

CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

20839Orig1s042

Trade Name: PLAVIX

Generic Name: clopidogrel bisulfate

Sponsor: Sanofi Aventis

Approval Date: March 12, 2010

Indication: Plavix is a P2Y₁₂ platelet inhibitor indicated for:

- Acute coronary syndrome

For patients with non-ST-segment elevation ACS [unstable angina (UA)/non-ST-elevation myocardial infarction (NSTEMI)] including patients who are to be managed medically and those who are to be managed with coronary revascularization, Plavix has been shown to decrease the rate of a combined endpoint of cardiovascular death, myocardial infarction (MI), or stroke as well as the rate of a combined endpoint of cardiovascular death, MI, stroke, or refractory ischemia.

For patients with ST-elevation myocardial infarction (STEMI), Plavix has been shown to reduce the rate of death from any cause and the rate of a combined endpoint of death, re-infarction, or stroke. The benefit for patients who undergo primary PCI is unknown.

- Recent myocardial infarction (MI), recent stroke, or established peripheral arterial disease. Plavix has been shown to reduce the combined endpoint of new ischemic stroke (fatal or not), new MI (fatal or not), and other vascular death.

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APPROVAL LETTER



DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 20-839/S-042

SUPPLEMENT APPROVAL

sanofi aventis U.S. LLC
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 June 17, 2009, received June 17, 2009, submitted under section 505(b)(1) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Plavix (clopidogrel bisulfate) 75 mg Tablets.

We also acknowledge receipt of your submissions dated September 15, October 6, 22, 30, November 19, December 14, 2009, and January 11, 13, 25, February 1, 12, and March 8, 10, 2010.

We have completed our review of this application, as amended. 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 March 10, 2010. A summary of the major changes appears in Appendix A of this letter, followed by the complete product labeling in Physician's Labeling Rule (PLR) format.

Please resubmit the enclosed content of labeling in SPL format as soon as possible, but no later than 14 days from the date of this letter. For administrative purposes, please designate this submission, "**SPL for approved NDA 20-839/S-042.**"

Within 14 days from the date of this letter, please amend all pending supplemental applications for this NDA, including pending "Changes Being Effected" (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 structured product labeling (SPL) format that includes the changes approved in this supplemental application.

We are waiving the requirements of 21 CFR 201.57(d)(8) regarding the length of Highlights of prescribing information. This waiver applies to all future supplements containing revised labeling unless we notify you otherwise.

PROMOTIONAL MATERIALS

All promotional materials for your drug product that include representations about your drug product must be promptly revised to make it consistent with the labeling changes approved in this supplement, including any new safety information [21 CFR 314.70(a)(4)]. The revisions to 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 following address or by facsimile at 301-847-8444:

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

In addition, as required under 21 CFR 314.81(b)(3)(i), you must submit your updated final promotional materials, and the package insert(s), at the time of initial dissemination or publication, accompanied by a Form FDA-2253, directly to the above address. For instruction on completing the Form FDA 2253, see 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>.

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

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:

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

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-20839	SUPPL-42	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/

ALISON L BLAUS
03/12/2010

NORMAN L STOCKBRIDGE
03/12/2010

**CENTER FOR DRUG EVALUATION AND
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LABELING

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use PLAVIX safely and effectively. See full prescribing information for PLAVIX.

PLAVIX (clopidogrel bisulfate) tablets
Initial U.S. Approval: 1997

WARNING: DIMINISHED EFFECTIVENESS IN POOR METABOLIZERS

See full prescribing information for complete boxed warning.

- Effectiveness of Plavix depends on activation to an active metabolite by the cytochrome P450 (CYP) system, principally CYP2C19. (5.1)
- Poor metabolizers treated with Plavix at recommended doses exhibit higher cardiovascular event rates following acute coronary syndrome (ACS) or percutaneous coronary intervention (PCI) than patients with normal CYP2C19 function. (12.5)
- Tests are available to identify a patient's CYP2C19 genotype and can be used as an aid in determining therapeutic strategy. (12.5)
- Consider alternative treatment or treatment strategies in patients identified as CYP2C19 poor metabolizers. (2.3, 5.1)

RECENT MAJOR CHANGES

Boxed Warning	03/2010
Dosage and Administration (2.3)	03/2010
Warnings and Precautions (5.1, 5.2, 5.3)	03/2010

INDICATIONS AND USAGE

Plavix is a P2Y₁₂ platelet inhibitor indicated for:

- Acute coronary syndrome
 - For patients with non-ST-segment elevation ACS [unstable angina (UA)/non-ST-elevation myocardial infarction (NSTEMI)] including patients who are to be managed medically and those who are to be managed with coronary revascularization, Plavix has been shown to decrease the rate of a combined endpoint of cardiovascular death, myocardial infarction (MI), or stroke as well as the rate of a combined endpoint of cardiovascular death, MI, stroke, or refractory ischemia. (1.1)
 - For patients with ST-elevation myocardial infarction (STEMI), Plavix has been shown to reduce the rate of death from any cause and the rate of a combined endpoint of death, re-infarction, or stroke. The benefit for patients who undergo primary PCI is unknown. (1.1)
- Recent myocardial infarction (MI), recent stroke, or established peripheral arterial disease. Plavix has been shown to reduce the combined endpoint of new ischemic stroke (fatal or not), new MI (fatal or not), and other vascular death. (1.2)

DOSAGE AND ADMINISTRATION

- Acute coronary syndrome (2.1)

- Non-ST-segment elevation ACS (UA/NSTEMI): 300 mg loading dose followed by 75 mg once daily, in combination with aspirin (75-325 mg once daily)
- STEMI: 75 mg once daily, in combination with aspirin (75-325 mg once daily), with or without a loading dose and with or without thrombolytics
- Recent MI, recent stroke, or established peripheral arterial disease: 75 mg once daily (2.2)

DOSAGE FORMS AND STRENGTHS

Tablets: 75 mg, 300 mg (3)

CONTRAINDICATIONS

- Active pathological bleeding, such as peptic ulcer or intracranial hemorrhage (4.1)
- Hypersensitivity to clopidogrel or any component of the product (4.2)

WARNINGS AND PRECAUTIONS

- Reduced effectiveness in impaired CYP2C19 function: Avoid concomitant use with drugs that inhibit CYP2C19 (e.g., omeprazole). (5.1)
- Bleeding: Plavix increases risk of bleeding. Discontinue 5 days prior to elective surgery. (5.2)
- Discontinuation of Plavix: Premature discontinuation increases risk of cardiovascular events. (5.3)
- Recent transient ischemic attack or stroke: Combination use of Plavix and aspirin in these patients was not shown to be more effective than Plavix alone, but was shown to increase major bleeding. (5.4)
- Thrombotic thrombocytopenic purpura (TTP): TTP has been reported with Plavix, including fatal cases. (5.5)

ADVERSE REACTIONS

Bleeding, including life-threatening and fatal bleeding, is the most commonly reported adverse reaction. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Bristol-Myers Squibb/Sanofi Pharmaceuticals Partnership at 1-800-633-1610 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

DRUG INTERACTIONS

- CYP2C19 inhibitors (e.g., omeprazole): Avoid concomitant use. (7.1)
- Nonsteroidal anti-inflammatory drugs (NSAIDs): Combination use increases risk of gastrointestinal bleeding. (7.2)
- Warfarin: Combination use increases risk of bleeding. (7.3)

USE IN SPECIFIC POPULATIONS

Nursing mothers: Discontinue drug or nursing, taking into consideration importance of drug to mother. (8.3)

See 17 for PATIENT COUNSELING INFORMATION.

Revised: March 2010

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FULL PRESCRIBING INFORMATION

WARNING: DIMINISHED EFFECTIVENESS IN POOR METABOLIZERS

The effectiveness of Plavix is dependent on its activation to an active metabolite by the cytochrome P450 (CYP) system, principally CYP2C19 [see *Warnings and Precautions (5.1)*]. Plavix at recommended doses forms less of that metabolite and has a smaller effect on platelet function in patients who are CYP2C19 poor metabolizers. Poor metabolizers with acute coronary syndrome or undergoing percutaneous coronary intervention treated with Plavix at recommended doses exhibit higher cardiovascular event rates than do patients with normal CYP2C19 function. Tests are available to identify a patient's CYP2C19 genotype; these tests can be used as an aid in determining therapeutic strategy [see *Clinical Pharmacology (12.5)*]. Consider alternative treatment or treatment strategies in patients identified as CYP2C19 poor metabolizers [see *Dosage and Administration (2.3)*].

1 INDICATIONS AND USAGE

1.1 Acute Coronary Syndrome (ACS)

- For patients with non-ST-segment elevation ACS [unstable angina (UA)/non-ST-elevation myocardial infarction (NSTEMI)], including patients who are to be managed medically and those who are to be managed with coronary revascularization, Plavix has been shown to decrease the rate of a combined endpoint of cardiovascular death, myocardial infarction (MI), or stroke as well as the rate of a combined endpoint of cardiovascular death, MI, stroke, or refractory ischemia.
- For patients with ST-elevation myocardial infarction (STEMI), Plavix has been shown to reduce the rate of death from any cause and the rate of a combined endpoint of death, re-infarction, or stroke. The benefit for patients who undergo primary percutaneous coronary intervention is unknown.

The optimal duration of Plavix therapy in ACS is unknown.

1.2 Recent MI, Recent Stroke, or Established Peripheral Arterial Disease

For patients with a history of recent myocardial infarction (MI), recent stroke, or established peripheral arterial disease, Plavix has been shown to reduce the rate of a combined endpoint of new ischemic stroke (fatal or not), new MI (fatal or not), and other vascular death.

2 DOSAGE AND ADMINISTRATION

2.1 Acute Coronary Syndrome

Plavix can be administered with or without food [see *Clinical Pharmacology (12.3)*]

- For patients with non-ST-elevation ACS (UA/NSTEMI), initiate Plavix with a single 300 mg oral loading dose and then continue at 75 mg once daily. Initiate aspirin (75-325 mg once daily) and continue in combination with Plavix [see *Clinical Studies (14.1)*].

- For patients with STEMI, the recommended dose of Plavix is 75 mg once daily orally, administered in combination with aspirin (75-325 mg once daily), with or without thrombolytics. Plavix may be initiated with or without a loading dose [*see Clinical Studies (14.1)*].

