DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 20-903/S-042, 043, 044, 045
NDA 21-546/S-001

SUPPLEMENT APPROVAL

Schering Corporation
Attention: Ripal Shah, Pharm D.
Manager, Global Regulatory Affairs
2000 Galloping Hill Road
Kenilworth, NJ 07033

Dear Dr. Shah,

Please refer to your supplemental new drug applications dated June 25, 2008, received June 26, 2008 (NDA 20-903/S-042), dated July 22, 2008, received July 23, 2008 (NDA 20-903/S-043), dated September 3, 2008, received September 4, 2008 (NDA 20-903/S-044), dated October 20, 2008, received October 21, 2008 (NDA 20-903/S-045), and dated October 6, 2009, received October 7, 2009 (NDA 21-546/S-001), submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for REBETOL® (ribavirin) 200 mg Capsules and 40 mg per mL Oral Solution.

We acknowledge receipt of your submissions dated October 10, 2008 (NDA 20-903/S-042) December 23, 2008 (NDA 20-903/S-042 and S-043), March 25, 2009 (NDA 20-903/S-042, S-043, and S-045), June 10, 2009 (NDA 20-903/S-042, S-043, S-044, and S-045), July 16, 2009 (NDA 20-903/S-042, S-043, S-044, and S-045) , August 6, 2009 (NDA 20-903/S-045), September 3, 2009 (NDA 20-903/S-042) and September 30, 2009 (NDA 20-903/S-042).

These Prior Approval supplemental new drug applications were submitted to provide the label in PLR format and to update the package insert and Medication Guide with the following information approved for the treatment of chronic hepatitis C (CHC) with the combination regimen of PegIntron™ and REBETOL® (Ribavirin):

- weight-based dosing for interferon alfa therapy-naïve, adult patients infected with CHC, a shorter duration of treatment for CHC patients infected with genotypes 2 and 3, to add information regarding the risk of stroke and the 800 number for Med Watch Adverse Event Reporting to the Medication Guides;

- retreatment of CHC patients who failed to respond or relapsed after treatment with combination alpha interferon/ribavirin therapy;

- treatment of pediatric patients 3-17 years of age with CHC and to modify the Medication Guide to include information regarding impaired growth and weight loss during treatment in this age group; and

- the results of the IDEAL study, P03471, which includes adding a two-step dose reduction scheme for PegIntron and increasing the dose of REBETOL® (Ribavirin) to 1200 mg/day for patients who weigh between 81 and 85 kilograms.

These supplemental new drug applications also provide for a Risk Evaluation and Mitigation Strategy (REMS) for REBETOL® (ribavirin). The REMS consists of a Medication Guide and a timetable for submission of assessments of the REMS.

We have completed our review of these applications, as amended. These supplemental new drug applications are approved, effective on the date of this letter, for use as recommended in the enclosed, agreed-upon labeling text.

CONTENT OF LABELING

To facilitate the transmission of labeling to the National Library of Medicine for public dissemination, please resubmit the enclosed content of labeling in SPL format as soon as possible, but no later than 14 days from the date of this letter. For administrative purposes, please designate the submissions "**SPL for approved NDA 20-903/S-042, 20-903/S-043, 20-903-S-044, 20-903-S-045 and 21-546-S-001".**

We request that the revised labeling approved today be available on your website within 10 days of receipt of this letter.

RISK EVALUATION AND MITIGATION STRATEGY REQUIREMENTS

Section 505-1 of the FDCA authorizes FDA to require the submission of a REMS if FDA becomes aware of new safety information and makes a determination that such a strategy is necessary to ensure that the benefits of the drug outweigh the risks (section 505-1(a)).

Since REBETOL® (ribavirin) was approved on June 3, 1998, we have become aware of impaired growth and weight loss in pediatric patients during treatment with PegIntron and REBETOL® (ribavirin) based on data submitted in a PegIntron supplemental application. We consider this information to be "new safety information" as defined in section 505-1(b) of FDCA.

Your proposed REMS, submitted on November 6, 2009, to NDA 20-903/S-042, S-043, S-044, and S-045, and submitted on November 6, 2009 to NDA 21-546/S-001 and appended to this letter, is approved. The REMS consists of the Medication Guide included with this letter and the timetable for submission of assessments of the REMS.

