



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 20-839/S-040

Sanofi-Aventis U.S. Inc.
Attention: Colleen M. Davenport, Ph.D.
Associate 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 (sNDA) dated January 14, 2009 and received January 14, 2009, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Plavix (clopidogrel bisulfate) 75 mg Tablets.

We also acknowledge receipt of your submission dated April 3, 2009. This submission constituted a complete response to our March 6, 2009 action letter

Reference is also made to our letter dated March 6, 2009 notifying you, under Section 505(o)(4) of the FDCA, of new safety information that we believe should be included in the labeling for Plavix (clopidogrel bisulfate). This information pertains to the risk addressed in several published reports describing the metabolic pathway of clopidogrel in vivo, investigating factors involved in the bioavailability of its active metabolite, and reporting an increased reporting rate of cardiovascular ischemic events in poor responders to Plavix (clopidogrel bisulfate).

Lastly, we refer to our May 5, 2009 approval letter and our subsequent telephone conversation, which noted some inaccuracies in that letter. As a result of that conversation, this letter has been revised and supersedes the previous (May 5, 2009) approval letter.

This supplemental new drug application provides for revisions to the labeling for Plavix (clopidogrel bisulfate). The agreed upon labeling changes to the language included in our March 6, 2009 letter are included in Appendix A.

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

Within 14 days of the date of this letter, submit content of labeling [21 CFR 314.50(1)] in structured product labeling (SPL) format, as described at <http://www.fda.gov/oc/datacouncil/spl.html>, that is identical in content to the submitted electronic draft labeling text. Upon receipt, we will transmit that version to the National Library of Medicine for public dissemination. For administrative purposes, please designate the attached "SPL for approved supplement NDA 20-839/S-040." Approval of this submission by FDA is not required before the labeling is used.

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

We request that the revised labeling approved today be available on your website within 10 days of receipt of this letter.

We also 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:

Alison Blaus
Regulatory Health Project Manager
301-796-1138

Sincerely,

{ See appended electronic signature page }

Norman Stockbridge, M.D., Ph.D.
Director
Division of Cardiovascular and Renal Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

Enclosures:
Agreed-upon labeling text

Appendix A:

Agreed upon labeling (as different from labeling in the March 6, 2009 Safety Labeling Notification Letter)

1. Under the **CLINICAL PHARMACOLOGY, Pharmacokinetics** section, we requested you to add the 1st paragraph that reads:

“Because the active metabolite is formed by CYP P450 enzymes, some of which are polymorphic or subject to inhibition by other drugs, not all patients will have adequate platelet inhibition. Some will have no response.”

This paragraph was placed under the **Mechanism of Action and Pharmacodynamic Properties** subsection and agreed upon to read:

“Because the active metabolite is formed by CYP450 enzymes, some of which are polymorphic or subject to inhibition by other drugs, not all patients will have adequate platelet inhibition.”

2. Under the **CLINICAL PHARMACOLOGY, Pharmacokinetics: Effect of Food** section, we asked you to remove the statement regarding inactive metabolite and to update this section to include information from the literature or other data related to the parent or active metabolite.

The following section was added:

“Effect of Food: The effect of food on the bioavailability of the parent compound or active metabolite is currently not known.”

3. In the **CLINICAL PHARMACOLOGY, Pharmacokinetics: Metabolism** section, we requested the following section be removed:

“Metabolism: Clopidogrel is extensively metabolized by the liver. *In vitro* and *in vivo*, clopidogrel is metabolized according to two main metabolic pathways: one mediated by esterases and leading to hydrolysis into its carboxylic acid derivative and one mediated by multiple cytochromes P450 leading to the active metabolite(s) of clopidogrel.

The main circulating metabolite is the carboxylic acid derivative which has no effect on platelet aggregation. This inactive metabolite represents about 85% of the circulating drug-related compounds in plasma.

The active metabolite, a thiol derivative, is generated through formation of 2-oxo-clopidogrel. *In vitro*, this metabolic pathway is mediated by CYP3A4, CYP2C19, CYP1A2 and CYP2B6. The active thiol metabolite which has been isolated *in vitro*, binds rapidly and irreversibly to platelet receptors, thus inhibiting platelet aggregation.”

And be replaced as follows:

“Metabolism: Clopidogrel is extensively metabolized by the liver. *In vitro* and *in vivo*, clopidogrel is metabolized according to two main metabolic pathways: one mediated by esterases and leading to hydrolysis into its inactive carboxylic acid derivative (85% of circulating metabolites), and one mediated by multiple cytochromes P450. Clopidogrel is first metabolized

to a 2-oxo-clopidogrel intermediate metabolite. Subsequent metabolism of the 2-oxo-clopidogrel intermediate metabolite results in formation of the active metabolite, a thiol derivative of clopidogrel. *In vitro*, this metabolic pathway is mediated by CYP3A4, CYP2C19, CYP1A2 and CYP2B6. The active thiol metabolite which has been isolated *in vitro*, binds rapidly and irreversibly to platelet receptors, thus inhibiting platelet aggregation.”