2.2 Recent MI, Recent Stroke, or Established Peripheral Arterial Disease

The recommended daily dose of Plavix is 75 mg once daily orally, with or without food [*see Clinical Pharmacology (12.3)*].

2.3 CYP2C19 Poor Metabolizers

CYP2C19 poor metabolizer status is associated with diminished antiplatelet response to clopidogrel. Although a higher dose regimen (600 mg loading dose followed by 150 mg once daily) in poor metabolizers increases antiplatelet response [*see Clinical Pharmacology (12.5)*], an appropriate dose regimen for this patient population has not been established in clinical outcome trials.

3 DOSAGE FORMS AND STRENGTHS

- 75 mg tablets: Pink, round, biconvex, film-coated tablets debossed with “75” on one side and “1171” on the other
- 300 mg tablets: Pink, oblong, film-coated tablets debossed with “300” on one side and “1332” on the other

4 CONTRAINDICATIONS

4.1 Active Bleeding

Plavix is contraindicated in patients with active pathological bleeding such as peptic ulcer or intracranial hemorrhage.

4.2 Hypersensitivity

Plavix is contraindicated in patients with hypersensitivity (e.g., anaphylaxis) to clopidogrel or any component of the product [*see Adverse Reactions (6.2)*].

5 WARNINGS AND PRECAUTIONS

5.1 Diminished Antiplatelet Activity Due to Impaired CYP2C19 Function

Clopidogrel is a prodrug. Inhibition of platelet aggregation by clopidogrel is entirely due to 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. Avoid concomitant use of Plavix and drugs that inhibit CYP2C19 activity. 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 [*see Drug Interactions (7.1)*].

5.2 General Risk of Bleeding

Thienopyridines, including Plavix, increase the risk of bleeding. If a patient is to undergo surgery and an antiplatelet effect is not desired, discontinue Plavix 5 days prior to surgery. In patients who stopped therapy more than five days prior to CABG the rates of major bleeding were similar (event rate 4.4% Plavix + aspirin; 5.3% placebo + aspirin). In patients who remained on therapy within five days of CABG, the major bleeding rate was 9.6% for Plavix + aspirin, and 6.3% for placebo + aspirin.

Thienopyridines inhibit platelet aggregation for the lifetime of the platelet (7-10 days), so withholding a dose will not be useful in managing a bleeding event or the risk of bleeding associated with an invasive procedure. Because the half-life of clopidogrel's active metabolite is short, it may be possible to restore hemostasis by administering exogenous platelets; however, platelet transfusions within 4 hours of the loading dose or 2 hours of the maintenance dose may be less effective.

5.3 Discontinuation of Plavix

Avoid lapses in therapy, and if Plavix must be temporarily discontinued, restart as soon as possible. Premature discontinuation of Plavix may increase the risk of cardiovascular events.

5.4 Patients with Recent Transient Ischemic Attack (TIA) or Stroke

In patients with recent TIA or stroke who are at high risk for recurrent ischemic events, the combination of aspirin and Plavix has not been shown to be more effective than Plavix alone, but the combination has been shown to increase major bleeding.

5.5 Thrombotic Thrombocytopenic Purpura (TTP)

TTP, sometimes fatal, has been reported following use of Plavix, sometimes after a short exposure (<2 weeks). TTP is a serious condition that requires urgent treatment including plasmapheresis (plasma exchange). It is characterized by thrombocytopenia, microangiopathic hemolytic anemia (schistocytes [fragmented RBCs] seen on peripheral smear), neurological findings, renal dysfunction, and fever [*see Adverse Reactions (6.2)*].

6 ADVERSE REACTIONS

The following serious adverse reactions are discussed below and elsewhere in the labeling:

- Bleeding [*see Warnings and Precautions (5.2)*]
- Thrombotic thrombocytopenic purpura [*see Warnings and Precautions (5.5)*]

6.1 Clinical Studies Experience

Because clinical trials are conducted under widely varying conditions and durations of follow up, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

Plavix has been evaluated for safety in more than 54,000 patients, including over 21,000 patients treated for 1 year or more. The clinically important adverse reactions observed in trials comparing Plavix plus aspirin to placebo plus aspirin and trials comparing Plavix alone to aspirin alone are discussed below.

Bleeding

CURE

In CURE, Plavix use with aspirin was associated with an increase in major bleeding (primarily gastrointestinal and at puncture sites) compared to placebo with aspirin (see Table 1). The incidence of intracranial hemorrhage (0.1%) and fatal bleeding (0.2%) were the same in both groups. Other bleeding events that were reported more frequently in the clopidogrel group were epistaxis, hematuria, and bruise.

The overall incidence of bleeding is described in Table 1.

Table 1: CURE Incidence of Bleeding Complications (% patients)

Event	Plavix (+ aspirin)* (n=6259)	Placebo (+ aspirin)* (n=6303)	p-value
Major bleeding †	3.7 ‡	2.7 §	0.001
Life-threatening bleeding	2.2	1.8	0.13
Fatal	0.2	0.2	
5 g/dL hemoglobin drop	0.9	0.9	
Requiring surgical intervention	0.7	0.7	
Hemorrhagic strokes	0.1	0.1	
Requiring inotropes	0.5	0.5	
Requiring transfusion (≥4 units)	1.2	1.0	
Other major bleeding	1.6	1.0	0.005
Significantly disabling	0.4	0.3	
Intraocular bleeding with significant loss of vision	0.05	0.03	
Requiring 2-3 units of blood	1.3	0.9	
Minor bleeding ¶	5.1	2.4	< 0.001

* Other standard therapies were used as appropriate.

† Life-threatening and other major bleeding.

‡ Major bleeding event rate for Plavix + aspirin was dose-dependent on aspirin: <100 mg = 2.6%; 100-200 mg = 3.5%; >200 mg = 4.9%
Major bleeding event rates for Plavix + aspirin by age were: <65 years = 2.5%, ≥65 to <75 years = 4.1%, ≥75 years = 5.9%

§ Major bleeding event rate for placebo + aspirin was dose-dependent on aspirin: <100 mg = 2.0%; 100-200 mg = 2.3%; >200 mg = 4.0%
Major bleeding event rates for placebo + aspirin by age were: <65 years = 2.1%, ≥65 to <75 years = 3.1%, ≥75 years = 3.6%

¶ Led to interruption of study medication.

Ninety-two percent (92%) of the patients in the CURE study received heparin or low molecular weight heparin (LMWH), and the rate of bleeding in these patients was similar to the overall results.

COMMIT

In COMMIT, similar rates of major bleeding were observed in the Plavix and placebo groups, both of which also received aspirin (see Table 2).

Table 2: Incidence of Bleeding Events in COMMIT (% patients)

Type of bleeding	Plavix (+ aspirin) (n=22961)	Placebo (+ aspirin) (n=22891)	p-value
Major* noncerebral or cerebral bleeding**	0.6	0.5	0.59
Major noncerebral	0.4	0.3	0.48
Fatal	0.2	0.2	0.90
Hemorrhagic stroke	0.2	0.2	0.91
Fatal	0.2	0.2	0.81
Other noncerebral bleeding (non-major)	3.6	3.1	0.005
Any noncerebral bleeding	3.9	3.4	0.004

* Major bleeds were cerebral bleeds or non-cerebral bleeds thought to have caused death or that required transfusion.

** The relative rate of major noncerebral or cerebral bleeding was independent of age. Event rates for Plavix + aspirin by age were: <60 years = 0.3%, ≥60 to <70 years = 0.7%, ≥70 years = 0.8%. Event rates for placebo + aspirin by age were: <60 years = 0.4%, ≥60 to <70 years = 0.6%, ≥70 years = 0.7%.

CAPRIE (Plavix vs. Aspirin)

In CAPRIE, gastrointestinal hemorrhage occurred at a rate of 2.0% in those taking Plavix vs. 2.7% in those taking aspirin; bleeding requiring hospitalization occurred in 0.7% and 1.1%, respectively. The incidence of intracranial hemorrhage was 0.4% for Plavix compared to 0.5% for aspirin.

Other bleeding events that were reported more frequently in the Plavix group were epistaxis and hematoma.

Other Adverse Events

In CURE and CHARISMA, which compared Plavix plus aspirin to aspirin alone, there was no difference in the rate of adverse events (other than bleeding) between Plavix and placebo.

In CAPRIE, which compared Plavix to aspirin, pruritus was more frequently reported in those taking Plavix. No other difference in the rate of adverse events (other than bleeding) was reported.

6.2 Postmarketing Experience

The following adverse reactions have been identified during post-approval use of Plavix. Because these reactions are reported voluntarily from a population of an unknown size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

- *Blood and lymphatic system disorders:* Agranulocytosis, aplastic anemia/pancytopenia, thrombotic thrombocytopenic purpura (TTP)
- *Gastrointestinal disorders:* Gastrointestinal and retroperitoneal hemorrhage with fatal outcome, colitis (including ulcerative or lymphocytic colitis), pancreatitis, stomatitis
- *General disorders and administration site condition:* Fever, hemorrhage of operative wound
- *Hepato-biliary disorders:* Acute liver failure, hepatitis (non-infectious), abnormal liver function test
- *Immune system disorders:* Hypersensitivity reactions, anaphylactoid reactions, serum sickness
- *Musculoskeletal, connective tissue and bone disorders:* Musculoskeletal bleeding, myalgia, arthralgia, arthritis
- *Nervous system disorders:* Taste disorders, fatal intracranial bleeding
- *Eye disorders:* Eye (conjunctival, ocular, retinal) bleeding
- *Psychiatric disorders:* Confusion, hallucinations
- *Respiratory, thoracic and mediastinal disorders:* Bronchospasm, interstitial pneumonitis, respiratory tract bleeding
- *Renal and urinary disorders:* Glomerulopathy, increased creatinine levels
- *Skin and subcutaneous tissue disorders:* Maculopapular or erythematous rash, urticaria, bullous dermatitis, eczema, toxic epidermal necrolysis, Stevens-Johnson syndrome, angioedema, erythema multiforme, skin bleeding, lichen planus
- *Vascular disorders:* Vasculitis, hypotension

7 DRUG INTERACTIONS

7.1 CYP2C19 Inhibitors

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, e.g., omeprazole [*see Warnings and Precautions (5.1) and Clinical Pharmacology (12.5)*].

Omeprazole

In a crossover clinical study, 72 healthy subjects were administered Plavix (300 mg loading dose followed by 75 mg per 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 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 and Precautions (5.1)*].

