



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration  
Rockville, MD 20857

BL 103949/5171  
BL 103949/5174

**December 11, 2008**

Schering Corporation  
Attention: Rachael A. Steiner  
Associate Director & Liaison  
Global Regulatory Affairs  
2000 Galloping Hill Rd  
Kenilworth, NJ 07033

Dear Ms. Steiner:

Please refer to your supplement to your biologics license application (BLA) 103949/5171, dated June 10, 2008, for PegIntron™ (peginterferon alfa-2b).

We acknowledge receipt of your amendments to this supplement, dated August 15, 2008, September 17, 2008, September 18, 2008, September 30, 2008, October 3, 2008, November 10, 2008, November 13, 2008, and December 1, 2008, December 3, 2008 and December 8, 2008.

We also acknowledge receipt of your supplement 103949/5174, dated August 22, 2008. This supplement was submitted in response to the Agency's letter dated August 8, 2008, which notified you that FDA had determined that a REMS consisting of the Medication Guide approved on March 26, 2008, which included information regarding the risk of cerebrovascular complications due to stroke and a timetable for assessments, was required. Your August 22, 2008 supplement included a proposed REMS with a Medication Guide revised to include the risk of cerebrovascular complications due to stroke and a timetable for assessments. You submitted supplement 103949/5171 to expand the indication for PegIntron™ (peginterferon alfa-2b), given in combination with REBETOL® (ribavirin, USP), to include the treatment of pediatric patients 3-17 years of age with chronic hepatitis C (CHC) and to further modify the Medication Guide to include information regarding weight loss and impaired growth during treatment in pediatric patients 3-17 years of age who received PegIntron™ in combination with REBETOL® for the treatment of CHC.

We have completed our review of both of these supplemental applications, as amended. We are approving the enclosed REMS and the timetable for assessments. The supplemental applications are approved, effective on the date of this letter, for use as recommended in the enclosed agreed-upon labeling text.

Title IX, Subtitle A, Section 901 of the Food and Drug Administration Amendments Act of 2007 (FDAAA) amends the Federal Food, Drug, and Cosmetic Act (FDCA) to authorize FDA to require holders of approved drug and biological product applications to conduct postmarketing studies and clinical trials for certain purposes, if FDA makes certain findings required by the statute (section 505(6)(3)(A), 21 U.S.C. 355(0)(3)(A)). FDA may also require a sponsor of an approved drug to develop and comply with a Risk Evaluation and Mitigation Strategy (REMS) (section 505-1 of the FDCA) if FDA determines that a REMS is necessary to ensure that the benefits of the drug outweigh the risks. These provisions took effect on March 25, 2008.

Since PegIntron™ was approved on August 7, 2001 for the treatment of CHC in adults in combination with REBETOL® we have become aware of new safety information for PegIntron™. Data from the pediatric clinical trial submitted in this application demonstrate that pediatric patients 3-17 years of age who received PegIntron™ in combination with REBETOL® for the treatment of CHC experienced weight loss and impaired growth during treatment. Although patients enrolled in the trial appeared to experience “catch-up” weight gain and some “catch-up” growth after treatment was stopped or completed, it is not known whether patients receiving PegIntron™/ REBETOL® will attain their full predicted adult height. This information was not available when PegIntron™ in combination with REBETOL® was granted marketing authorization. Therefore, we consider this information to be "new safety information" as defined in FDAAA.

**POSTMARKETING REQUIRMENTS UNDER 505(o)**

We have determined that an analysis of spontaneous postmarketing adverse events reported under subsection 505(k)(1) of the FDCA will not be sufficient to assess this known serious risk specific to PegIntron™.

Furthermore, the new pharmacovigilance system that FDA is required to establish under section 505(k)(3) of the FDCA has not yet been established and is not sufficient to assess this serious risk.

Therefore, based on appropriate scientific data, FDA has determined that you are required, pursuant to section 505(0)(3) of the FDCA, to conduct the following study:

Completion of the 5-year follow-up observational study of subjects enrolled in Part 2 of the pediatric study P02538, to assess long-term or delayed toxicity including the effect of PegIntron™ on height and weight and the durability of treatment response. Submit data for at least 50 pediatric subjects completing the 5 year follow-up.

The timetable you submitted on December 8, 2008, states that you will conduct this study according to the following timetable:

Protocol Submission:	Completed
Study Start Date:	Completed
Final Report Submission:	March 31, 2014

Submit all final reports to your BLA 103949. Use the following designators to prominently label all submissions, including supplements, relating to this postmarketing study as appropriate:

- **Required Postmarketing Protocol under 505(o)**
- **Required Postmarketing Final Report under 505(0)**
- **Required Postmarketing Correspondence under 505(0)**

Section 505(0)(3)(E)(ii) of the FDCA requires you to report periodically on the status of any study or clinical trial required under this section. This section also requires you to periodically report to FDA on the status of any study or clinical trial otherwise undertaken to investigate a safety issue. Section 506B of the FDCA, as well as 21 CFR 601.70 requires you to report annually on the status of any postmarketing commitments or required studies or clinical trials.

