DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 020839/S-055

SUPPLEMENT APPROVAL

sanofi-aventis U.S. LLC
Attention: Nancy B. Kribbs, Ph.D.
Senior Director, Global Regulatory Affairs
55 Corporate Drive
Mail Stop: 55D-225A
Bridgewater, NJ 08807

Dear Dr. Kribbs:

Please refer to your Supplemental New Drug Application (sNDA) dated and received October 5, 2011, submitted under section 505(b)(1) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Plavix (clopidogrel bisulfate) 75 mg Tablets.

We acknowledge receipt of your amendment dated December 8, 2011.

This "Prior Approval" supplemental new drug application provides for labeling revised as follows:

1. In **HIGHLIGHTS/RECENT MAJOR CHANGES**, the section was updated to reflect the changes made to the **DOSAGE AND ADMINISTRATION** and **WARNINGS AND PRECAUTIONS** sections.

2. In **HIGHLIGHTS/WARNINGS AND PRECAUTIONS,** the words "or esomeprazole" were added to the first bullet. The bullet now reads:

    - Reduced effectiveness in impaired CYP2C19 function: Avoid concomitant use with omeprazole or esomeprazole. (5.1)

3. Under **DOSAGE AND ADMINISTRATION/Use with Proton Pump Inhibitors (PPI),** the first paragraph was changed from:

(b) (4)

To:

Avoid using omeprazole or esomeprazole with Plavix. Omeprazole and esomeprazole significantly reduce the antiplatelet activity of Plavix. When concomitant administration of a PPI is required, consider using another acid-reducing agent with minimal or no

CYP2C19 inhibitory effect on the formation of clopidogrel active metabolite *[see Warnings and Precautions (5.1), Drug Interactions (7.1) and Clinical Pharmacology (12.3)]*.

4. Under **WARNINGS AND PRECAUTIONS/Diminished Antiplatelet Activity Due to Impaired CYP2C19 Function**, the section was changed from:

To:

Clopidogrel is a prodrug. Inhibition of platelet aggregation by clopidogrel is achieved through an active metabolite. The metabolism of clopidogrel to its active metabolite can be impaired by genetic variations in CYP2C19 *[see Boxed Warning]* and by concomitant medications that interfere with CYP2C19.

Proton Pump Inhibitors
Avoid concomitant use of Plavix with omeprazole or esomeprazole because both significantly reduce the antiplatelet activity of Plavix *[see Drug Interactions (7.1) and Dosage and Administration (2.4)]*.

5. Under **DRUG INTERACTIONS/CYP2C19 Inhibitors**, the word "certain" was added to the second sentence of the firs paragraph. The paragraph now reads:

Clopidogrel is metabolized to its active metabolite in part by CYP2C19. Concomitant use of certain 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 *[see Warnings and Precautions (5.1) and Dosage and Administration (2.4)]*.

6. Under **DRUG INTERACTIONS/CYP2C19 Inhibitors**/*Proton Pump Inhibitors,* the sentence "A higher dose regimen of clopidogrel concomitantly administered with omeprazole increases antiplatelet response; an appropriate dose regimen has not been established" was added as the second paragraph. The paragraph now reads:

Proton Pump Inhibitors (PPI)
Avoid concomitant use of Plavix with omeprazole or esomeprazole. In clinical studies, omeprazole was shown to reduce the antiplatelet activity of Plavix when given concomitantly or 12 hours apart. A higher dose regimen of clopidogrel concomitantly administered with omeprazole increases antiplatelet response; an appropriate dose

regimen has not been established. A similar reduction in antiplatelet activity was observed with esomeprazole when given concomitantly with Plavix. Consider using another acid-reducing agent with minimal or no CYP2C19 inhibitory effect on the formation of clopidogrel active metabolite. Dexlansoprazole, lansoprazole and pantoprazole had less effect on the antiplatelet activity of Plavix than did omeprazole or esomeprazole *[see Dosage and Administration (2.4), Warnings and Precautions (5.1) and Clinical Pharmacology (12.3)]*.

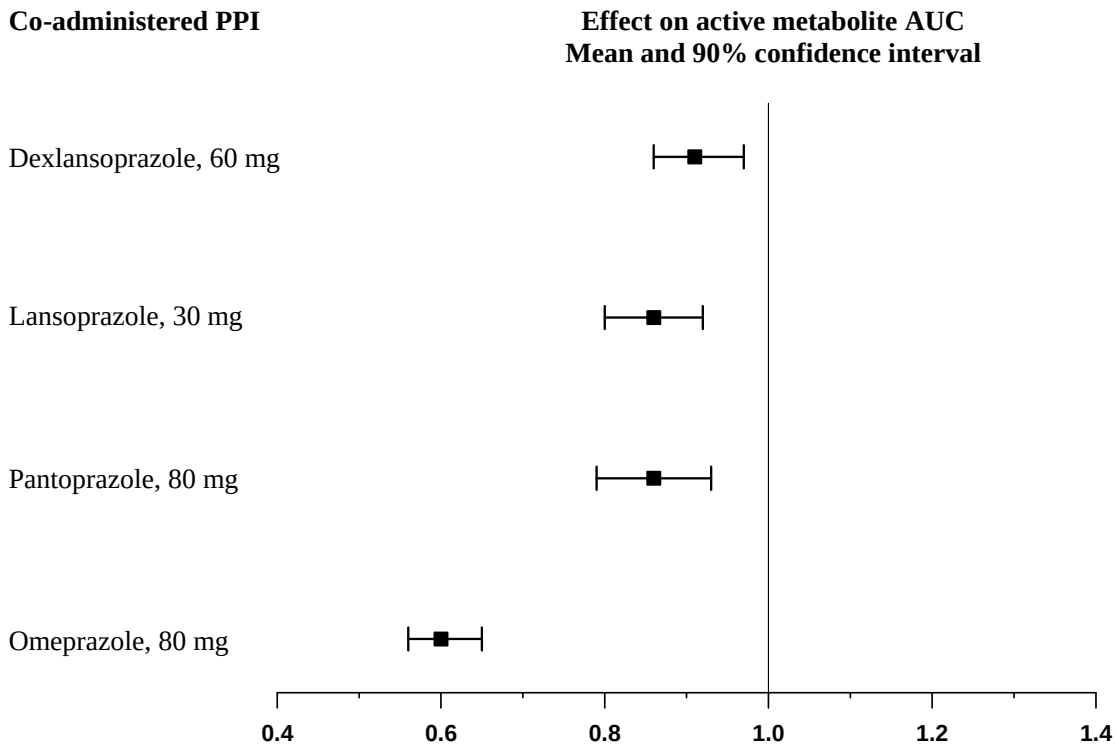
7. Under **CLINICAL PHARMACOLOGY/Pharmacokinetics** a new section was added:

