DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Silver Spring, MD 20993

TRANSMITTED BY FACSIMILE

Ketna Patel
Manager, Regulatory Affairs
The Medicines Company
8 Sylvan Way
Parsippany, NJ 07054

RE: NDA 020873
Angiomax® (bivalirudin) For Injection
MA #252

Dear Ms. Patel:

The Office of Prescription Drug Promotion (OPDP), Division of Professional Promotion (DPP) of the U.S. Food and Drug Administration (FDA) has reviewed a professional Booth Panel (ANG-PEP-644-01) for Angiomax® (bivalirudin) For Injection (Angiomax) submitted by The Medicines Company under cover of Form FDA-2253. The booth panel is false or misleading because it omits important risk information associated with the drug and presents unsubstantiated superiority claims. Thus, the booth panel misbrands Angiomax in violation of the Federal Food, Drug, and Cosmetic Act (the FD&C Act), 21 U.S.C. 352(a) & 321(n). 21 CFR 1.21(a). *Cf.* 21 CFR 202.1(e)(5)(i),(iii); (e)(6)(ii),(x); & (e)(7)(i).

Background

Below are the indication and summary of the most serious and common risks associated with the use of Angiomax.[1] The INDICATIONS and USAGE section of the PI states the following (in pertinent part):

> Angiomax® (bivalirudin) is indicated for use as an anticoagulant in patients with unstable angina undergoing percutaneous transluminal coronary angioplasty (PTCA).
>
> Angiomax with provisional use of glycoprotein IIb/IIIa inhibitor (GPI) as listed in the REPLACE-2 trial is indicated for use as an anticoagulant in patients undergoing percutaneous coronary intervention (PCI).
>
> Angiomax is indicated for patients with, or at risk of, heparin induced thrombocytopenia (HIT) or heparin induced thrombocytopenia and thrombosis syndrome (HITTS) undergoing PCI.

[1] This information is for background purposes only and does not necessarily represent the risk information that should be included in the promotional piece cited in this letter.

> Angiomax in these indications is intended for use with aspirin and has been studied only in patients receiving concomitant aspirin.
>
> The safety and effectiveness of Angiomax have not been established in patients with acute coronary syndromes who are not undergoing PTCA or PCI.

Angiomax is contraindicated in patients with active major bleeding and hypersensitivity to Angiomax or its components. Additionally, the PI contains WARNINGS AND PRECAUTIONS regarding bleeding events and coronary artery brachytherapy. The most common adverse reaction observed with the use of Angiomax was bleeding (28%). Other adverse reactions (incidence >0.5%) were headache, thrombocytopenia, and fever.

Omission of Risk Information

Promotional materials are misleading if they fail to reveal facts that are material in light of representations made or with respect to consequences that may result from the use of the drug as recommended or suggested in the materials.

The booth panel makes several efficacy claims for Angiomax, but omits important risk information for the drug. We note that the booth panel includes the CONTRAINDICATIONS, part of the WARNING and PRECAUTION regarding bleeding events, and mentions some adverse events. However, the booth panel completely omits the WARNING and PRECAUTION regarding coronary artery brachytherapy. It also fails to include the following important material information from the WARNINGS AND PRECAUTIONS section of the PI regarding the risk of bleeding events:

> Although most bleeding associated with the use of Angiomax in PCI/PTCA occurs at the site of arterial puncture, **hemorrhage can occur at any site. . . . Angiomax should be used with caution in patients with disease states associated with an increased risk of bleeding.** (emphasis added)

Additionally, the booth panel fails to convey that the most common adverse event associated with Angiomax was bleeding, which was experienced in 28% of patients. By omitting this important risk information, the booth panel misleadingly suggests that Angiomax is safer than has been demonstrated by substantial evidence or substantial clinical experience. We note that the bottom of the booth panel includes the statement, “Please see representative at exhibit for full Prescribing Information.” However, this does not mitigate the omission of risk information from the booth panel.

