DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-511

Hoffmann-La Roche
Attention: Jennifer Dudinak, Pharm. D.
Program Director, Drug Regulatory Affairs
340 Kingsland Street
Nutley, NJ 07110-1199

Dear Dr. Dudinak:

Please refer to your new drug application (NDA) dated May 31, 2002, received June 3,2002, submitted under section 505(b) (1) of the Federal Food, Drug, and Cosmetic Act for COPEGUS™ (ribavirin) 200 mg Tablets.

We acknowledge receipt of your submissions dated June 17, 2002, June 26, 2002, July 29, 2002, September 4, 2002, October 8, 2002, October 16, 2002, October 17, 2002, October 18, 2002, October 31, 2002, November 1, 2002, November 11, 2002, November 12, 2002, November 19, 2002, November 22, November 27, December 2, and December 3, 2002.

This new drug application provides for the use of COPEGUS™ (ribavirin) 200 mg Tablets for the treatment of chronic hepatitis C virus infection for use in combination with the approved biologic product PEGASYS® (peginterferon alfa-2a).

We have completed the review of this 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. Accordingly, this application is approved effective on the date of this letter.

The final printed labeling (FPL) must be identical to the enclosed labeling (text for the package insert, text for the patient package insert, Medication Guide, immediate container and carton labels) and/or submitted labeling (package insert submitted December 3, 2002**,** patient package insert submitted December 3, 2002, Medication Guide submitted December 3, 2002, immediate container and carton labels submitted December 3, 2002). Marketing the product(s) with FPL that is not identical to the approved labeling text may render the product misbranded and an unapproved new drug.

Please submit an electronic version of the FPL according to the guidance for industry titled *Providing Regulatory Submissions in Electronic Format - NDA*. 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. Individually mount ten of the copies on heavy-weight paper or similar material. For administrative purposes, designate this submission as "**FPL for approved NDA 21-511**." Approval of this submission by FDA is not required before the labeling is used.

We remind you of your postmarketing study commitments in your submission dated December 3, 2002. These commitments are listed below:

1. You are required to submit the on-going 2-year rat carcinogenicity final study report to us for review when the study is completed.

   Final Report Submission: Within 24 months of the date of this letter

2. Determine the metabolic route and enzymes involved in the metabolism of ribavirin.

   Protocol Submission: Within two months of the date of this letter
   Study Start: Within five months of the date of this letter
   Final Report Submission: Within 12 months of the date of this letter

3. Determine appropriate dosing recommendations for patients with renal impairment.

   Protocol Submission: Within three months of the date of this letter
   Study Start: Within six months of the date of this letter
   Final Report Submission: Within 16 months of the date of this letter

4. Determine whether race affects ribavirin pharmacokinetics.

   Population Pharmacokinetics:
   Report Submission: Within two months of date of this letter

   Clinical Pharmacology Study:
   Protocol Submission: Within three months of the approval letter
   Study Start: Within six months of the approval letter
   Final Report Submission: Within 14 months of the approval letter

5. Determine whether ribavirin induces CYP enzymes.

   Protocol Submission: Within one month of the date of this letter
   Study Start: Within one month of the date of this letter
   Final Report Submission: Within three months of the date of this letter

6. Determine the extent to which ribavirin is bound to plasma proteins.

   Protocol Submission: Within two months of the date of this letter
   Study Start: Within five months of the date of this letter
   Final Report Submission: Within eight months of the date of this letter

7. To provide a ribavirin pregnancy registry post-marketing surveillance study.

   Protocol Submission: Within 2.5 months of the date of this post-approval commitment letter.
   Follow-up teleconference: Within three months of the date of this post-approval commitment letter.

Study Start:	Within four months of the date of this post-approval commitment letter or no later than March 31, 2003.

Submit clinical protocols to your IND for this product. Submit non-clinical and chemistry, manufacturing, and controls protocols and all study final reports to this NDA. In addition, under 21 CFR 314.81(b)(2)(vii) and 314.81(b)(2)(viii), you should include a status summary of each commitment in your annual report to this NDA. The status summary should include expected summary completion and final report submission dates, any changes in plans since the last annual report, and, for clinical studies, number of patients entered into each study. All submissions, including supplements, relating to these postmarketing study commitments must be prominently labeled "**Postmarketing Study Protocol", "Postmarketing Study Final Report", or "Postmarketing Study Correspondence."**

We have determined that COPEGUS™ poses a serious and significant public health concern relating to the teratogenic potential and other significant adverse events associated with COPEGUS™. This concern has led to the development of a Medication Guide under 21 CFR 208 in order to prevent serious adverse effects, inform patients of information concerning risks that could affect their decision to use or continue to use the drug, and/or assure effective use of the drug.

We acknowledge your submission of a Medication Guide on June 3, 2002. You are reminded that under 21 CFR 208, you are responsible for ensuring that the Medication Guide is available for every patient who is dispensed COPEGUS™. Therefore, format the proposed Medication Guide in a manner that will assure its appropriate distribution to patients and include a plan to ensure distribution. In addition, submit proposed container and/or carton labels for COPEGUS™ that include a prominent and conspicuous instruction to provide the Medication Guide to each patient dispensed the drug. The labels must that state how the Medication Guide is provided (e.g., affixed on the container, provided with the product, etc.).

The text in italics below addresses the application of FDA's Pediatric Rule at [21 CFR 314.55/21 CFR 601.27] to this [NDA/BLA]. The Pediatric Rule has been challenged in court. On October 17, 2002, the court ruled that FDA did not have the authority to issue the Pediatric Rule and has barred FDA from enforcing it. The government has not yet decided whether to seek a stay of the court's order. In addition, the government has not yet decided whether to appeal the decision; an appeal must be filed within 60 days. **Therefore, this letter contains a description of the pediatric studies that would be required under the Pediatric Rule, if the Pediatric Rule remained in effect and/or were upheld on appeal.** Please be aware that whether or not these pediatric studies will be required will depend upon the resolution of the litigation. FDA will notify you as soon as possible as to whether this application will be subject to the requirements of the Pediatric Rule as described below. In any event, we hope you will decide to conduct these pediatric studies to provide important information on the safe and effective use of this drug in the relevant pediatric populations.

All applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens must contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred (21 CFR 314.55).

Your application does not address the pediatric study requirements. Submit your pediatric drug development plans or a request for a waiver, if you believe one is appropriate, within 180 days from the date of this letter. If you believe a waiver is justified, submit your request with supporting information and documentation.

The pediatric exclusivity provisions of FDAMA as re-authorized by the Best Pharmaceuticals for Children Act are not affected by the court's ruling. Pediatric studies conducted under the terms of section 505A of the Federal Food, Drug, and Cosmetic Act may result in additional marketing exclusivity for certain products (pediatric exclusivity). You should refer to the Guidance for Industry on Qualifying for Pediatric Exclusivity (available on our web site at www.fda.gov/cder/pediatric) for details. If you wish to qualify for pediatric exclusivity you should submit a "Proposed Pediatric Study Request". FDA generally does not consider studies submitted to an NDA before issuance of a Written Request as responsive to the Written Request. Applicants should obtain a Written Request before submitting pediatric studies to an NDA.

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 Drug Products and two copies of both the promotional materials and the package insert(s) directly to:

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

We have not completed validation of the regulatory methods. However, we expect your continued cooperation to resolve any problems that may be identified.

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

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, please call Destry Sillivan, Regulatory Project Manager, at (301) 827-2335.

Sincerely,

{See appended electronic signature page}

Debra Birnkrant, M.D.
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/

Debra Birnkrant
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