7.2 Nonsteroidal Anti-Inflammatory Drugs (NSAIDs)

Coadministration of Plavix and NSAIDs increases the risk of gastrointestinal bleeding.

7.3 Warfarin (CYP2C9 Substrates)

Although the administration of clopidogrel 75 mg per day did not modify the pharmacokinetics of S-warfarin (a CYP2C9 substrate) or INR in patients receiving long-term warfarin therapy, coadministration of Plavix with warfarin increases the risk of bleeding because of independent effects on hemostasis.

However, at high concentrations *in vitro*, clopidogrel inhibits CYP2C9.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category B

Reproduction studies performed in rats and rabbits at doses up to 500 and 300 mg/kg/day, respectively (65 and 78 times the recommended daily human dose, respectively, on a mg/m² basis), revealed no evidence of impaired fertility or fetotoxicity due to clopidogrel. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of a human response, Plavix should be used during pregnancy only if clearly needed.

8.3 Nursing Mothers

Studies in rats have shown that clopidogrel and/or its metabolites are excreted in the milk. It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from clopidogrel, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

8.4 Pediatric Use

Safety and effectiveness in the pediatric population have not been established.

8.5 Geriatric Use

Of the total number of subjects in the CAPRIE and CURE controlled clinical studies, approximately 50% of patients treated with Plavix were 65 years of age and older, and 15% were 75 years and older. In COMMIT, approximately 58% of the patients treated with Plavix were 60 years and older, 26% of whom were 70 years and older.

The observed risk of thrombotic events with clopidogrel plus aspirin versus placebo plus aspirin by age category is provided in Figures 2 and 5 for the CURE and COMMIT trials, respectively [see *Clinical Studies (14.1)*]. The observed risk of bleeding events with clopidogrel plus aspirin versus placebo plus aspirin by age category is provided in Tables 1 and 2 for the CURE and COMMIT trials, respectively [see *Adverse Reactions (6.1)*]. No dosage adjustment is necessary in elderly patients.

8.6 Renal Impairment

Experience is limited in patients with severe and moderate renal impairment [see *Clinical Pharmacology* (12.2)].

8.7 Hepatic Impairment

No dosage adjustment is necessary in patients with hepatic impairment [see *Clinical Pharmacology* (12.2)].

10 OVERDOSAGE

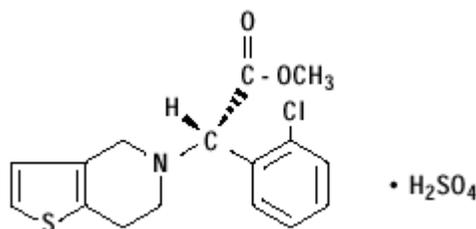
Platelet inhibition by Plavix is irreversible and will last for the life of the platelet. Overdose following clopidogrel administration may result in bleeding complications. A single oral dose of clopidogrel at 1500 or 2000 mg/kg was lethal to mice and to rats and at 3000 mg/kg to baboons. Symptoms of acute toxicity were vomiting, prostration, difficult breathing, and gastrointestinal hemorrhage in animals.

Based on biological plausibility, platelet transfusion may restore clotting ability.

11 DESCRIPTION

Plavix (clopidogrel bisulfate) is a thienopyridine class inhibitor of P2Y₁₂ ADP platelet receptors. Chemically it is methyl (+)-(S)- α -(2-chlorophenyl)-6,7-dihydrothieno[3,2-c]pyridine-5(4H)-acetate sulfate (1:1). The empirical formula of clopidogrel bisulfate is C₁₆H₁₆ClNO₂S•H₂SO₄ and its molecular weight is 419.9.

The structural formula is as follows:



Clopidogrel bisulfate is a white to off-white powder. It is practically insoluble in water at neutral pH but freely soluble at pH 1. It also dissolves freely in methanol, dissolves sparingly in methylene chloride, and is practically insoluble in ethyl ether. It has a specific optical rotation of about +56°.

Plavix for oral administration is provided as either pink, round, biconvex, debossed, film-coated tablets containing 97.875 mg of clopidogrel bisulfate which is the molar equivalent of 75 mg of clopidogrel base or pink, oblong, debossed film-coated tablets containing 391.5 mg of clopidogrel bisulfate which is the molar equivalent of 300 mg of clopidogrel base.

Each tablet contains hydrogenated castor oil, hydroxypropylcellulose, mannitol, microcrystalline cellulose and polyethylene glycol 6000 as inactive ingredients. The pink film coating contains ferric oxide, hypromellose 2910, lactose monohydrate, titanium dioxide and triacetin. The tablets are polished with Carnauba wax.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Clopidogrel is an inhibitor of platelet activation and aggregation through the irreversible binding of its active metabolite to the P2Y₁₂ class of ADP receptors on platelets.

12.2 Pharmacodynamics

Clopidogrel must be metabolized by CYP450 enzymes to produce the active metabolite that inhibits platelet aggregation. The active metabolite of clopidogrel selectively inhibits the binding of adenosine diphosphate (ADP) to its platelet P2Y₁₂ receptor and the subsequent ADP-mediated activation of the glycoprotein GPIIb/IIIa complex, thereby inhibiting platelet aggregation. This action is irreversible. Consequently, platelets exposed to clopidogrel's active metabolite are affected for the remainder of their lifespan (about 7 to 10 days). Platelet aggregation induced by agonists other than ADP is also inhibited by blocking the amplification of platelet activation by released ADP.

Dose-dependent inhibition of platelet aggregation can be seen 2 hours after single oral doses of Plavix. Repeated doses of 75 mg Plavix per day inhibit ADP-induced platelet aggregation on the first day, and inhibition reaches steady state between Day 3 and Day 7. At steady state, the average inhibition level observed with a dose of 75 mg Plavix per day was between 40% and 60%. Platelet aggregation and bleeding time gradually return to baseline values after treatment is discontinued, generally in about 5 days.

Geriatric Patients

Elderly (≥ 75 years) and young healthy subjects had similar effects on platelet aggregation.

Renally-Impaired Patients

After repeated doses of 75 mg Plavix per day, patients with severe renal impairment (creatinine clearance from 5 to 15 mL/min) and moderate renal impairment (creatinine clearance from 30 to 60 mL/min) showed low (25%) inhibition of ADP-induced platelet aggregation.

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.

Gender

In a small study comparing men and women, less inhibition of ADP-induced platelet aggregation was observed in women.

12.3 Pharmacokinetics

Clopidogrel is a prodrug and is metabolized to a pharmacologically active metabolite and inactive metabolites.

Absorption

After single and repeated oral doses of 75 mg per day, clopidogrel is rapidly absorbed. Absorption is at least 50%, based on urinary excretion of clopidogrel metabolites.

Effect of Food

Plavix can be administered with or without food. In a study in healthy male subjects when Plavix 75 mg per day was given with a standard breakfast, mean inhibition of ADP-induced platelet aggregation was reduced by less than 9%. The active metabolite AUC₀₋₂₄ was unchanged in the presence of food, while there was a 57% decrease in active metabolite C_{max}. Similar results were observed when a Plavix 300 mg loading dose was administered with a high-fat breakfast.

Metabolism

Clopidogrel is extensively metabolized by two main metabolic pathways: one mediated by esterases and leading to hydrolysis into an inactive carboxylic acid derivative (85% of circulating metabolites) and one mediated by multiple cytochrome P450 enzymes. 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. This metabolic pathway is mediated by CYP2C19, CYP3A, CYP2B6 and CYP1A2. The active thiol metabolite binds rapidly and irreversibly to platelet receptors, thus inhibiting platelet aggregation for the lifespan of the platelet.

The C_{max} of the active metabolite is twice as high following a single 300 mg clopidogrel loading dose as it is after four days of 75 mg maintenance dose. C_{max} occurs approximately 30 to 60 minutes after dosing. In the 75 to 300 mg dose range, the pharmacokinetics of the active metabolite deviates from dose proportionality: increasing the dose by a factor of four results in 2.0- and 2.7-fold increases in C_{max} and AUC, respectively.

Elimination

Following an oral dose of ¹⁴C-labeled clopidogrel in humans, approximately 50% of total radioactivity was excreted in urine and approximately 46% in feces over the 5 days post-dosing. After a single, oral dose of 75 mg, clopidogrel has a half-life of approximately 6 hours. The half-life of the active metabolite is about 30 minutes.

12.5 Pharmacogenomics

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. Genetic variants of other CYP450 enzymes may also affect the formation of clopidogrel's active metabolite.

The CYP2C19*1 allele corresponds to fully functional metabolism while the CYP2C19*2 and *3 alleles are nonfunctional. CYP2C19*2 and *3 account for the majority of reduced function alleles in white (85%) and Asian (99%) poor metabolizers. Other alleles associated with absent

or reduced metabolism are less frequent, and include, but are not limited to, CYP2C19*4, *5, *6, *7, and *8. A patient with poor metabolizer status will possess two loss-of-function alleles as defined above. Published frequencies for poor CYP2C19 metabolizer genotypes are approximately 2% for whites, 4% for blacks and 14% for Chinese. Tests are available to determine a patient's CYP2C19 genotype.

A crossover study in 40 healthy subjects, 10 each in the four CYP2C19 metabolizer groups, evaluated pharmacokinetic and antiplatelet responses using 300 mg followed by 75 mg per day and 600 mg followed by 150 mg per day, each for a total of 5 days. Decreased active metabolite exposure and diminished inhibition of platelet aggregation were observed in the poor metabolizers as compared to the other groups. When poor metabolizers received the 600 mg/150 mg regimen, active metabolite exposure and antiplatelet response were greater than with the 300 mg/75 mg regimen (see Table 3). An appropriate dose regimen for this patient population has not been established in clinical outcome trials.

