

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

20-873

APPROVAL LETTER



NDA 20-873

DEC 15 2000

The Medicines Company
Attention: Sonja Loar, Pharm. D.
One Cambridge Center
Cambridge, Massachusetts 02142

Dear Ms. Loar:

Please refer to your new drug application (NDA) dated December 23, 1997, received December 23, 1997, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Angiomax™ (bivalirudin) Injection.

We acknowledge receipt of your submissions dated April 6, May 12 and 17, July 14, October 9, November 9, and December 1, 2000. Your submission of July 14, 2000, constituted a complete response to our May 11, 2000, action letter.

This new drug application provides for the use of Angiomax™ (bivalirudin) Injection as an anticoagulant in conjunction with aspirin in patients with unstable angina undergoing percutaneous transluminal coronary angioplasty (PTCA).

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 enclosed labeling text. Accordingly, the 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) and submitted draft labeling (immediate container and carton labels submitted July 14, 2000). 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 20 paper copies of the FPL as soon as it is available, in no case more than 30 days after it is printed. Please individually mount ten of the copies on heavy-weight paper or similar material. Alternatively, you may submit the FPL electronically according to the guidance for industry titled *Providing Regulatory Submissions in Electronic Format - NDAs* (January 1999). For administrative purposes, this submission should be designated "FPL for approved NDA 20-873." Approval of this submission by FDA is not required before the labeling is used.

We remind you of your postmarketing commitment in your submission dated December 1, 2000. This commitment is listed below.

Commit to completing Study TMC 98-10 entitled "Anticoagulant Therapy with Bivalirudin to Assist in the Performance of Percutaneous Coronary Intervention in Patients with Heparin-Induced Thrombocytopenia: An Open Label Study of Bivalirudin for Heparin-Induced Thrombocytopenia (HIT) or Heparin-Induced Thrombocytopenia and Thrombosis Syndrome (HITTS)" and submitting the full report for that study.

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."

Validation of the regulatory methods has not been completed. At the present time, it is the policy of the Center not to withhold approval because the methods are being validated. Nevertheless, we expect your continued cooperation to resolve any problems that may be identified.

Be advised that, as of April 1, 1999, all applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred (63 FR 66632). We are waiving the pediatric study requirement for this action on this application.

In addition, please submit three copies of the introductory promotional materials that you propose to use for this product. All proposed materials should be submitted in draft or mock-up form, not final print. Please send one copy to the Division of Gastrointestinal and Coagulation Drug Products 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, Maryland 20857

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

We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 314.80 and 314.81.

If you have any questions, call Julieann DuBeau, Regulatory Health Project Manager, at (301) 827-7310.

Sincerely,

/s/

12/15/00 FOR FH

Florence Houn, M.D., M.P.H., F.A.C.P.
Director
Office of Drug Evaluation III
Center for Drug Evaluation and Research

Enclosure

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:
20-873

APPROVABLE LETTER

MAY 11 2000

The Medicines Company
Attention: Phyllis Collins
One Cambridge Center
Cambridge, Massachusetts 02142

Dear Ms. Collins:

Please refer to your new drug application (NDA) dated December 23, 1997, received December 23, 1997, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Angiomax™ (bivalirudin) Injection.

We acknowledge receipt of your submissions dated October 15, 21, 25, 27, and 29, November 3 and 11, December 20 and 21, 1999, January 7, 19, and 28, February 14 and 24, March 15, 28, and 30, and April 10 and 25, 2000. Your submission of November 11, 1999, constituted a complete response to our October 28, 1999, action letter.

We also refer to your submission dated April 6, 2000. This submission has not been reviewed in the current review cycle. You may incorporate this submission by specific reference as part of your response to the deficiencies cited in this letter.

We have completed the review of this application, as amended, and it is approvable for the following indication: "Angiomax™ is indicated for use as an anticoagulant in patients with unstable angina undergoing percutaneous transluminal coronary angioplasty (PTCA)."

Before this application may be approved, you must adequately address the following deficiencies:

I. Biopharmaceutics

- A. Explain why the dose of bivalirudin is to be reduced by half for patients with moderate renal impairment as specified in Table 1 of your proposed package insert submitted November 11, 1999. Results from your ongoing study entitled "The influence of dose and kidney function on bivalirudin pharmacokinetics (PK) and pharmacodynamics (PD) in patients undergoing percutaneous coronary artery angioplasty (PTCA)" (Study No. TMC-98-09) demonstrate that there is only a 21% reduction in total clearance of bivalirudin in this group.
- B. Explain why the proposed 0.2 mg/kg/h dosing regimen is not adjusted for renal function.
- C. Determine the half-lives of bivalirudin in patients with normal renal function and in patients with mildly and moderately impaired renal function by modeling the observed

data obtained from Study No. TMC-98-09.

- D. Upon completion of Study No. TMC-98-09, provide PK/PD analyses of the activated clotting time (i.e., PK/PD modeling, etc. if appropriate) along with analyses for age and gender effects on PK and PD. When gender analyses have been completed, please assess PK/PD as a function of glomerular filtration rate (GFR). If recruitment of patients with severe renal disease is problematic, please contact the Division to discuss possible study modifications that might make patient enrollment easier (e.g., a reduced blood collection scheme).

