CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 020807

APPROVABLE LETTER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 20-807

SEP 8 1997

Hoechst Marion Roussel
C/O ClinTrials Research, Inc. (U.S. Agent)
Attention: B. Randall Vestal
P.O. Box 13991
Research Triangle Park, North Carolina 27709

Dear Mr. Vestal:

Please refer to your new drug application dated December 31, 1996, received December 31, 1996 , submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Refludan® [lepirudin (rDNA) for Injection].

We acknowledge receipt of your submissions dated February 1, 20, and 21, March 24, 25, and 26, April 24, 25, and 30, May 6, 13, and 19, July 8, August 4, 13, and 28, 1997. The original User Fee goal date for this application was June 29, 1997. Your submission of May 13, 1997, extended the User Fee goal date to September 30, 1997.

This new drug application provides for the use of Refludan® [lepirudin (rDNA) for Injection] for anticoagulation in patients with heparin-associated thrombocytopenia (HAT) Type II and thromboembolic disease in order to prevent further thromboembolic complications.

We have completed the review of this application as submitted with draft labeling, and it is approvable. Before this application may be approved, however, it will be necessary for you to provide an adequate response to our August 11, 1997, letter requesting additional chemistry, manufacturing, and controls (CMC) information. For your convenience, our requests are reiterated below:

A. DRUG SUBSTANCE:

1.

2.

3.

B. DRUG PRODUCT:

C. MICROBIOLOGY:

1. Submit validation data

2. Provide validation data supporting sterile bulk solution for the maximum specified holding time (one week) at 2-8°C in room 110 before filling.

Further, it will be necessary for you to submit final printed labeling (FPL) identical in content to the enclosed marked-up draft labeling. Please submit 20 copies of the final printed labeling, ten of which are individually mounted on heavy-weight paper or similar material. If additional information relating to the safety or effectiveness of this drug becomes available, revision of the labeling may be required.

Although not required for approval, please address the following at your earliest opportunity:

1. Provide a list of all samples that will be needed for validation of each of the analytical methods. The list should include lot number, identity, size, and quantity for the drug substance, drug product, and reference standards and blanks as stated under 21 CFR 314.50(e).

2. Provide updated methods validation volumes including both the detailed protocol (so it can be reproduced by the FDA Laboratories), followed by the validation report for each method.

3.

4.

Under 21 CFR 314.50(d)(5)(vi)(*b*), we request that you update your NDA by submitting all safety information you now have regarding your new drug. Please provide updated information as listed below:

1. Retabulate all safety data including results of trials that were still ongoing at the time of NDA submission. The tabulation can take the same form as in your initial submission. Tables comparing adverse reactions at the time the NDA was submitted vs now will certainly facilitate review.

2. Retabulate drop-outs with new drop-outs identified. Discuss, if appropriate.

3. Provide details of any significant changes or findings, if any.

4. Summarize worldwide experience on the safety of this drug.

5. Submit case report forms for each patient who died during a clinical study or who did not complete a study because of an adverse event.

Please also update the new drug application with respect to reports of relevant safety information, including all deaths and any adverse events that led to discontinuation of the drug and any information suggesting a substantial difference in the rate of occurrence of common but less serious adverse events. The update should cover all studies and uses of the drug including: (1) those involving indications not being sought in the present submission, (2) other dosage forms, and (3) other dose levels, etc.

In addition, please submit three copies of the introductory promotional material 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 material and the package insert directly to:

Food and Drug Administration
Division of Drug Marketing, Advertising and Communications, HFD-40
5600 Fishers Lane
Rockville, Maryland 20857

Within 10 days after the date of this letter, you are required to amend the application, notify us of your intent to file an amendment, or follow one of your other options under 21 CFR 314.110. In the absence of such action FDA may take action to withdraw the application.

The drug may not be legally marketed until you have been notified in writing that the application is approved.

If you have any questions, please contact Julieann DuBeau, Regulatory Health Project Manager, at (301) 443-0487.

Sincerely yours,

/S/

Paula Botstein, M.D.
Acting Director
Office of Drug Evaluation III
Center for Drug Evaluation and Research

APPEARS THIS WAY
ON ORIGINAL

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