DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

**TRANSMITTED VIA FACSIMILE**

NOV 23 1998

Gregory M. Torre, Ph.D., J.D.
Senior Director, Drug Regulatory Affairs
Sanofi Pharmaceuticals, Inc.
90 Park Avenue
New York, NY 10016

RE: **NDA 20-839**
Plavix (clopidogrel bisulfate) tablets
MACMIS ID # 6889

Dear Dr. Torre:

Reference is made to Sanofi Pharmaceuticals, Inc.'s letter, dated October 7, 1998, in response to a letter from the Division of Drug Marketing, Advertising and Communications (DDMAC), dated September 23, 1998. DDMAC's letter concerned the alleged dissemination a letter (the Letter), written by a physician to Sanofi's Senior Medical Director, that described the use of Plavix (clopidogrel bisulfate) in patients undergoing coronary artery stent placement. The Letter was allegedly disseminated by, or on behalf of, Bristol-Myers Squibb/Sanofi Pharmaceuticals, Inc. (BMS/Sanofi). In our letter, DDMAC requested that Sanofi investigate the extent to which promotion of Plavix with the Letter has occurred, including the number of health care providers who have received the Letter.

In response, Sanofi acknowledged that the Letter was disseminated for promotion of Plavix to a small number of health care providers by Sanofi and BMS sales representatives. In addition, Sanofi stated that both Sanofi and BMS have policies that prohibit the creation, dissemination, or use of unapproved sales aids in detailing. Further, Sanofi described the corrective actions taken to ensure that promotional use of the Letter will not continue.

DDMAC has reviewed the Letter and has determined that it is in violation of the Federal Food, Drug, and Cosmetic Act (Act) and its implementing regulations because it promotes Plavix for an unapproved use, promotes an off-label dose, and is lacking in fair balance.

Unapproved use/Off-label dose

The Letter describes administering a loading dose of clopidogrel 300 mg to patients immediately prior to coronary artery stent placement. However, the approved product labeling (PI) for Plavix states that it is indicated for the reduction of atherosclerotic events

(myocardial infarction, stroke, and vascular death) in patients with atherosclerosis documented by recent stroke, recent myocardial infarction, or established peripheral artery disease. Sanofi's statements or suggestions that Plavix is safe and effective for use in patients receiving coronary artery stent placements are inconsistent with the PI and are not supported by substantial evidence.

In addition, the Letter describes the use of clopidogrel 300 mg as a loading dose. However, the Dosing and Administration section of the PI states that the recommended dose of Plavix is 75 mg once daily. Therefore, the Letter is in violation of the Act because it implies that Plavix is safe and effective at a dose of 300 mg (four times higher than the dose recommended in the PI), which is not supported by substantial evidence.

Lacking in fair balance

Promotional materials are lacking in fair balance, or otherwise misleading, if they fail to present information relating to the contraindications, warnings, precautions, and side effects associated with the use of a drug in a manner reasonably comparable with the presentation of information relating to the effectiveness of the drug. The Letter is misleading because it fails to disclose any of the risks associated with the use of Plavix.

Further, the Letter states that the 300 mg dose of Plavix will be administered to patients who will be concomitantly receiving several other antiplatelet and/or anticoagulant agents. This presentation implies that coadministration of Plavix with other antiplatelet and/or anticoagulant agents is safe. However, the Precautions section of the PI describes that the safety of Plavix, when used concomitantly with heparin, warfarin, or chronic aspirin therapy, has not been established, and that coadministration of Plavix with any of these agents should be undertaken with caution. DDMAC considers that this presentation of drug interaction information is misleading because it overstates the safety profile of Plavix with respect to drug-drug interactions.

DDMAC is very concerned with the dissemination of the Letter because it states or suggests that Plavix is safe and effective in patients undergoing stent procedures, at an off-label dose, and in patients who will be concomitantly receiving other antiplatelet and/or anticoagulant agents. Further, no risk information was provided in the Letter to alert the reader to the adverse events associated with Plavix therapy. Because Plavix is associated with hemorrhagic adverse events at the recommended 75 mg/day dose, promotion of Plavix in patients receiving coronary artery interventions, at four times the recommended dose, in combination with other agents known to increase the risk of bleeding, raises significant patient safety concerns.

DDMAC has reviewed Sanofi's response and actions taken with respect to the dissemination of the Letter. Although DDMAC does not wish to comment on the internal processes of Sanofi or

BMS, we do note Sanofi's investigation and the corrective actions taken to prevent reoccurrence of this type of violative promotional activity. At this time, DDMAC considers this matter closed, however, we will continue to closely monitor this issue.

If Sanofi has any further questions or comments, please direct them to the undersigned by facsimile at (301) 594-6771, or at the Food and Drug Administration, Division of Drug Marketing, Advertising and Communications, HFD-40, Rm. 17B-20, 5600 Fishers Lane, Rockville, MD 20857. DDMAC reminds Sanofi that only written communications are considered official.

In all future correspondence regarding the issues raised in this letter, please refer to MACMIS ID #6889 in addition to the NDA number.

Sincerely,

Janet Norden, MSN, RN
Regulatory Review Officer
Division of Drug Marketing,
Advertising and Communications