Unsubstantiated Superiority Claims

Promotional materials are misleading if they represent or suggest that a drug is safer or more effective than another drug, when this has not been demonstrated by substantial evidence or substantial clinical experience. The booth panel includes claims such as the following:

- “ANGIOMAX: documented **victories** across a broad spectrum of patients from stable to STEMI” (emphasis added)

- "Data-Driven ***victories***" (bolded emphasis added)

- "**Unsurpassed ischemic efficacy throughout the risk spectrum**
  - Demonstrated unsurpassed ischemic efficacy and reduced bleeding vs heparin with or without glycoprotein (GP) IIb/IIIa inhibitor" (emphasis in original)

The above claims are presented in conjunction with a graphic that shows an increased risk of ischemic complications as stable angina progresses to unstable angina to NSTEMI to STEMI. The presentation further includes an arrow indicating that as the risk of ischemic complications increases, the ability of heparin to penetrate thrombus decreases. The names of various clinical trials for Angiomax are also included along the disease continuum. The totality of the above claims and presentations misleadingly implies that Angiomax is more effective than heparin with or without glycoprotein IIb/IIIa inhibitor (GPI) for patients with stable angina, unstable angina, NSTEMI, and STEMI, who are undergoing PCI, when this has not been demonstrated by substantial evidence or substantial clinical experience.

The booth panel cites numerous references to support the above claims and presentations. The Rich, et al.[2] study, is cited in support of the claim regarding heparin's decreased ability to penetrate thrombus. However, this study measured, *ex vivo*, the variability of activated partial thromboplastin time (APTT) values after adding a fixed concentration of heparin or bivalirudin to plasma samples obtained from normal volunteers and patients with coronary artery disease, unstable angina, and acute myocardial infarction. *Ex vivo* findings do not correlate with claims of clinical benefit implying that heparin has a decreased ability to penetrate the thrombus as the risk of ischemic complications increases. Therefore, the cited reference does not constitute substantial evidence to support claims and presentations implying that Angiomax is clinically superior to heparin "throughout the risk spectrum."

Furthermore, the booth panel cites the ACUITY PCI study[3] and the HORIZONS AMI study[4] to support the above-mentioned claims and presentations. In general, claims of superiority must be supported by adequate and well-controlled head-to-head clinical trials comparing appropriate doses and dose regimens of your drug and the comparator drug or drugs. The ACUITY PCI study was a non-inferiority trial in patients with unstable angina and NSTEMI undergoing PCI that compared enoxaparin or unfractionated (UFH) plus GPI, Angiomax plus GPI, and Angiomax alone. Non-inferiority trials are not designed to demonstrate superiority over other agents. Rather, they are intended to show that the effect of a new treatment is not worse than that of an active control by more than a specified margin. Therefore, the ACUITY PCI study does not constitute substantial evidence to support that Angiomax is clinically superior to heparin as implied by the above-mentioned claims and presentations. In fact, we note that the ACUITY PCI study failed to show non-inferiority of Angiomax to enoxaparin or UFH when analyzed for the endpoint of death or MI at 30 days. Also, both the ACUITY PCI and HORIZONS AMI studies were confounded by the administration of other anti-thrombin

[2] Rich JD, Maraganore JM, Young EM, et al. Heparin resistance in acute coronary syndromes. *J Thromb Thrombolysis.* 2007;23:93-100.
[3] Stone GW, White HD, Ohman EM, et al. for the Acute Catheterization and Urgent Intervention Triage strategy (ACUITY) Trial Investigators. Bivalirudin in patients with acute coronary syndromes undergoing percutaneous coronary intervention. *Lancet.* 2007;369:907-919.
[4] Stone GW, Witzenbichler B, Guagliumi G, et al. Bivalirudin during primary PCI in acute myocardial infarction. *N Engl J Med.* 2008;358:2218-2230.

agents prior to the randomized study drugs. In the ACUITY PCI study, 63-64% of patients either received enoxaparin or UFH prior to initiation of the randomized study drug, and in the HORIZONS AMI study, 65.6% of patients received UFH prior to randomization. Pre-treatment with enoxaparin or UFH could have contributed to the anticoagulation effect in the Angiomax treatment arms, thus making it difficult to determine the efficacy attributed solely to Angiomax.

The Bittl, et al.[5] reference describes a reanalysis of the Bivalirudin Angioplasty Trial study, which only included patients undergoing PTCA, and therefore does not constitute substantial evidence or substantial clinical experience to support the above claims and presentations relevant to PCI. Two other references cited, Fuster, et al.[6] and Yeghiazarians, et al.,[7] are review articles and do not mention Angiomax at all.