Table 3: Active Metabolite Pharmacokinetics and Antiplatelet Responses by CYP2C19 Metabolizer Status

	Dose	Ultrarapid (n=10)	Extensive (n=10)	Intermediate (n=10)	Poor (n=10)
C _{max} (ng/mL)	300 mg (24 h)	24 (10)	32 (21)	23 (11)	11 (4)
	600 mg (24 h)	36 (13)	44 (27)	39 (23)	17 (6)
	75 mg (Day 5)	12 (6)	13 (7)	12 (5)	4 (1)
	150 mg (Day 5)	16 (9)	19 (5)	18 (7)	7 (2)
IPA (%)*	300 mg (24 h)	40 (21)	39 (28)	37 (21)	24 (26)
	600 mg (24 h)	51 (28)	49 (23)	56 (22)	32 (25)
	75 mg (Day 5)	56 (13)	58 (19)	60 (18)	37 (23)
	150 mg (Day 5)	68 (18)	73 (9)	74 (14)	61 (14)
VASP-PRI (%) †	300 mg (24 h)	73 (12)	68 (16)	77 (12)	91 (12)
	600 mg (24 h)	51 (20)	48 (20)	56 (26)	85 (14)
	75 mg (Day 5)	40 (9)	39 (14)	50 (16)	83 (13)
	150 mg (Day 5)	20 (10)	24 (10)	29 (11)	61 (18)
Values are mean (SD)					
* Inhibition of platelet aggregation with 5µM ADP; larger value indicates greater platelet inhibition					
† Vasodilator-stimulated phosphoprotein – platelet reactivity index; smaller value indicates greater platelet inhibition					

Some published studies suggest that intermediate metabolizers have decreased active metabolite exposure and diminished antiplatelet effects.

The relationship between CYP2C19 genotype and Plavix treatment outcome was evaluated in retrospective analyses of Plavix-treated subjects in CHARISMA (n=4862) and TRITON-TIMI 38 (n=1477), and in several published cohort studies. In TRITON-TIMI 38 and the majority of the cohort studies, the combined group of patients with either intermediate or poor metabolizer status had a higher rate of cardiovascular events (death, myocardial infarction,

and stroke) or stent thrombosis compared to extensive metabolizers. In CHARISMA and one cohort study, the increased event rate was observed only in poor metabolizers.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

There was no evidence of tumorigenicity when clopidogrel was administered for 78 weeks to mice and 104 weeks to rats at dosages up to 77 mg/kg per day, which afforded plasma exposures >25 times that in humans at the recommended daily dose of 75 mg.

Clopidogrel was not genotoxic in four *in vitro* tests (Ames test, DNA-repair test in rat hepatocytes, gene mutation assay in Chinese hamster fibroblasts, and metaphase chromosome analysis of human lymphocytes) and in one *in vivo* test (micronucleus test by oral route in mice).

Clopidogrel was found to have no effect on fertility of male and female rats at oral doses up to 400 mg/kg per day (52 times the recommended human dose on a mg/m² basis).

14 CLINICAL STUDIES

The clinical evidence of the efficacy of Plavix is derived from three double-blind trials involving 77,599 patients. The CAPRIE study (Clopidogrel vs. Aspirin in Patients at Risk of Ischemic Events) was a comparison of Plavix to aspirin. The CURE (Clopidogrel in Unstable Angina to Prevent Recurrent Ischemic Events) and the COMMIT/CCS-2 (Clopidogrel and Metoprolol in Myocardial Infarction Trial / Second Chinese Cardiac Study) studies were comparisons of Plavix to placebo, given in combination with aspirin and other standard therapy. The CHARISMA (Clopidogrel for High Atherothrombotic Risk Ischemic Stabilization, Management, and Avoidance) study (n=15,603) also compared Plavix to placebo, given in combination with aspirin and other standard therapy.

14.1 Acute Coronary Syndrome

CURE

The CURE study included 12,562 patients with ACS without ST-elevation (UA or NSTEMI) and presenting within 24 hours of onset of the most recent episode of chest pain or symptoms consistent with ischemia. Patients were required to have either ECG changes compatible with new ischemia (without ST-elevation) or elevated cardiac enzymes or troponin I or T to at least twice the upper limit of normal. The patient population was largely Caucasian (82%) and included 38% women, and 52% patients ≥65 years of age.

Patients were randomized to receive Plavix (300-mg loading dose followed by 75 mg once daily) or placebo, and were treated for up to one year. Patients also received aspirin (75-325 mg once daily) and other standard therapies such as heparin. The use of GPIIb/IIIa inhibitors was not permitted for three days prior to randomization.

The number of patients experiencing the primary outcome (CV death, MI, or stroke) was 582 (9.3%) in the Plavix-treated group and 719 (11.4%) in the placebo-treated group, a 20% relative risk reduction (95% CI of 10%-28%; p < 0.001) for the Plavix-treated group (see Table 4).

Table 4: Outcome Events in the CURE Primary Analysis

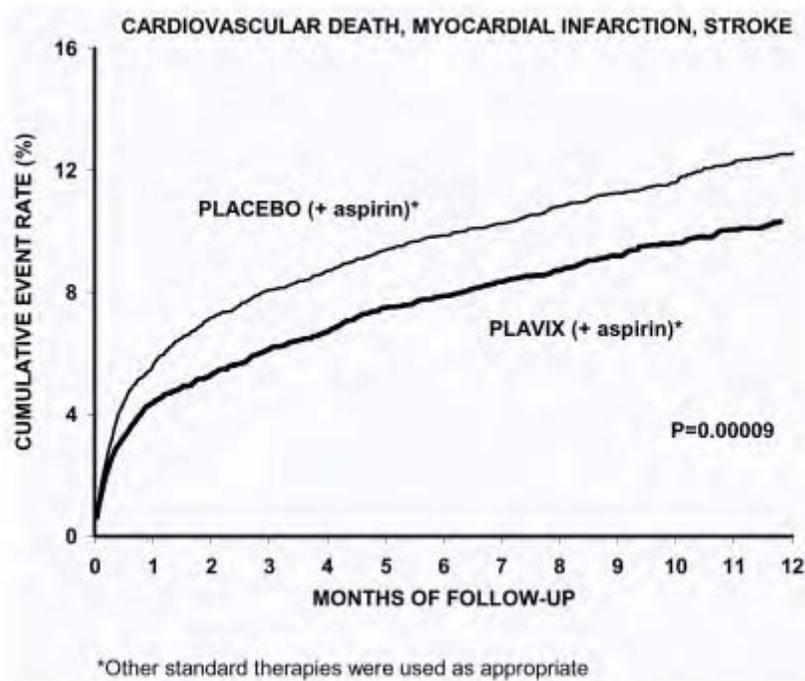
Outcome	Plavix (+ aspirin)* (n=6259)		Placebo (+ aspirin)* (n=6303)		Relative Risk Reduction (%) (95% CI)
Primary outcome (Cardiovascular death, MI, stroke)	582	(9.3%)	719	(11.4%)	20% (10.3, 27.9) p < 0.001
All Individual Outcome Events:†					
CV death	318	(5.1%)	345	(5.5%)	7% (-7.7, 20.6)
MI	324	(5.2%)	419	(6.6%)	23% (11.0, 33.4)
Stroke	75	(1.2%)	87	(1.4%)	14% (-17.7, 36.6)

* Other standard therapies were used as appropriate.

† The individual components do not represent a breakdown of the primary and co-primary outcomes, but rather the total number of subjects experiencing an event during the course of the study.

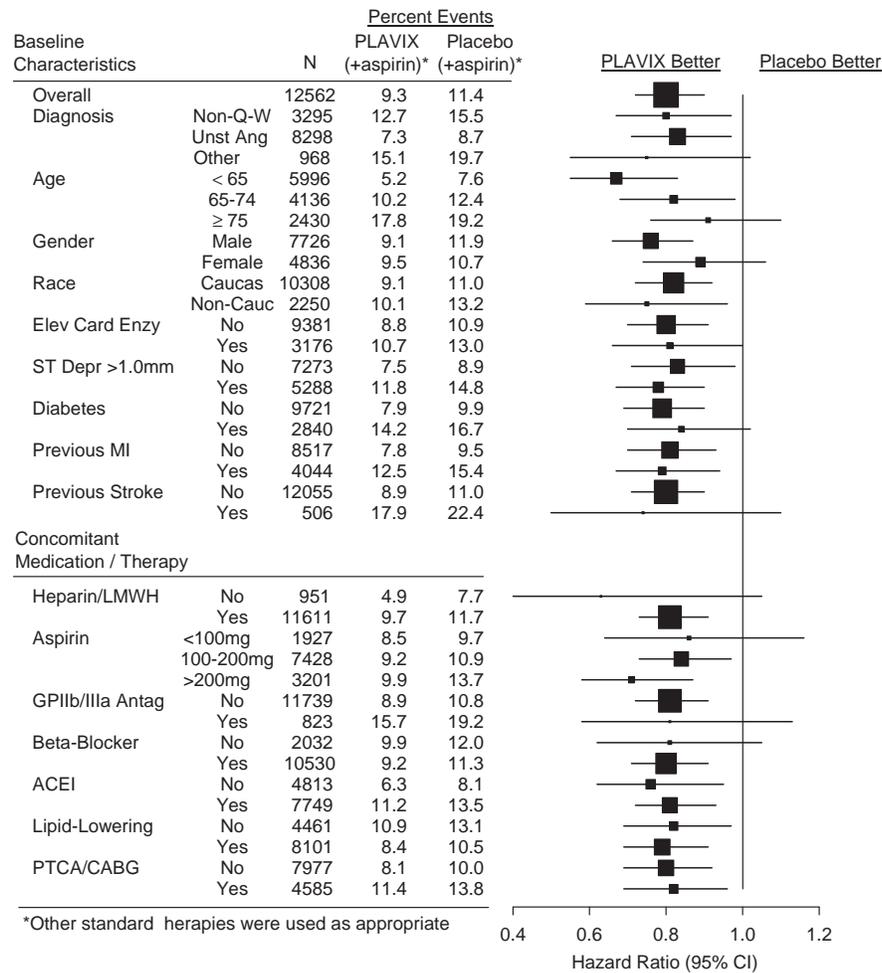
Most of the benefit of Plavix occurred in the first two months, but the difference from placebo was maintained throughout the course of the trial (up to 12 months) (see Figure 1).

Figure 1: Cardiovascular Death, Myocardial Infarction, and Stroke in the CURE Study



In CURE, the use of Plavix was associated with a lower incidence of CV death, MI or stroke in patient populations with different characteristics, as shown in Figure 2. The benefits associated with Plavix were independent of the use of other acute and long-term cardiovascular therapies, including heparin/LMWH, intravenous glycoprotein IIb/IIIa (GPIIb/IIIa) inhibitors, lipid-lowering drugs, beta-blockers, and ACE-inhibitors. The efficacy of Plavix was observed independently of the dose of aspirin (75-325 mg once daily). The use of oral anticoagulants, non-study anti-platelet drugs, and chronic NSAIDs was not allowed in CURE.