Upon further discussion, this section was later updated to read:

“Metabolism: Clopidogrel is extensively metabolized by the liver. *In vitro* and *in vivo*, clopidogrel is metabolized according to two main metabolic pathways: one mediated by esterases and leading to hydrolysis into its inactive carboxylic acid derivative (85% of circulating metabolites), and one mediated by multiple cytochromes P450. Cytochromes first oxidize clopidogrel to a 2-oxo-clopidogrel intermediate metabolite. Subsequent metabolism of the 2-oxo-clopidogrel intermediate metabolite results in formation of the active metabolite, a thiol derivative of clopidogrel. *In vitro*, this metabolic pathway is mediated by CYP3A4, CYP2C19, CYP1A2 and CYP2B6. The active thiol metabolite, which has been isolated *in vitro*, binds rapidly and irreversibly to platelet receptors, thus inhibiting platelet aggregation.”

4. Under the **CLINICAL PHARMACOLOGY**, section, we requested you to add a new section entitled, **Pharmacogenetics**. After further discussion with you, the section was agreed to read as follows:

“Pharmacogenetics

Several polymorphic CYP450 enzymes activate clopidogrel. CYP2C19 is involved in the formation of both the active metabolite and the 2-oxo-clopidogrel intermediate metabolite. Clopidogrel active metabolite pharmacokinetics and antiplatelet effects, as measured by *ex vivo* platelet aggregation assays, differ according to CYP2C19 genotype. The CYP2C19*1 allele corresponds to fully functional metabolism while the CYP2C19*2 and CYP2C19*3 alleles correspond to reduced metabolism. The CYP2C19*2 and CYP2C19*3 alleles account for 85% of reduced function alleles in whites and 99% in Asians. Other alleles associated with reduced metabolism include CYP2C19*4, *5, *6, *7, and *8, but these are less frequent in the general population. Published frequencies for the common CYP2C19 phenotypes and genotypes are listed in the table below.

Table 1 - CYP2C19 Phenotype and Genotype Frequency

	Frequency (%) ¹		
	White (n=1356)	Black (n=966)	Chinese (n=573)
Extensive metabolism: CYP2C19*1/*1	74	66	38
Intermediate metabolism: CYP2C19*1/*2 or *1/*3	26	29	50
Poor metabolism: CYP2C19*2/*2, *2/*3 or *3/*3	2	4	14

¹Xie, et al. Annu Rev Pharmacol Toxicol 2001; 41: 815-50

To date, the impact of CYP2C19 genotype on the pharmacokinetics of clopidogrel’s active metabolite has been evaluated in 227 subjects from 7 reported studies. Reduced CYP2C19 metabolism in intermediate and poor metabolizers decreased the C_{max} and AUC of the active metabolite by 30-50% following 300- or 600mg loading doses and 75mg maintenance doses.

Lower active metabolite exposure results in less platelet inhibition or higher residual platelet reactivity. To date, diminished antiplatelet responses to clopidogrel have been described for intermediate and poor metabolizers in 21 reported studies involving 4,520 subjects. The relative difference in antiplatelet response between genotype groups varies across studies depending on the method used to evaluate response, but is typically greater than 30%.

The association between CYP2C19 genotype and clopidogrel treatment outcome was evaluated in 2 post-hoc clinical trial analyses (substudies of CLARITY-TIMI 28¹ [n=465] and TRITON-TIMI 38² [n=1,477]) and 5 cohort studies (total n=6,489). In CLARITY-TIMI 28 and one of the cohort studies (n=765; Trenk³), cardiovascular event rates did not differ significantly by genotype. In TRITON-TIMI 38 and 3 of the cohort studies (n= 3,516; Collet,⁴ Sibbing,⁵ Giusti⁶), patients with an impaired metabolizer status (intermediate and poor combined) had a higher rate of cardiovascular events (death, myocardial infarction, and stroke) or stent thrombosis compared to extensive metabolizers. In the fifth cohort study (n=2,208; Simon⁷), the increased event rate was observed only in poor metabolizers.

Pharmacogenetic testing can identify genotypes associated with variability in CYP2C19 activity.

There may be genetic variants of other CYP450 enzymes with effects on the ability to form clopidogrel's active metabolite.”

5. Under the **CLINICAL PHARMACOLOGY, Special Populations** section, we requested that you provide information regarding effects of age, sex, and/or renal impairment as it applied to the active metabolite. If such information was not known, we asked you to 1) remove these sections because information about the inactive metabolite is not relevant and 2) state explicitly that the effects of age, sex, and/or renal impairment on the pharmacokinetics of the active metabolite are unknown.

The following sentence was added at the beginning of the Special Populations section:

“The pharmacokinetics of clopidogrel's active metabolite is not known in these special populations.”

