAL PHARMACOLOGY.)**

Pediatrics

Efficacy of REBETOL and INTRON A for pediatric patients has not been established. Based on pharmacokinetic data, the following doses of REBETOL and INTRON A provide similar exposures in pediatric patients as observed in adult patients treated with the approved doses of REBETOL and INTRON A (see **TABLE 8).**

Table 8. Pediatric Dosing

Body weight	REBETOL Capsules	INTRON A Injection
25-36 kg	1 x 200 mg capsule AM 1 x 200 mg capsule PM daily p.o.	3 million IU/m^2 3 times weekly s.c.
37-49 kg	1 x 200 mg capsule AM 2 x 200 mg capsules PM daily p.o.	3 million IU/m^2 3 times weekly s.c.
50-61 kg	2 x 200 mg capsules AM 2 x 200 mg capsules PM daily p.o.	3 million IU/m^2 3 times weekly s.c.
>61 kg	Refer to adult dosing table	Refer to adult dosing table

Under no circumstances should REBETOL capsules be opened, crushed or broken (see Contraindications and Warnings).

Finally, this supplemental new drug application also provides for the inclusion of an amended version of the Rebetron Combination Therapy™ Medguide, in the "**How should I take REBETRON Combination Therapy?"** section, to include the following wording, as amended by the Division of Antiviral Drug Products (DAVDP) on December 28, 2001. This revision to the Medguide was implemented to provide consistency with information contained in the current package insert for Rebetron Combination Therapy™:

Ask your health care provider about the right amount of INTRON A Injection and REBETOL Capsules needed to treat a child with hepatitis C. This amount will depend on a child's weight.

We have completed the review of this supplemental application, 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 and with the minor editorial revisions listed above and detailed in the label appended to this letter. Accordingly, the supplemental application is approved effective on the date of this letter.

The final printed labeling (FPL) must be identical, and include the minor editorial revisions indicated, to the submitted draft labeling (package insert submitted December 21, 2001, patient package insert submitted December 21, 2001, Medguide submitted December 21, 2001). These revisions are terms of the approval of this application.

Please submit the copies of final printed labeling (FPL) electronically 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, this submission should be designated "FPL for approved supplement NDA 20-903/S-013." Approval of this submission by FDA is not required before the labeling is used.

Be advised that, as of April 1, 1999, all applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred (63 *FR* 66632 and 21CFR 314.55). Based on the information submitted in the application to your NDA, dated February 28, 2001, we are deferring submission of additional pediatric studies until August 1, 2002, pending the review of final study reports for studies P00018 and P00321 in pediatric patients infected with HCV. If we determine that additional pediatric studies are necessary, we will specify a date by which you must submit the required assessments.

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

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,

{See appended electronic signature page}

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

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

/s/

Jeffrey Murray

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