Figure 2: Hazard Ratio for Patient Baseline Characteristics and On-Study Concomitant Medications/Interventions for the CURE Study



The use of Plavix in CURE was associated with a decrease in the use of thrombolytic therapy (71 patients [1.1%] in the Plavix group, 126 patients [2.0%] in the placebo group; relative risk reduction of 43%), and GPIIb/IIIa inhibitors (369 patients [5.9%] in the Plavix group, 454 patients [7.2%] in the placebo group, relative risk reduction of 18%). The use of Plavix in CURE did not affect the number of patients treated with CABG or PCI (with or without stenting), (2253 patients [36.0%] in the Plavix group, 2324 patients [36.9%] in the placebo group; relative risk reduction of 4.0%).

COMMIT

In patients with STEMI, the safety and efficacy of Plavix were evaluated in the randomized, placebo-controlled, double-blind study, COMMIT. COMMIT included 45,852 patients presenting within 24 hours of the onset of the symptoms of myocardial infarction with supporting ECG abnormalities (*i.e.*, ST-elevation, ST-depression or left bundle-branch block). Patients were randomized to receive Plavix (75 mg once daily) or placebo, in combination with aspirin (162 mg per day), for 28 days or until hospital discharge, whichever came first.

The primary endpoints were death from any cause and the first occurrence of re-infarction, stroke or death.

The patient population included 28% women, 58% age ≥ 60 years (26% age ≥ 70 years), 55% patients who received thrombolytics, 68% who received ACE-inhibitors, and only 3% who underwent PCI.

As shown in Table 5 and Figures 3 and 4 below, Plavix significantly reduced the relative risk of death from any cause by 7% ($p=0.029$), and the relative risk of the combination of re-infarction, stroke or death by 9% ($p=0.002$).

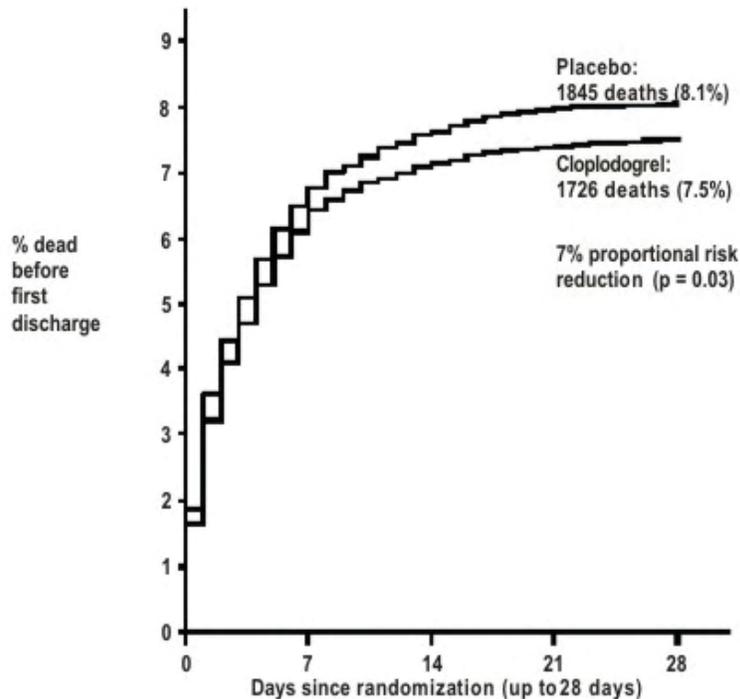
Table 5: Outcome Events in the COMMIT Analysis

Event	Plavix (+ aspirin) (N=22961)	Placebo (+ aspirin) (N=22891)	Odds ratio (95% CI)	p-value
Composite endpoint: Death, MI, or Stroke*	2121 (9.2%)	2310 (10.1%)	0.91 (0.86, 0.97)	0.002
Death	1726 (7.5%)	1845 (8.1%)	0.93 (0.87, 0.99)	0.029
Non-fatal MI**	270 (1.2%)	330 (1.4%)	0.81 (0.69, 0.95)	0.011
Non-fatal Stroke**	127 (0.6%)	142 (0.6%)	0.89 (0.70, 1.13)	0.33

* The difference between the composite endpoint and the sum of death+non-fatal MI+non-fatal stroke indicates that 9 patients (2 clopidogrel and 7 placebo) suffered both a non-fatal stroke and a non-fatal MI.

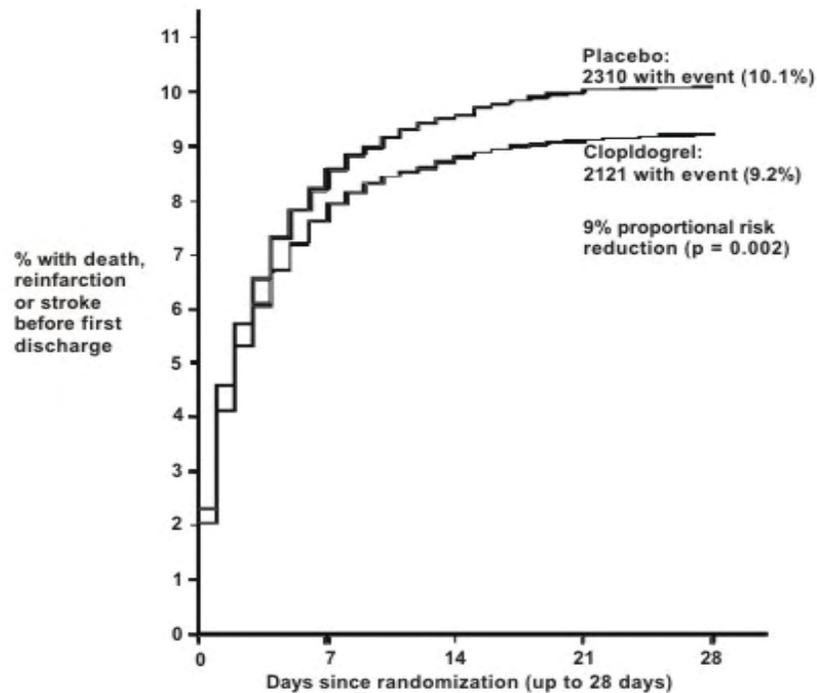
** Non-fatal MI and non-fatal stroke exclude patients who died (of any cause).

Figure 3: Cumulative Event Rates for Death in the COMMIT Study*



* All treated patients received aspirin.

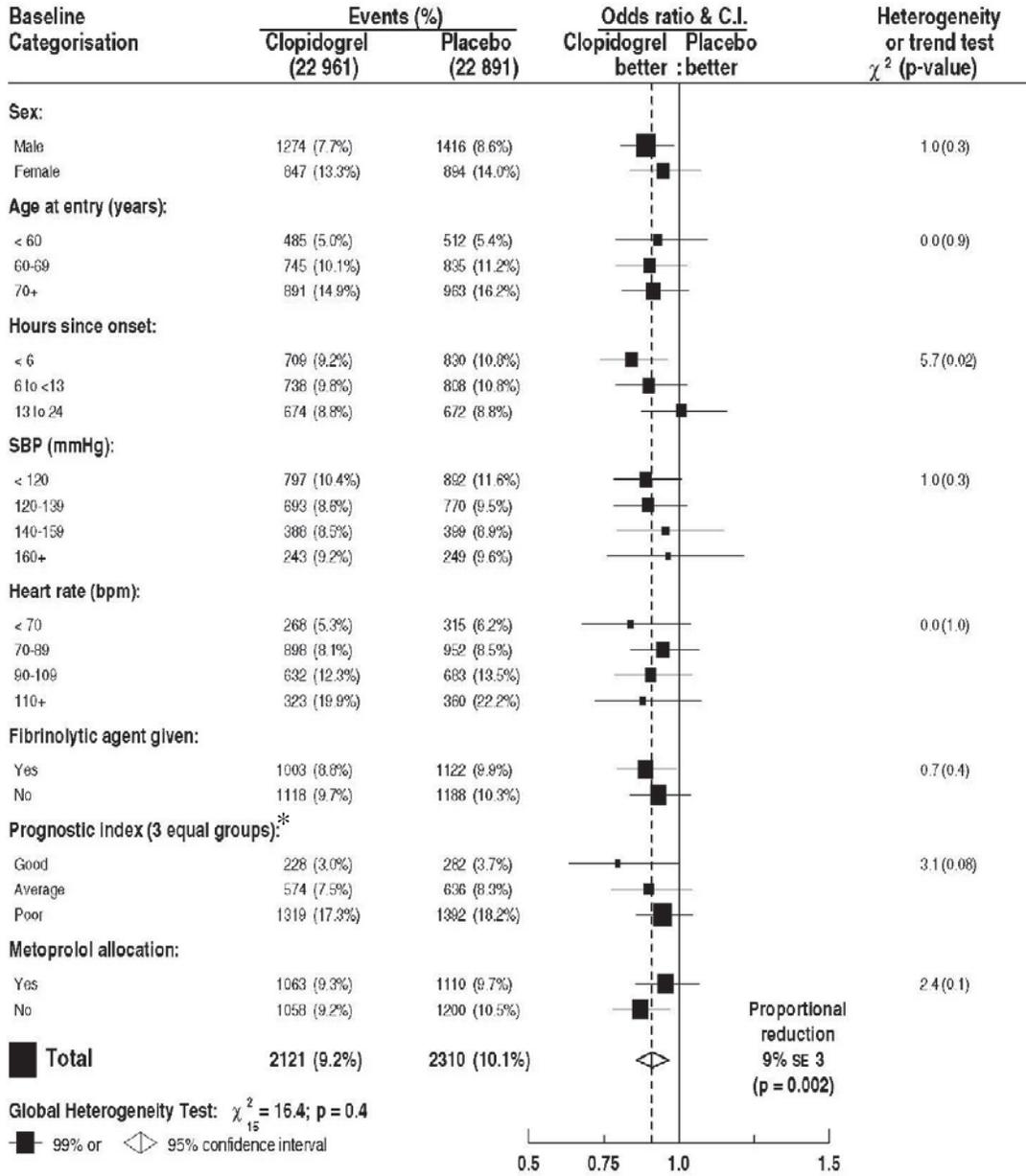
Figure 4: Cumulative Event Rates for the Combined Endpoint Re-Infarction, Stroke or Death in the COMMIT Study*



* All treated patients received aspirin.