Finally, the booth panel cites the REPLACE-2 clinical study,[8] which is included in the PI and supported the approval of Angiomax for patients undergoing PCI. This study included patients undergoing PCI with unstable angina, myocardial infarction within 7 days prior to intervention, stable angina, and positive ischemic stress test. REPLACE-2 was a non-inferiority trial designed to compare Angiomax with provisional use of GPI to heparin with mandatory use of GPI for a quadruple endpoint – a composite of death, MI, or urgent revascularization procedure up to 30 days post-PCI and in-hospital major hemorrhage; and a triple endpoint – a composite of death, MI, or urgent revascularization procedure up to 30 days post-PCI. As previously mentioned, non-inferiority trials are not designed to demonstrate superiority over other agents. Therefore, this study does not provide substantial evidence to support claims and presentations implying that Angiomax is clinically superior to heparin with or without GPI.

Conclusion and Requested Action

For the reasons discussed above, the booth panel misbrands Angiomax in violation of the Act, 21 U.S.C. 352(a) & 321(n). 21 CFR 1.21(a). *Cf.* 21 CFR 202.1(e)(5)(i),(iii); (e)(6)(ii),(x); & (e)(7)(i).

OPDP requests that The Medicines Company immediately cease the dissemination of violative promotional materials for Angiomax such as those described above. Please submit a written response to this letter on or before April 30, 2012, stating whether you intend to comply with this request, listing all promotional materials (with the 2253 submission date) for Angiomax that contain violations such as those described above, and explaining your plan for discontinuing use of such violative materials.

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[5] Bittl JA, Chaitman BR, Feit F, et al. Bivalirudin versus heparin during coronary angioplasty for unstable or postinfarction angina: final report reanalysis of the Bivalirudin Angioplasty Study. *Am Heart J*. 2001;142:952-959.

[6] Fuster V, Badimon JJ, Chesebro JH. Mechanisms of disease: the pathogenesis of coronary artery disease and the acute coronary syndromes. *N Engl J Med*. 1992;326:242-250.

[7] Yeghiazarians Y, Braustein JB, Askari A, Stone P. Unstable angina pectoris. *N Engl J Med*. 2000;342:101-114.

[8] Lincoff AM, Bittl JA, Harrington RA, et al. Bivalirudin and provisional glycoprotein IIb/IIIa blockade compared with heparin and planned glycoprotein IIb/IIIa blockade during percutaneous coronary intervention: REPLACE-2 randomized trial. *JAMA*. 2003;289:853-863.

Please direct your response to the undersigned by facsimile at (301) 847-8444, or at the **Food and Drug Administration, Center for Drug Evaluation and Research, Office of Prescription Drug Promotion, Division of Professional Promotion, 5901-B Ammendale Road, Beltsville, Maryland 20705-1266**. Please note that the Division of Drug Marketing, Advertising, and Communications (DDMAC) has been reorganized and elevated to the Office of Prescription Drug Promotion (OPDP). OPDP consists of the Immediate Office, the Division of Professional Promotion (DPP) and the Division of Direct-to-Consumer Promotion (DDTCP). To ensure timely delivery of your submissions, please use the full address above and include a prominent directional notation (e.g., a sticker) to indicate that the submission is intended for OPDP. In addition, OPDP recently migrated to a different tracking system. Therefore, OPDP letters will now refer to MA numbers instead of MACMIS numbers. Please refer to the MA # in addition to the NDA number in all future correspondence relating to this particular matter. OPDP reminds you that only written communications are considered official.

The violations discussed in this letter do not necessarily constitute an exhaustive list. It is your responsibility to ensure that your promotional materials for Angiomax comply with each applicable requirement of the FD&C Act and FDA implementing regulations.

Sincerely,

{See appended electronic signature page}

James S. Dvorsky, PharmD
Regulatory Review Officer
Division of Professional Promotion
Office of Prescription Drug Promotion

Karen Rulli, Ph.D.
Team Leader
Division of Professional Promotion
Office of Prescription Drug Promotion

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

JAMES S DVORSKY
04/13/2012

KAREN R RULLI
04/13/2012