The REMS assessment plan should include but is not limited to the following:

a. An evaluation of patients' understanding of the serious risks of impaired growth and weight loss in pediatric patients during treatment with REBETOL® (Ribavirin) in combination with PegIntron.

b. A report on periodic assessments of the distribution and dispensing of the Medication Guide in accordance with 21 CFR 208.24.

c. A report on failures to adhere to distribution and dispensing requirements, and corrective actions taken to address noncompliance.

The requirements for assessments of an approved REMS under section 505-1(g)(3) include, in section 505-1(g)(3)(B) and (C), requirements for information on the status of any post approval study or clinical trial required under section 505(o) or otherwise undertaken to investigate a safety issue. You can satisfy these requirements in your REMS assessments by referring to relevant information included in the most recent annual report required under section 506B and 21 CFR 314.81(b)(2)(vii) and including any updates to the status information since the annual report was prepared. Failure to comply with the REMS assessments provisions in 505-1(g) could result in enforcement action.

We remind you that in addition to the assessments submitted according to the timetable included in the approved REMS, you must submit a REMS assessment and may propose a modification to the approved REMS when you submit a supplemental application for a new indication for use as described in Section 505-1(g)(2)(A) of FDCA.

Prominently identify submissions containing REMS assessments or proposed modifications of the REMS with the following wording in bold capital letters at the top of the first page of the submission:

NDA 20-903 REMS ASSESSMENT
NDA 21-546 REMS ASSESSMENT

NEW SUPPLEMENT FOR NDA 20-903 or NDA 21-546
PROPOSED REMS MODIFICATION
REMS ASSESSMENT

NEW SUPPLEMENT FOR (NEW INDICATION FOR USE)
FOR NDA 20-903 or NDA 21-546
REMS ASSESSMENT
PROPOSED REMS MODIFICATION (if included)

If you do not submit electronically, please send five copies of REMS-related submissions.

LABELING

The final printed labeling (FPL) must be identical to the enclosed labeling (text for the package insert and text for the Medication Guide).

PROMOTIONAL MATERIALS

All promotional materials for your drug product that include representations about your drug product must be promptly revised to make it consistent with the labeling changes approved in this supplement, including any new safety information [21 CFR 314.70(a)(4)]. The revisions to your promotional materials should include prominent disclosure of the important new safety information that appears in the revised package labeling. Within 7 days of receipt of this letter, submit your statement of intent to comply with 21 CFR 314.70(a)(4) to the following address or by facsimile at 301-847-8444:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Drug Marketing, Advertising, and Communications
5901-B Ammendale Road
Beltsville, MD 20705-1266

In addition, as required under 21 CFR 314.81(b)(3)(i), you must submit your updated final promotional materials, and the package insert(s), at the time of initial dissemination or publication, accompanied by a Form FDA-2253, directly to the above address. For instruction on completing the Form FDA 2253, see page 2 of the Form. For more information about submission of promotional materials to the Division of Drug Marketing, Advertising, and Communications (DDMAC), see http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm.

LETTERS TO HEALTH CARE PROFESSIONALS

If you decide to issue a letter communicating important safety related information about this drug product (i.e., a "Dear Health Care Professional" letter), we request that you submit, at least 24 hours prior to issuing the letter, an electronic copy of the letter to this NDA, to CDERMedWatchSafetyAlerts@fda.hhs.gov, and to the following address:

MedWatch
Food and Drug Administration
5600 Fishers Lane, Room 12B05
Rockville, MD 20857

REPORTING REQUIREMENTS

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

If you have any questions, call Victoria Tyson, Chief, Project Management Staff, at (301) 796-0827.

Sincerely,

{See appended electronic signature page}

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

Enclosures
Package Insert (PI)
Medication Guide/REMS

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-20903	SUPPL-42	SCHERING PLOUGH RESEARCH INSTITUTE	REBETOL (RIBAVIRIN) CAPSULES
NDA-20903	SUPPL-43	SCHERING PLOUGH RESEARCH INSTITUTE	REBETOL (RIBAVIRIN) CAPSULES
NDA-20903	SUPPL-44	SCHERING PLOUGH RESEARCH INSTITUTE	REBETOL (RIBAVIRIN) CAPSULES
NDA-20903	SUPPL-45	SCHERING PLOUGH RESEARCH INSTITUTE	REBETOL (RIBAVIRIN) CAPSULES
NDA-21546	SUPPL-1	SCHERING CORP	REBETOL SYRUP (RIBAVIRIN) 40 MG/ML

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

/s/

VICTORIA L TYSON
11/06/2009

KENDALL A MARCUS
11/06/2009