



NDA 20-839/S-044

SUPPLEMENT APPROVAL

Sanofi-Aventis U.S. Inc.
Attention: Colleen M. Davenport, Ph.D.
Director, Drug Regulatory Affairs
11 Great Valley Parkway
P.O. Box 3026
Malvern, PA 19355

Dear Dr. Davenport:

Please refer to your supplemental new drug application dated November 2, 2009, received November 2, 2009, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Plavix (clopidogrel bisulfate) 75 mg Tablets.

This Changes Being Effected supplemental new drug application provides information regarding a potential drug interaction between clopidogrel and CYP2C19 inhibitors. The new label revisions are as follows:

1. The following text was added to the beginning of the **WARNINGS** section:

Reduced effectiveness due to impaired CYP2C19 function:

The inhibition of platelet aggregation by clopidogrel is entirely due to an active metabolite. Clopidogrel is metabolized to this active metabolite in part by CYP2C19. This metabolism can be impaired by genetic variations in CYP2C19 and by concomitant medications that interfere with CYP2C19. Avoid use of Plavix in patients with impaired CYP2C19 function due to known genetic variation or due to drugs that inhibit CYP2C19 activity.

Genetic variations: Patients with genetically reduced CYP2C19 function have diminished antiplatelet responses and generally exhibit higher cardiovascular event rates following myocardial infarction than do patients with normal CYP2C19 function (see **CLINICAL PHARMACOLOGY: Pharmacogenetics**).

Drug interactions: Co-administration of Plavix with omeprazole, a proton pump inhibitor that is an inhibitor of CYP2C19, reduces the pharmacological activity of Plavix if given concomitantly or if given 12 hours apart. There is no evidence that other drugs that reduce stomach acid, such as most H2 blockers (except cimetidine, which is a CYP2C19

inhibitor) or antacids interfere with the antiplatelet activity of clopidogrel (see **PRECAUTIONS: Drug Interactions**).

2. In the **PRECAUTIONS** section, the **Information for Patients** subsection was reworded and reordered to appear as below:

Information for Patients

Patients should be told that while taking Plavix or Plavix combined with aspirin:

- it may take them longer than usual to stop bleeding;
- they may bruise and/or bleed more easily;
- they should report any unusual bleeding to their physician;
- they should tell their physician about any other medications they are taking, including prescription or over-the-counter omeprazole;
- they should inform physicians and dentists that they are taking Plavix and/or any other product known to affect bleeding before any surgery is scheduled and before any new drug is taken.

3. Under **PRECAUTIONS, Drug Interactions**, the first paragraph was replaced with the following:

Clopidogrel is metabolized to its active metabolite in part by CYP2C19. Concomitant use of drugs that inhibit the activity of this enzyme results in reduced plasma concentrations of the active metabolite of clopidogrel and a reduction in platelet inhibition. Avoid concomitant use of drugs that inhibit CYP2C19, including omeprazole, esomeprazole, cimetidine, fluconazole, ketoconazole, voriconazole, etravirine, felbamate, fluoxetine, fluvoxamine, and ticlopidine (See **WARNINGS**).

4. Upon completion of two clinical studies involving clopidogrel and omeprazole, the following description of those two studies was added to the **Drug Interaction** subsection of **PRECAUTIONS**:

Omeprazole: In a crossover clinical study, 72 healthy subjects were administered Plavix (300-mg loading dose followed by 75 mg/day) alone and with omeprazole (80 mg at the same time as Plavix) for 5 days. The exposure to the active metabolite of clopidogrel was decreased by 46% (Day 1) and 42% (Day 5) when Plavix and omeprazole were administered together. Mean inhibition of platelet aggregation (IPA) was diminished by 47% (24 hours) and 30% (Day 5) when Plavix and omeprazole were administered together. In another study 72 healthy subjects were given the same doses of Plavix and omeprazole but the drugs were administered 12 hours apart; the results were similar indicating that administering Plavix and omeprazole at different times does not prevent their interaction (see **WARNINGS**).

We have completed our review of this application. It is approved, effective on the date of this letter, for use as recommended in the enclosed, agreed upon labeling text, which is identical to the content of labeling [21 CFR 314.50(l)(1)(i)] in structured product labeling (SPL) format submitted on November 2, 2009.

LETTERS TO HEALTH CARE PROFESSIONALS

If you issue a letter communicating important safety related information about this drug product (*i.e.*, a “Dear Health Care Professional” letter), we request that you submit an electronic copy of the letter to both this NDA and to the following address:

MedWatch
Food and Drug Administration
5600 Fishers Lane, Room 12B05
Rockville, MD 20857

If you have any questions, please contact:

Alison Blaus
Regulatory Project Manager
(301) 796-1138

Sincerely,

{See appended electronic signature page}

Mary Ross Southworth, Pharm.D.
Deputy Director for Safety
Division of Cardiovascular and Renal Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

Enclosure:
Agreed-upon labeling

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-20839	SUPPL-44	SANOFI AVENTIS US LLC	PLAVIX

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

/s/

MARY R SOUTHWORTH
11/12/2009