Drug Interactions
Clopidogrel is metabolized to its active metabolite in part by CYP2C19. Concomitant use of certain inhibitors of this enzyme results in reduced plasma concentrations of the active metabolite of clopidogrel and a reduction in platelet inhibition.

8. Under **CLINICAL PHARMACOLOGY/Pharmacokinetics** a new section was added:

Proton Pump Inhibitors (PPI)
The effect of proton pump inhibitors (PPI) on the systemic exposure to the clopidogrel active metabolite following multiple doses of Plavix 75 mg evaluated in dedicated drug interaction studies is presented in Figure 1.

Figure 1: Exposure to Clopidogrel Active Metabolite Following Multiple Doses of Plavix 75 mg Alone or with Proton Pump Inhibitors (PPIs)



Pharmacodynamic and pharmacokinetic parameters measured in these studies showed that the interaction was highest with omeprazole and least with dexlansoprazole.

9. Under **PATIENT COUNSELING INFORMATION/Concomitant Medications**, the paragraph was changed from:

[redacted] (b) (4)

To:

Ask patients to list all prescription medications, over-the-counter medications, or dietary supplements they are taking or plan to take, including prescription or over-the-counter proton pump inhibitors (e.g., omeprazole), warfarin or NSAIDs *[see Warnings and Precautions (5)]*.

10. Under **PATIENT COUNSELING INFORMATION/Medication Guide/What is the most important information I should know about Plavix**, the words "or esomeprazole (Nexium ®)" were added to the second bullet. The bullet now reads:

    - **take certain medicines, especially omeprazole (Prilosec®) or esomeprazole (Nexium®).** Your doctor may change the medicine you take for stomach acid problems while you take Plavix.

11. The figures throughout the label were re-numbered.

We have completed our review of this supplemental application as amended, and it is approved, effective on the date of this letter, for use as recommended in the enclosed, agreed-upon labeling text.

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, submit the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format using the FDA automated drug registration and listing system (eLIST), as described at http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm. Content of labeling must be identical to the enclosed labeling (text for the package insert), with the addition of any labeling changes in pending "Changes Being Effected" (CBE) supplements, as well as annual reportable changes not included in the enclosed labeling.

Information on submitting SPL files using eLIST may be found in the guidance for industry titled "SPL Standard for Content of Labeling Technical Qs and As" at http://www.fda.gov/downloads/DrugsGuidanceComplianceRegulatoryInformation/Guidances/UCM072392.pdf.

The SPL will be accessible from publicly available labeling repositories.

Also within 14 days, amend all pending supplemental applications for this NDA, including CBE supplements for which FDA has not yet issued an action letter, with the content of labeling [21 CFR 314.50(l)(1)(i)] in MS Word format, that includes the changes approved in this supplemental

application, as well as annual reportable changes and annotate each change. To facilitate review of your submission, provide a highlighted or marked-up copy that shows all changes, as well as a clean Microsoft Word version. The marked-up copy should provide appropriate annotations, including supplement number(s) and annual report date(s).

PROMOTIONAL MATERIALS

You may request advisory comments on proposed introductory advertising and promotional labeling. To do so, submit the following, in triplicate, (1) a cover letter requesting advisory comments, (2) the proposed materials in draft or mock-up form with annotated references, and (3) the package insert(s) to:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Drug Marketing, Advertising, and Communications
5901-B Ammendale Road
Beltsville, MD 20705-1266

You must submit final promotional materials and package insert(s), accompanied by a Form FDA 2253, at the time of initial dissemination or publication [21 CFR 314.81(b)(3)(i)]. Form FDA 2253 is available at http://www.fda.gov/opacom/morechoices/fdaforms/cder.html; instructions are provided on page 2 of the form. For more information about submission of promotional materials to the Division of Drug Marketing, Advertising, and Communications (DDMAC), see http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm.

All promotional materials that include representations about your drug product must be promptly revised to be consistent with the labeling changes approved in this supplement, including any new safety information [21 CFR 314.70(a)(4)]. The revisions in your promotional materials should include prominent disclosure of the important new safety information that appears in the revised package labeling. Within 7 days of receipt of this letter, submit your statement of intent to comply with 21 CFR 314.70(a)(4) to the address above or by fax to 301-847-8444.

REPORTING REQUIREMENTS

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, please call:

Lori Anne Wachter, RN, BSN
Regulatory Project Manager for Safety
(301) 796-3975

Sincerely,
{See appended electronic signature page}

Mary Ross Southworth, PharmD.
Deputy Director for Safety
Division of Cardiovascular and Renal Products
Office of Drug Evaluation 1
Center for Drug Evaluation and Research

ENCLOSURE:
Content of Labeling

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
12/20/2011