CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 21-271

APPROVAL LETTER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-271

Aventis Pharmaceuticals, Inc.
Attention: Mary E. Elicone, RPh
Mailstop: BX2-206-B
200 Crossing Blvd
Bridgewater, NJ 08807

Dear Ms. Elicone:

Please refer to your new drug application (NDA) dated June 28, 2000, received June 28, 2000, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Iprivask™ (Desirudin for Injection).

We acknowledge receipt of your submissions dated October 3, October 14, October 18, December 10, December 19, 2002, January 7, January 24, January 28, February 20, February 21, February 28, March 6, March 14, March 31, and April 1, 2003.

The October 3, 2002 submission constituted a complete response to our May 14, 2001 action letter.

This new drug application provides for the use of Iprivask™ (Desirudin for Injection) for the prophylaxis of deep vein thrombosis, which may lead to pulmonary embolism, in patients undergoing elective hip replacement surgery.

We completed our review of this application, as amended. It is approved, effective on the date of this letter, for use as recommended in the agreed-upon labeling text.

The final printed labeling (FPL) must be identical to the enclosed agreed-upon labeling (text for the package insert, immediate container and carton labels). Marketing the product 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 "**FPL for approved NDA 21-271**." Approval of this submission by FDA is not required before the labeling is used.

We remind you of your postmarketing study commitment in your submission dated March 14, 2003. This commitment is listed below.

Description of Commitment: To conduct a clinical study in hepatically impaired patients to provide safety information and an appropriate dosing regimen for those patients.

Protocol Submission:	Within 6 months of the date of this letter
Study Start:	Within 12months of the date of this letter
Final Report Submission:	Within 36 months of the date of this letter

Submit clinical protocols to your IND for this product. Submit nonclinical 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."**

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 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, MD 20857

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

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

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 Alice Kacuba, MSN, RN, RAC, Regulatory Health Project Manager, at (301) 827-1602.

Sincerely,

{See appended electronic signature page}

Robert L. Justice, M.D., M.S.
Director
Division of Gastrointestinal & Coagulation Drug Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

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/s/

Robert Justice
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APPROVABLE LETTER

Immediate Container Label - [redacted] Vial

1. Add the following information to the [redacted] vial label:

   a. the name and place of business of the manufacturer, packer, or distributor;

   b. the statement "Rx Only":

   c. the names and quantities of inactive ingredients;

2. Change the storage statement to read, "Store at 25°C (77°F); excursions permitted to 15 - 30°C (59 - 86°F). See USP Controlled Room Temperature.

3. Delete the descriptive term [redacted] from the established name.

Immediate Container Label - Solvent for [redacted]

1. Label the vial as "Mannitol Injection 3%, For Use as a Diluent" rather than [redacted] Change the label to read that the net volume is 0.6 mL.

2. Do not include the proprietary name, established name, and strength of the active drug on the label to avoid confusion between the active drug and the diluent.

3. Add the following information to the label:

   a. the name and place of business of the manufacturer. packer, or distributor;

   b. the statement "Rx Only".

2-Count and 10-Count Carton Labels

1. Revise the statement, "Directions for Use and Reconstitution" to read, "Usual Dosage: See package insert." Follow this with the phrase, "Directions for Reconstitution:" followed by the appropriate directions. Follow the recommendations stated in 21 CFR 201.5(g). Include the final concentration after reconstitution.

2. Delete the statement, [redacted] to avoid confusion concerning the amount of active drug contained in the vial.

3. Delete the drug name and strength [redacted] from the following statements: "2 x 0.5 mL Ampules of Solvent for [redacted] and "10 x 0.5 mL Ampules of Solvent for [redacted] " to avoid confusion between [redacted] and the diluent.

4. Revise the statement, ' [redacted] ' to read "Single dose vials. Discard unused portion."

5. Add the statement "Rx only".

6. Add the quantities of inactive ingredients in the ——— vial.

7. Delete the descriptive term ——— from the established name

If additional information relating to the safety or effectiveness of this drug becomes available, revision of the labeling may be required.

As stated in our November 28, 2000 Information Request Letter, we have completed our review of your proposed proprietary name, ———, and find the proposed name unacceptable because there is a potential for confusion with two sound-alike, look-alike names that already exist in the U.S. market place (i.e., Prevacid and Norvasc). Submit an alternate proposed proprietary name.

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. The safety update should include data from all nonclinical and clinical studies of the drug under consideration regardless of indication, dosage form, or dose level.

1. Describe in detail any significant changes or findings in the safety profile.

2. When assembling the sections describing discontinuations due to adverse events, serious adverse events, and common adverse events, incorporate new safety data as follows:

   - Present new safety data from the studies for the proposed indication using the same format as the original NDA submission.

   - Present tabulations of the new safety data combined with the original NDA data.

   - Include tables that compare frequencies of adverse events in the original NDA with the retabulated frequencies described in the bullet above.

   - For indications other than the proposed indication, provide separate tables for the frequencies of adverse events occurring in clinical trials.

3. Present a retabulation of the reasons for premature study discontinuation by incorporating the drop-outs from the newly completed studies. Describe any new trends or patterns identified.

4. Provide case report forms and narrative summaries for each patient who died during a clinical study or who did not complete a study because of an adverse event. In addition, provide narrative summaries for serious adverse events.

5. Describe any information that suggests a substantial change in the incidence of common, but less serious, adverse events between the new data and the original NDA data.

6. Provide a summary of worldwide experience on the safety of this drug. Include an updated

estimate of use for drug marketed in other countries.

7. Provide English translations of current approved foreign labeling not previously submitted.

Although not required for approval, we request that you provide the following at your earliest convenience:

Clinical Pharmacology and Biopharmaceutics

Calculated pharmacokinetic parameters were based on plasma concentration data obtained by a non-specific ELISA method that does not discriminate between native desirudin and its metabolites. Attempt to develop a specific assay method, such as an LC/MS assay, to analyze the plasma and urine samples from any future pharmacokinetic studies and revise your package insert accordingly.

Clinical

1. Provide safety information from the first market date of [redacted] (Malaysia - November 1995) to the start of the Safety Update (May 1, 1999).

2. Provide clinical information to support the labeling recommendations for switching from desirudin to other anticoagulants and from other anticoagulants to desirudin.

In addition, information provided in the NDA did not address the use of [redacted] provide safety information and the optimal dosing regimen in hepatically impaired patients. [redacted]

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 any such action FDA may proceed to withdraw the application. Any amendment should respond to all the deficiencies listed. We will not process a partial reply as a major amendment nor will the review clock be reactivated until all deficiencies have been addressed.

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

APPEARS THIS WAY
ON ORIGINAL

If you have any questions, call Brian Strongin, Project Manager, at (301) 827-7310.

Sincerely,

{See appended electronic signature page}

Lilia Talarico, M.D.
Director
Division of Gastrointestinal and Coagulation Drug Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

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/s/

Lilia Talarico
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