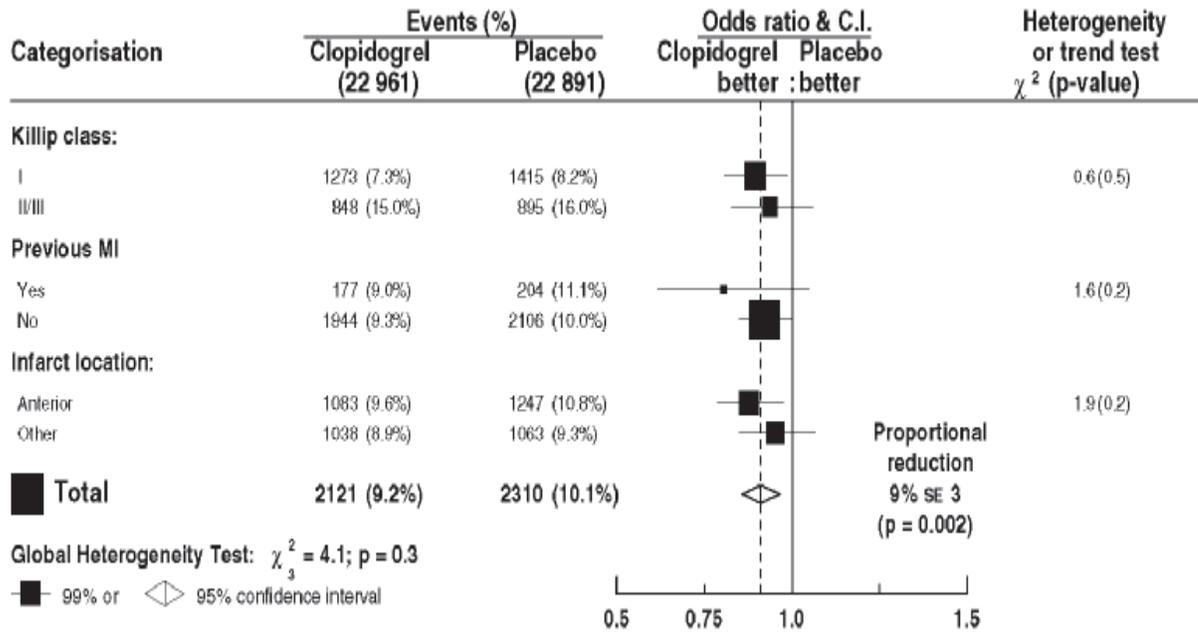
The effect of Plavix did not differ significantly in various pre-specified subgroups as shown in Figure 5. The effect was also similar in non-prespecified subgroups including those based on infarct location, Killip class or prior MI history (see Figure 6). Such subgroup analyses should be interpreted cautiously.

Figure 5: Effects of Adding Plavix to Aspirin on the Combined Primary Endpoint across Baseline and Concomitant Medication Subgroups for the COMMIT Study



* Three similar-sized prognostic index groups were based on absolute risk of primary composite outcome for each patient calculated from baseline prognostic variables (excluding allocated treatments) with a Cox regression model.

Figure 6: Effects of Adding Plavix to Aspirin in the Non-Prespecified Subgroups in the COMMIT Study



14.2 Recent Myocardial Infarction, Recent Stroke, or Established Peripheral Arterial Disease

CAPRIE

The CAPRIE trial was a 19,185-patient, 304-center, international, randomized, double-blind, parallel-group study comparing Plavix (75 mg daily) to aspirin (325 mg daily). The patients randomized had: 1) recent histories of myocardial infarction (within 35 days); 2) recent histories of ischemic stroke (within 6 months) with at least a week of residual neurological signs; or 3) established peripheral arterial disease. Patients received randomized treatment for an average of 1.6 years (maximum of 3 years).

The trial's primary outcome was the time to first occurrence of new ischemic stroke (fatal or not), new myocardial infarction (fatal or not), or other vascular death. Deaths not easily attributable to nonvascular causes were all classified as vascular.

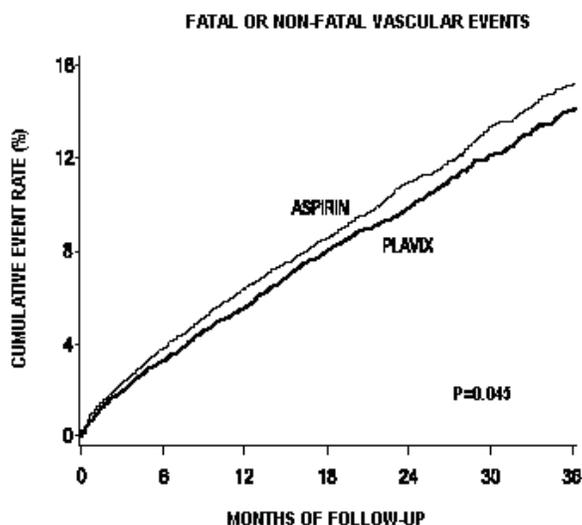
Table 6: Outcome Events in the CAPRIE Primary Analysis

	Plavix n=9599	aspirin n=9586
Patients		
Ischemic stroke (fatal or not)	438 (4.6%)	461 (4.8%)
MI (fatal or not)	275 (2.9%)	333 (3.5%)
Other vascular death	226 (2.4%)	226 (2.4%)
Total	939 (9.8%)	1020 (10.6%)

As shown in the table, Plavix was associated with a lower incidence of outcome events, primarily MI. The overall relative risk reduction (9.8% vs. 10.6%) was 8.7%, $p=0.045$. Similar results were obtained when all-cause mortality and all-cause strokes were counted instead of vascular mortality and ischemic strokes (risk reduction 6.9%). In patients who survived an on-study stroke or myocardial infarction, the incidence of subsequent events was lower in the Plavix group.

The curves showing the overall event rate are shown in Figure 7. The event curves separated early and continued to diverge over the 3-year follow-up period.

Figure 7: Fatal or Non-Fatal Vascular Events in the CAPRIE Study



The statistical significance favoring Plavix over aspirin was marginal ($p=0.045$). However, because aspirin is itself effective in reducing cardiovascular events in patients with recent myocardial infarction or stroke, the effect of Plavix is substantial.

The CAPRIE trial included a population that was randomized on the basis of 3 entry criteria. The efficacy of Plavix relative to aspirin was heterogeneous across these randomized subgroups ($p=0.043$). It is not clear whether this difference is real or a chance occurrence. Although the CAPRIE trial was not designed to evaluate the relative benefit of Plavix over aspirin in the individual patient subgroups, the benefit appeared to be strongest in patients who were enrolled because of peripheral vascular disease (especially those who also had a history of myocardial infarction) and weaker in stroke patients. In patients who were enrolled in the trial on the sole basis of a recent myocardial infarction, Plavix was not numerically superior to aspirin.

14.3 Lack of Established Benefit of Plavix plus Aspirin in Patients with Multiple Risk Factors or Established Vascular Disease

CHARISMA

The CHARISMA trial was a 15,603 subject, randomized, double-blind, parallel group study comparing Plavix (75 mg daily) to placebo for prevention of ischemic events in patients with

vascular disease or multiple risk factors for atherosclerosis. All subjects were treated with aspirin 75-162 mg daily. The mean duration of treatment was 23 months. The study failed to demonstrate a reduction in the occurrence of the primary endpoint, a composite of CV death, MI, or stroke. A total of 534 (6.9%) patients in the Plavix group versus 573 (7.4%) patients in the placebo group experienced a primary outcome event (p=0.22). Bleeding of all severities was more common in the subjects randomized to Plavix.

16 HOW SUPPLIED/STORAGE AND HANDLING

Plavix (clopidogrel bisulfate) 75 mg tablets are available as pink, round, biconvex, film-coated tablets debossed with “75” on one side and “1171” on the other. Tablets are provided as follows:

NDC 63653-1171-6	Bottles of 30
NDC 63653-1171-1	Bottles of 90
NDC 63653-1171-5	Bottles of 500
NDC 63653-1171-3	Blisters of 100

Plavix (clopidogrel bisulfate) 300 mg tablets are available as pink, oblong, film-coated tablets debossed with “300” on one side and “1332” on the other. Tablets are provided as follows:

NDC 63653-1332-2	Unit-dose packages of 30
NDC 63653-1332-3	Unit-dose packages of 100

Store at 25° C (77° F); excursions permitted to 15°–30° C (59°–86° F) [see USP Controlled Room Temperature].

17 PATIENT COUNSELING INFORMATION

17.1 Benefits and Risks

- Summarize the effectiveness features and potential side effects of Plavix.
- Tell patients to take Plavix exactly as prescribed.
- Remind patients not to discontinue Plavix without first discussing it with the physician who prescribed Plavix.

17.2 Bleeding

Inform patients that they:

- will bruise and bleed more easily.
- will take longer than usual to stop bleeding.
- should report any unanticipated, prolonged, or excessive bleeding, or blood in their stool or urine.

17.3 Other Signs and Symptoms Requiring Medical Attention

- Inform patients that TTP is a rare but serious condition that has been reported with Plavix and other drugs in this class of drugs.
- Instruct patients to get prompt medical attention if they experience any of the following symptoms that cannot otherwise be explained: fever, weakness, extreme skin paleness, purple skin patches, yellowing of the skin or eyes, or neurological changes.

17.4 Invasive Procedures

Instruct patients to:

- inform physicians and dentists that they are taking Plavix before any invasive procedure is scheduled.
- tell the doctor performing the invasive procedure to talk to the prescribing health care professional before stopping Plavix.

17.5 Concomitant Medications

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 omeprazole, so the physician knows about other treatments that may affect how Plavix works (e.g., warfarin and NSAIDs) [*see Warnings and Precautions (5)*].

