



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service  
Food and Drug Administration  
Rockville, MD 20857

NDA 20-873/S-006

The Medicines Company  
Attention: Gary Knappenberger  
The Medicines Company  
8 Campus Drive  
Parsippany, NJ 07054

Dear Mr. Knappenberger:

Please refer to your supplemental new drug application dated December 10, 2004, received December 13, 2004, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Angiomax<sup>®</sup> (bivalirudin) for Injection.

We acknowledge receipt of your submissions dated October 7, October 11, October 19, October 27, November 8, November 30, December 8, December 10, December 21, December 23, 2004, January 10, February 22, March 14, April 15, May 4, May 11, June 7, June 8, June 9, and June 13, 2005.

Your submission of December 10, 2004 constituted a complete response to our May 28, 2004 action letter.

This supplemental new drug application provides for the use of Angiomax<sup>®</sup> (bivalirudin) for Injection with provisional use of glycoprotein IIb/IIIa inhibitor (GPI) as listed in the **CLINICAL TRIALS REPLACE-2** section for use as an anticoagulant in patients undergoing percutaneous coronary intervention (PCI).

We completed our review of this application, as amended. This application 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 submitted labeling (package insert submitted June 13, 2005).

The totality of evidence indicates that Angiomax (bivalirudin) with provisional use of glycoprotein IIb/IIIa inhibitor (GPI) is safe and effective for anticoagulation during percutaneous coronary interventions, including placement of intracoronary stents. Although statistical non-inferiority was not demonstrated for the triple endpoint (composite of death, myocardial

infarction or urgent revascularization procedure) in the REPLACE-2 study, the rate of the triple endpoint for bivalirudin with provisional use of GPI treatment in the study is similar to the event rates observed with bivalirudin treatment in the studies that led to approval of bivalirudin for percutaneous transluminal coronary angioplasty (PTCA), a related indication. In the REPLACE-2 study there was significantly less protocol-defined major bleeding in the bivalirudin with provisional use of GPI treatment arm than in the heparin plus GPI treatment arm. In your PTCA studies major bleeding was less in the bivalirudin treatment arm than in the comparator (heparin) treatment arm. Finally, in the REPLACE-2 study, at 12 months follow-up, mortality was 1.9% among patients randomized to bivalirudin with provisional GPI and 2.5% among patients randomized to heparin plus GPI. From a clinical viewpoint, the benefit/risk relationship for bivalirudin with provisional use of GPI is acceptable.

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 15 of the copies on heavy-weight paper or similar material. For administrative purposes, designate this submission "**FPL for approved supplement NDA 20-873/S-006.**" Approval of this submission by FDA is not required before the labeling is used.

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. We are waiving the pediatric study requirement for ages birth to 16 years of age for this application.

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

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, HFD-410  
FDA  
5600 Fishers Lane  
Rockville, MD 20857

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, Regulatory Health Project Manager, at (301) 827-9334.

Sincerely,

*{See appended electronic signature page}*

Joyce Korvick, M.D., M.P.H.  
Deputy Director  
Division of Gastrointestinal and Coagulation Drug Products  
Office of Drug Evaluation III  
Center for Drug Evaluation

Enclosure

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**This is a representation of an electronic record that was signed electronically and  
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/s/

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Kathy Robie-Suh  
6/13/05 06:22:26 PM  
signing for Dr. Joyce Korvick