II. Chemistry, Manufacturing, and Controls (CMC)

A. Drug Product

1. Include a maximum mixing time for the dissolution step of the bulk drug, with instructions on how to proceed if the drug does not dissolve in the stated time.
2. Provide a copy of the revised manufacturing procedure for the drug product that incorporates the changes described in the November 11, 1999, submission.
3. Specify the in-process control tests to be performed as part of the batch record that incorporates the latest appropriate versions of the methods. In addition, explain why the in-process control methods are stamped "Unofficial Not for Regulatory Submission."
4. Submit revised specifications for the finished drug product that include current versions of the methods.

(a) State whether the specifications described on the second page after Tab B.6 represent those that will be used.

(b) Clarify why there is no test for enantiomeric purity in these specifications or in the Certificate of Analysis (COA) from _____ described on the sixth page after Tab B.6.

(d) Explain why the acceptance criterion in the specification for the mass (2080.6

m.u.) differs from the mass (2180.3 m.u.) in the specification from _____
_____ described on the fifth page after Tab B.6. and in the COA from

6. Provide a copy of method 931-00-020D using Ben Venue Laboratories' procedures rather than Biogen's.
7. Provide copies of the revised procedures for the chromogenic assay that specify that the concentration of peptide should be 0.6 mg/mL.
8. Provide validation data for the chromogenic assay that show the stability of diluted test samples at 5 µg/mL for up to one month at 2° to 8° C.
9. Provide data, including stability data, for new batches of drug product assayed using the new calculation methods. Set acceptance criteria for impurities using these data.

B. Drug Master File (DMF)

_____ for the synthesis of the drug substance is deficient. The DMF holder, _____
_____ was informed of the deficiencies in a letter dated April 13, 2000.

C. Facilities Inspections

During inspections of the manufacturing facilities for your NDA, a number of deficiencies were noted and conveyed by the inspector to you or your suppliers. Satisfactory inspections will be required before this application may be approved.

In addition, it will be necessary for you to submit draft labeling incorporating the requested revisions as identified in the enclosed marked-up draft labeling as well as the following revisions to the immediate container and carton labels (submitted February 24, 2000):

1. Replace the statement "CAUTION: Federal law prohibits dispensing without prescription" with "Rx Only" on the immediate container and secondary package labels.
2. Clarify the distributor/manufacturer relationship between Ben Venue Laboratories and The Medicines Company on the immediate container, secondary package, and tertiary package labels in accordance with 21 CFR 201.1(h)(5).
3. Add the statement "For Single Use Only" on the immediate container label.
4. Delete the terminal zeros on the immediate container and secondary package labels.

5. Increase the size and prominence of the strength (250 mg) on the immediate container, secondary package, and tertiary package labels.
6. Increase the size of the established name on the tertiary package label so that the letters are at least half as large as the letters comprising the proprietary name in accordance with 21 CFR 201.10(g)(2).
7. Revise the phrase "sterile water for injection" to "Sterile Water for Injection" on the immediate container and secondary package labels.

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

Please note that sufficient data have been submitted to support a 12-month expiration date. However, an expiration date of eighteen months may be granted if an acceptable statistical analysis of data that includes the 9 month data point (5° C) is provided. Provide stability data in tabular format on diskette. Include the following parameters in the data-set: Assay, _____

chromogenic assay.

Regarding your request of waiver for pediatric studies under 21 CFR 314.55, we have reviewed the information you have submitted on November 11, 1999, and agree that a waiver is justified for the pediatric population. Accordingly, a waiver for pediatric studies for this application is granted under 21 CFR 314.55.

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. 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.

1. Retabulation of 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 versus now will certainly facilitate review.
2. Retabulation of drop-outs with new drop-outs identified. Discuss, if appropriate.
3. Details of any significant changes or findings.

4. Summary of worldwide experience on the safety of this drug.
5. Case report forms for each patient who died during a clinical study or who did not complete a study because of an adverse event.
6. English translations of any approved foreign labeling not previously submitted.
7. Information suggesting a substantial difference in the rate of occurrence of common, but less serious, adverse events.

In addition, please submit three copies of the introductory promotional materials that you propose to use for this product. All proposed materials should be submitted in draft or mock-up form, not final print. Please send one copy to the Division of Gastrointestinal and Coagulation Drug Products and two copies of both the promotional materials and the package insert directly to:

Division of Drug Marketing, Advertising, and Communications, HFD-40
Food and Drug Administration
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 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.

If you have any questions, call Julieann DuBeau, Regulatory Health Project Manager, at (301) 827-7310.

Sincerely,

/S/

5/11/00 FOR

Florence Houn, M.D., M.P.H., F.A.C.P.
Director
Office of Drug Evaluation III
Center for Drug Evaluation and Research

Enclosure: Marked-up Draft Labeling