Distributed by:
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Bridgewater, NJ 08807

sanofi aventis



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Squibb Company**

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**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

20839Orig1s042

OTHER REVIEW(S)



Memorandum

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH
DIVISION OF CARDIOVASCULAR AND RENAL PRODUCTS

Date: March 17, 2010

From: Mary Ross Southworth, PharmD
Deputy Director for Safety
Division of Cardiovascular and Renal Products /CDER

To: File

Subject: Plavix (clopidogrel) labeling changes (NDA 20-839/TSI 386): Addition of omeprazole DDI information and boxed Warning about diminished efficacy in CYP2C19 poor metabolizers (conversion to PLR)

-
1. Key Results Memo, Sanofi-Aventis, A randomized, placebo controlled...crossover pharmacodynamic and pharmacokinetic interaction study after 5-days repeated oral doses of clopidogrel (300mg/75mg) alone or given concomitantly with omeprazole 80 mg/d. **INT 11146**, submitted 7/31/2009.
 2. Key Results Memo, Sanofi-Aventis, A randomized, placebo controlled...crossover pharmacodynamic and pharmacokinetic interaction study after 5-days repeated oral doses of clopidogrel (300mg/75mg) alone or given with omeprazole 80 mg/d (given 12 hours apart on the same day). **INT 11166**, submitted 7/31/2009.
 3. Nonclinical Final Study Report, Sanofi-Aventis Investigating potential mechanism-based inhibition of cytochrome P450 2C19 and 3A by omeprazole and pantoprazole in vitro MIH0804, submitted 11/30/2009.
 4. Memo to File (**INT11146**, **INT 11166**), Mary Ross Southworth, NDA #20-839/TSI #386, 09/16/2009
 5. Clinical Pharmacology Review (**PKM 11086**, **INT1146**, **INT11166**,), Elena Mishina, NDA # 20-83/TSI #3869, 11/2/2009

6. Key Results Memo, Sanofi-Aventis, A randomized, placebo controlled...crossover pharmacodynamic and pharmacokinetic study of clopidogrel given as a 5-days repeated oral dose (300mg/75mg and 600mg/150 mg) in 4 different groups of CYP2C19 genotyped healthy male and female subjects. **PKD 11147**, submitted 11/30/2009.
 7. Clinical Pharmacology Genomics Review **INT 11147**, Mike Pacanowski, Clopidogrel NDA #20-839/TSI #386, 1/7/2010.
 8. Clinical Pharmacology Genomics Group Review: General review of CYP 2C19 pharmacogenomics and the Plavix label, Mike Pacanowski, #NDA 20, 839/TSI #386, in preparation.
-

Executive summary

In the last year, several major changes have been made to the Plavix (clopidogrel) label describing the relationship between CYP2C19 functional activity and clopidogrel blood levels and platelet effects. A recommendation to avoid concomitant use of CYP2C19 inhibitors was based on two post-marketing studies that found substantially reduced anti-platelet activity and active metabolite drug levels when omeprazole and clopidogrel were coadministered. A second major change involved including information about reduced anti-platelet and drug levels in patients who are CYP2C19 “poor metabolizers”; poor metabolizers represent about 2 to 14% of the population and cannot efficiently convert clopidogrel to its active form. In the label, prescribers are advised to consider alternative anti-platelet therapies or dosing strategies in patients who are found to be poor metabolizers.

1. Background

Clopidogrel requires conversion to its pharmacologically active metabolite by the CYP 450 enzyme system, notably CYP2C19. Decreased pharmacodynamic (PD) and pharmacokinetic (PK) responses have been observed in patients with reduced function CYP2C19 and those on CYP2C19 inhibiting drugs (e.g., omeprazole). Worse clinical outcomes (death, myocardial infarction, stent thrombosis, and stroke) following acute coronary syndrome (ACS) and percutaneous intervention (PCI) have also been associated with reduced CYP2C19 function¹ as compared to those with “normal” (extensive) metabolizer status.

¹ Mega, JL et al. NEJM 2009; 360(4); 354-62.

Beginning in the fall of 2008, the Agency has held ongoing discussions with Sanofi-Aventis (sponsor for Plavix) for the purpose of updating Plavix labeling to describe clopidogrel's metabolic pathway, the contribution of the CYP 450 enzyme system, variability in response related to genetic variations in CYP2C19 activity, and drug interactions with CYP2C19 inhibiting drugs. This updated information was based on observed associations between diminished platelet response to clopidogrel and increased risk of ischemic events^{2,3}, the linkage between CYP2C19 poor metabolizer status and diminished effectiveness leading to adverse clinical outcomes^{1,4}, and potential decreases in clopidogrel's bioavailability relating to CYP450 mediated drug interactions⁵.

The agency required the sponsor to conduct further studies to develop a validated assay for measurement of clopidogrel's active metabolite and describe its PK and PD characteristics in various CYP 2C19 metabolizer types and when given concomitantly with CYP2C19 inhibitors.

Of note, the Agency issued an Early Communication on January 26, 2009 to advise health professionals that clopidogrel's effectiveness could be affected by genetic differences in 2C19 function^{6,7} or other drugs that influence the way clopidogrel is metabolized. Because there was evidence^{5,8} suggesting a reduction in the desired effect on platelets when omeprazole (a 2C19 inhibitor) was given with clopidogrel, the agency recommended that providers re-evaluate the need for starting or continuing therapy with a PPI in patients taking clopidogrel.

On March 6, 2009, exercising authority under the FDA Amendments Act (FDAAA) of 2007, the agency incorporated this new information by requiring drug label changes for clopidogrel (issued letter can be found in DARRTS). The sponsor was also required to perform 6 post-marketing trials (PMR).

1. An open-label, two-treatment crossover pharmacokinetic trial of clopidogrel hydrogen sulfate in healthy male and female subjects (**PKM 11086**)
2. A randomized, placebo-controlled, two-period, two treatment, cross-over pharmacodynamic and pharmacokinetic interaction trial after 5 day repeated oral doses

² Matetsky S et al. *Circulation* 2004; 109: 3171-5

³ Wiviott ST et al. *Circulation* 2004; 109: 3064-7.

⁴ Simon et al. *NEJM* 2009; 360 (4); 363-75.

⁵ Gilard M et al. *J Thromb Haemost* 2006; 4; 2508-9.

⁶ Frere C et al. *Am J Cardiol* 2008; 101; 1088-93.

⁷ Trenk D et al. *J Am Coll Cardiol* 2008; 51; 1925-34.

⁸ Gilard M, et al. *J Am Coll Cardiol* 2008; 51; 256-60.

of SR25990C (300mg/75 mg) given alone or concomitantly (same time) with omeprazole . (INT11146)

3. A randomized, placebo-controlled, two-period, two treatment, cross-over pharmacodynamic and pharmacokinetic interaction trial after 5 day repeated oral doses of SR25990C (600mg/150 mg) given alone or concomitantly (same time) with omeprazole. (INT11208)
4. A randomized, placebo-controlled, two-period, two treatment, cross-over pharmacodynamic and pharmacokinetic interaction trial after 5 day repeated oral doses of SR25990C (300mg/75 mg), given alone or with omeprazole 80mg/d given 12 hours apart in young healthy male and female subjects (INT11166)
5. Pharmacokinetic and pharmacodynamic trial of the active metabolite in 5-day repeated dosing in CYP2C19 genotyped healthy subjects (300mg/75 mg vs. 600mg/150mg). (INT11147)
6. *In vitro*-assessment to quantitate the involvement of the CYP isoforms in the formation of clopidogrel's active metabolite. (MIH0751)

This review will discuss the Agency's decision making process with regard to incorporating changes in the clopidogrel label (and related public communications) based on the results of several PMRs, other sponsor-run trials' and additional published studies that have become available during the time of this review. The most recent changes are reflected in the conversion of Plavix's label to the Physicians' Labeling Rule format (approved 3/12/2010).

2. Diminished effectiveness related to CYP 2C19 drug interactions: Proton Pump Inhibitor(PPI)-Clopidogrel interaction studies (INT 11146, INT 11166)

2.1 Published Literature/ Rationale for PMRs

As previously stated, concomitant use of omeprazole and clopidogrel has been shown to result in a loss of clopidogrel's desired antiplatelet effect compared to when clopidogrel is used alone^{5,8, 9,10}. However, this finding has not been observed with all PPIs; Studies of lansoprazole¹¹, esomeprazole^{9,12}, and pantoprazole^{9,10, 12} given with clopidogrel do not show significant differences in platelet reactivity compared to

⁹ Sibbing D, et al. Eur Heart J 2009; 30; 916-22.

¹⁰ Cuisset T, et al. J Am Coll Cardiol 2009; 54; 1149-53.

¹¹ Small et al. J Clin Pharmacol 2008; 48; 475-84.

¹² Siller-Matula JM et al. Am Heart J 2009; 157; 148.E1.

clopidogrel alone. An analysis from PRINCIPLE-TIMI 44¹³ found significantly higher platelet reactivity in those on clopidogrel plus PPI therapy compared to those on clopidogrel alone. The study did not distinguish between individual PPIs.

Several epidemiologic studies have demonstrated an association between PPI use and adverse clinical cardiovascular outcomes (compared to no PPI use) in patients on clopidogrel after acute coronary syndrome (ACS)^{14,15} or stent placement¹⁶. In contrast, a post hoc analysis¹³ showed no association between PPI use and adverse cardiovascular outcomes in the clopidogrel arm of the TRITON-TIMI 38.

An important limitation when considering epidemiologic data (non-randomized PPI use) is the possibility that the observed association may be due to some unmeasured confounder such as baseline morbidity or CV risk status. PPI users may be more likely have diabetes or other cardiovascular risk status¹⁷ which would put them at greater risk for adverse cardiovascular events.

Because some pharmacodynamic studies and epidemiologic analyses suggested a risk of worse cardiovascular outcomes relating to combined use of clopidogrel and PPIs (particularly the potent 2C19 inhibitor, omeprazole), the agency required the sponsor to perform two clinical studies (INT11146, INT11166) to measure clopidogrel active metabolite exposure and platelet effects in healthy subjects receiving omeprazole with clopidogrel vs. clopidogrel alone.

2.2 INT11146

A crossover design, interaction study after 5 days repeated doses of clopidogrel (300 mg loading dose followed by 75 mg/d alone or given concomitantly with omeprazole 80 mg/d in healthy male and female subjects)

This study demonstrated a **decrease in active metabolite levels** (C_{max} 34.1 ng/ml vs. 18.6 ng/ml) **of 46%** after a 300 mg loading dose of clopidogrel given after 5 days of therapy with omeprazole 80 mg vs. clopidogrel alone. After an additional 4 days of clopidogrel 75 mg daily, those taking concomitant omeprazole had a **42% reduction in active metabolite** (C_{max} 14.0 ng/ml vs 8.13 mg/ml) levels compared to clopidogrel alone.

¹³ O'Donoghugh ML, et al. Lancet 2009: 374; 989-97.