FDA will consider the submission of your annual report under section 506B and 21 CFR 601.70 to satisfy the periodic reporting requirement under section 505(0)(3)(E)(ii) provided that you include the elements listed in 505(0) and 21 CFR 21 CFR 601.70. We remind you that to comply with 505(0), your annual report must also include a report on the status of any study or clinical trial otherwise undertaken to investigate a safety issue. Failure to submit an annual report for studies or clinical trials required under 505(0) on the date required will be considered a violation of FDCA section 505(0)(3)(E)(ii) and could result in enforcement action.

### **RISK EVALUATION AND MITIGATION STRATEGY REQUIREMENT**

In accordance with section 505-1 of FDCA, as one element of a REMS, FDA may require the development of a Medication Guide as provided for under 21 CFR Part 208. Pursuant to 21 CFR Part 208, FDA has determined that PegIntron™ poses a serious and significant public health concern requiring the distribution of a Medication Guide. The Medication Guide is necessary for patients' safe and effective use of PegIntron™. FDA has determined that PegIntron™ is a product that has serious risks of which patients should be made aware because information concerning the risks could affect patients' decisions to use or continue to use PegIntron™. Under 21 CFR 208, you are responsible for ensuring that the Medication Guide is available for distribution to patients who are dispensed PegIntron™.

Your proposed REMS, initially received August 25, 2008, updated with the current supplement, 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 included in your August 22, 2008, submission.

The timetable you submitted is as follows:

1st FDAAA assessment:	November 2009 (18 months from approval)
2nd FDAAA assessment:	May 2011 (3 years from approval)
3rd FDAAA assessment:	May 2015 (7 years from approval)

Your assessment of the REMS should include an evaluation of:

- Patients' understanding of the serious risks of PegIntron™

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:

- **BLA 103949 REMS ASSESSMENT**
- **NEW SUPPLEMENT FOR BLA 103949 PROPOSED REMS MODIFICATION**  
< other supplement identification > [if included]  
<REMS ASSESSMENT> [if included]

If you do not submit electronically, please send five copies of submissions containing REMS assessments or proposed modifications of the REMS.

#### **REQUIRED PEDIATRIC ASSESSMENTS**

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indications in pediatric patients unless this requirement is waived, deferred, or inapplicable.

On September 16, 2004, we waived the pediatric study requirement for this application for patients ages 0-3 years because necessary studies are impossible or highly impracticable; very few pediatric patients aged 0-3 years with CHC require treatment.

This supplement fulfills the pediatric study requirement established under BLA 103949/5094, for ages 3-17 years as listed below:

To assess the safety, efficacy, tolerability, and pharmacokinetics of Peginterferon alfa-2b when used in combination with ribavirin in approximately 100 pediatric patients (ages 3-17) with chronic hepatitis C.

#### **CONTENT OF LABELING**

FDA previously approved a Medication Guide required for distribution with this product in accordance with 21 CFR Part 208. FDA hereby approves the revised draft Medication Guide you submitted on December 11, 2008.

Please note that:

- this Medication Guide must be reprinted immediately following the last section of labeling or, alternatively, accompany the prescription drug labeling (21 CFR 201.57(c)(18) or 21 CFR 201.80(f)(2));
- you are responsible for ensuring that this Medication Guide is available for distribution to every patient who is dispensed a prescription for this product (21 CFR 208.24);
- the final printed Medication Guide distributed to patients must conform to all conditions described in 21 CFR 208.20, including a minimum of 10 point text; and
- you are responsible for ensuring that the label of each container or package includes a prominent and conspicuous instruction to authorized dispensers to provide a Medication Guide to each patient to whom the drug is dispensed, and states how the Medication Guide is provided (21 CFR 208.24(d)).

As soon as possible, but no later than 14 days from the date of this letter, please submit the content of labeling (21 CFR 314.50(1)) in structured product labeling (SPL) format as described at <http://www.fda.gov/oc/datacouncil/spl/html> that is identical to the enclosed labeling (text for the package insert and text for the patient package insert). Upon receipt, we will transmit that version to the National Library of Medicine for public dissemination. **For administrative purposes, please designate this submission “SPL for approved BL 103949/5171.”**

In addition, within 21 days of the date of this letter, amend any pending applications for this BLA with content of labeling in structured product labeling (SPL) format to include the changes approved in this application.

Marketing the product with FPL that is not identical to the approved labeling text and in the required format may render the product misbranded and an unapproved new drug.

In addition, submit three copies of the introductory promotional materials that you propose to use for this product. Submit all proposed materials in draft or mock-up form, not final print. Send one copy to the Division of Antiviral Products and two copies of both the promotional materials and the package insert directly to:

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

#### **LETTERS TO HEALTH CARE PROFESSIONALS**

If you issue a letter communicating important information about this drug product (i.e., a “Dear Health Care Professional” letter), we request that you submit a copy of the letter to this NDA and a copy to the following address:

MEDWATCH  
Food and Drug Administration  
Suite 12B05  
5600 Fishers Lane  
Rockville, MD 20857

This information will be included in your biologics license application file.

If you have any questions, call Carrie Ceresa, Pharm D., Regulatory Project Manager, at (301) 796-3978.

Sincerely,

A handwritten signature in black ink, appearing to read "Debra Birnkrant", written in a cursive style.

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

Enclosures: Approved PI, Medication Guide, and approved REMS