¹ Mega JL, Thakuria JV, Cannon CP, Sabatine MS. Sequence variations in CYP metabolism genes and cardiovascular outcomes following treatment with clopidogrel: insights from the CLARITY-TIMI 28 genomic study. 2008 ACC Meeting Abstract

² Mega et al. Cytochrome P-450 Polymorphisms and Response to Clopidogrel. N Engl J Med 2009; 360:354-62

³ Trenk et al. Cytochrome P450 2C19 681G>A Polymorphism and High On-Clopidogrel Platelet Reactivity Associated With Adverse 1-Year Clinical Outcome of Elective Percutaneous Coronary Intervention With Drug-Eluting or Bare-Metal Stents. J Am Coll Cardiol 2008; 51, 20, 1952

⁴ Collet JP et al. Cytochrome P450 2C19 polymorphism in young patients treated with clopidogrel after myocardial infarction: a cohort study. The Lancet 2009; 373; 309-317

⁵ Sibbing D et al. Cytochrome P450 2C19 loss-of-function polymorphism and stent thrombosis following percutaneous coronary intervention. Eur Heart J 2009

⁶ Giusti et al. Relation of cytochrome P450 2C19 loss-of-function polymorphism to occurrence of drug-eluting coronary stent thrombosis. Am J Cardiol 2009; 103:806-811

⁷ Simon et al. Genetic Determinants of Response to Clopidogrel and Cardiovascular Events. N Engl J Med 2009; 360(4):363-75

The following sections have also been added to the **Special Populations** section:

Geriatric Patients: In elderly (≥ 75 years) volunteers compared to young healthy volunteers, there were no differences in platelet aggregation and bleeding time. No dosage adjustment is needed for the elderly.

Renally-Impaired Patients: After repeated doses of 75 mg PLAVIX per day in patients with severe renal impairment (creatinine clearance from 5 to 15 mL/min), inhibition of ADP-induced platelet aggregation was lower (25%) than that observed in healthy volunteers, however, the prolongation of bleeding time was similar to healthy volunteers receiving 75 mg of PLAVIX per day.

Hepatically-Impaired Patients: After repeated doses of 75 mg PLAVIX per day for 10 days in patients with severe hepatic impairment, inhibition of ADP-induced platelet aggregation was similar to that observed in healthy subjects. The mean bleeding time prolongation was also similar in the two groups.

Gender: In a small study comparing men and women, less inhibition of ADP-induced platelet aggregation was observed in women, but there was no difference in prolongation of bleeding time. In the large, controlled clinical study (Clopidogrel vs. Aspirin in Patients at Risk of Ischemic Events; CAPRIE), the incidence of clinical outcome events, other adverse clinical events, and abnormal clinical laboratory parameters was similar in men and women.”

6. Under **PRECAUTIONS**, we requested that you add a subsection, entitled, “**Pharmacogenetics**,” to appear after **General** subsection to read as follows:

“**Pharmacogenetics:** Patients with genetically reduced CYP2C19 function have lower systemic exposure to the active metabolite of clopidogrel and diminished antiplatelet responses, and higher cardiovascular event rates following myocardial infarction, as compared to patients with normal CYP2C19 function (see **CLINICAL PHARMACOLOGY: Pharmacogenetics**). Genotyping for *CYP2C19* polymorphisms is recommended in order to identify patients with these phenotypes.”

Upon further discussion, this subsection will read:

“**Pharmacogenetics:** Based on literature data, patients with genetically reduced CYP2C19 function have lower systemic exposure to the active metabolite of clopidogrel and diminished antiplatelet responses, and generally exhibit higher cardiovascular event rates following myocardial infarction than do patients with normal CYP2C19 function (see **CLINICAL PHARMACOLOGY: Pharmacogenetics**).”

7. Under **DOSAGE AND ADMINISTRATION, Acute Coronary Syndrome**, we requested that you add the following paragraph after the sentence, “Plavix can be administered with or without food.”

“Genotyping for polymorphisms in *CYP2C19* is recommended to identify patients with reduced metabolism phenotypes who are at greater risk for reduced antiplatelet response and adverse clinical outcomes. Higher loading doses and maintenance doses may be considered in patients who are intermediate or poor metabolizers (*i.e.*, have at least one reduced function allele of *CYP2C19*; see **CLINICAL PHARMACOLOGY: Pharmacogenetics**). While studies of short duration have not demonstrated increased bleeding rates with higher dose regimens, higher doses should be used with caution and the potential cardiovascular benefit of an increased dose should

be weighed against the potential risk of excessive bleeding. The optimal dose regimen for poor metabolizers (patients with 2 reduced function alleles) has yet to be determined.”

It was agreed that this paragraph will read as follows:

“Pharmacogenetics

CYP2C19 poor metabolizer status is associated with diminished response to clopidogrel. The optimal dose regimen for poor metabolizers has yet to be determined. (See **CLINICAL PHARMACOLOGY: Pharmacogenetics.**)”

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/s/

Norman Stockbridge
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