¹⁴ Ho PM et al. JAMA 2009: 301; 937-44.

¹⁵ Juurlink DN, et al. CMAJ 2009: 180; 713-8.

¹⁶ Aubert RE, et al. abstract presented at AHA Scientific Sessions November 2008

¹⁷ Pezalla E. et al. J Am Coll Cardiol 2008; 5.

Pharmacodynamic effects, measured by Light Transmittance Aggregometry (LTA-see Appendix 1 for discussion of platelet tests), are shown in **Figure 1**. Mean inhibition of platelet aggregation (mean IPA) was diminished by 47% (24 hours) and 30% (Day 5) when omeprazole was administered with clopidogrel.

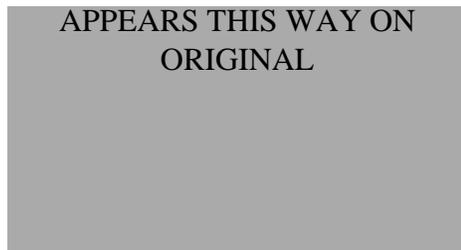
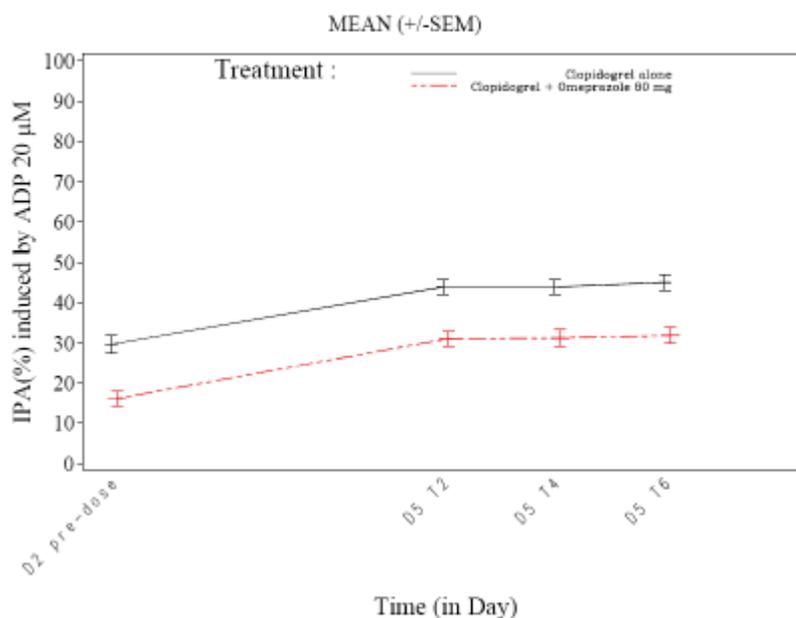


Figure 1: Pharmacodynamic effects in INT 11146

Mean \pm SEM of Inhibition Rate of Platelet Aggregation (%) induced by ADP 20 μ M pharmacodynamic population



2.3 INT11166

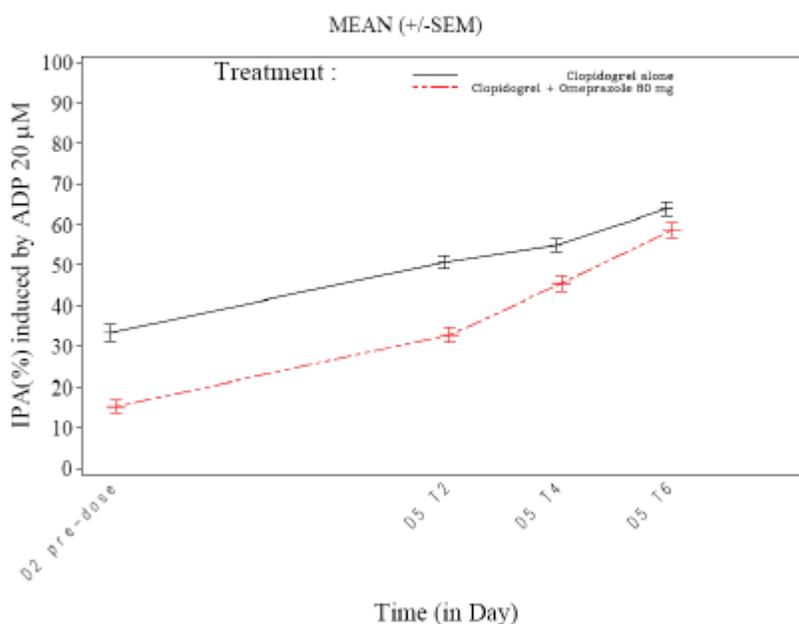
A crossover design, interaction study after 5 days repeated doses of clopidogrel (300 mg loading dose followed by 75 mg/d alone or given concomitantly with omeprazole 80 mg/d (12 hours apart) in healthy male and female subjects)

In this study, which administered omeprazole 12 hours apart from clopidogrel, concomitant use resulted in a **decrease in active metabolite levels (Cmax) of 55%** after a 300 mg loading dose and **56%** (Cmax) after 4 additional days of clopidogrel 75mg.

Pharmacodynamic effects in study 11166 are shown in **Figure 2**. Mean inhibition of platelet aggregation (IPA) was diminished by 55% (24 hours) and 35% (Day 5, 2 hours post dose), by 6 hours post dose on day 5, the effect of the interaction appeared to wane with a reduction in platelet inhibition of about 8%.

Figure 2: Pharmacodynamic effects in INT 11166

Mean \pm SEM of Inhibition Rate of Platelet Aggregation (%) induced by ADP 20 μ M pharmacodynamic population



2.4 Agency Comment and Recommendation

These studies confirm that co-administration of omeprazole with clopidogrel results in a notable decrease in the formation of clopidogrel's active metabolite and a diminished effect on pharmacodynamic measures of inhibition of platelet aggregation. It appears that the mechanism for interaction may not solely be related to competitive inhibition of 2C19 by omeprazole, and may be the result of a progressive inhibition of 2C19 with multiple daily doses. In fact, there is evidence that the AUCs of omeprazole, and its S-enantiomer, esomeprazole, steadily increase over 7 days of dosing^{18, 19}. This would provide an explanation for why, in study 11166, despite 12 hours separation between clopidogrel and omeprazole administration, nearly identical degrees of inhibition of formation of the active metabolite and the desired pharmacologic effects were demonstrated as compared to simultaneous administration of the drugs. Given the short half life of omeprazole (1 hour) one would expect virtually no effect on 2C19 and

¹⁸ Andersson T et al., Br J Clin Pharmacol 1990; 29: 557.

¹⁹ Hassan-Alin M et al, Eur J Clin Pharmacol 2000; 56: 665.

the formation of clopidogrel's active metabolite 12 hours after omeprazole dosing. The company provided in vitro data supporting omeprazole as an irreversible inhibitor of CYP2C19 (non clinical study report)

Clearly, these interaction studies reveal a significant effect on clopidogrel exposure and platelet effect when omeprazole is given concomitantly. Clopidogrel works by reducing platelet aggregation and therefore, the agency believed that any reduction in anti-platelet activity associated with a drug interaction should be described in the labeling. The agency recommended avoiding use of omeprazole and other CYP2C19 inhibitor concomitantly with clopidogrel because of the data supporting decreased exposure and platelet effects, even though the correlation between platelet activity and clinical outcomes was not completely defined.

To better determine the relationship between PPI use and clinical outcomes, a randomized study design would be required. Although the prematurely terminated-COAGENT²⁰ study randomized patients to receive a combination product (clopidogrel 75 mg+ omeprazole 20 mg) or clopidogrel 75 mg alone, the purpose of COAGENT was to determine whether the combination of clopidogrel and omeprazole, compared to clopidogrel, was safe and effective in reducing the incidence of important gastrointestinal events. COAGENT was neither designed nor powered to investigate the effect of the combination on cardiovascular endpoints. In fact, assuming a 3% event cardiovascular event rate (as suggested by the event rate in COAGENT), the study would have needed 1265 events from a total sample size of approximately 42,000 subjects to rule out, with 90% certainty, a 20% increase in risk for cardiovascular events with the combination therapy. COAGENT enrolled just over 3600 subjects and reported about 135 cardiovascular events. Therefore, the finding of no difference in rates of cardiovascular endpoints in a small study such as COAGENT does not provide adequate reassurance that there is no difference.

To reflect these findings, in November 2009, the results of these studies were incorporated into clopidogrel's label (in WARNINGS, PRECAUTIONS/Drug interactions, and PRECAUTIONS/Information for patients) with a general recommendation to avoid CYP2C19 inhibiting drugs (e.g., omeprazole) in patients receiving clopidogrel. Concurrently, follow ups to the January 2009 Early Communication describing the updated recommendations were drafted and released. These communications described the nearly 50% reduction in active metabolite levels

²⁰ Bhatt D. abstract presented at the TCT 2009 conference; September 2009.

and effect on platelets observed in these studies and recommended against co-administration of clopidogrel with potent inhibitors of CYP 2C19.

2.5 Studies to be Reviewed (INT11208, INT 11374)

The results from a third omeprazole-clopidogrel study, **INT11208**, evaluating a higher dose regimen for clopidogrel (600 mg load and 150 mg daily) will be reviewed separately. An additional post-marketing drug interaction study, **INT 11374** is similar in design to the previous clopidogrel-omeprazole interaction studies, but pantoprazole, a PPI with less 2C19 inhibitory effect than omeprazole, is being studied.

3. Diminished effectiveness related to 2C19 Genotype

3.1 Published Literature/ Rationale for PMRs

Genetic polymorphisms of the CYP 2C19 enzyme affect the pharmacokinetic, pharmacodynamic and clinical response to clopidogrel. CYP 2C19*2 or *3 variant allele carriers exhibit reduced drug metabolizing function and are classified as intermediate or poor metabolizers depending on whether they carry 1 (intermediate) or 2 (poor) copies of the loss of function alleles. The frequency of phenotype in the population is based on racial background; poor metabolizers represent about 2 % of Caucasians, 4% of Black, and 14% of Chinese (Asian)²¹.

Because clopidogrel's effect on platelet inhibition is entirely due to exposure to the active metabolite, which is formed primarily by CYP 2C19 metabolism, patients with reduced CYP 2C19 activity exhibit diminished platelet aggregation inhibition. This has been demonstrated in both healthy subjects^{1, 22, 23} and those with acute coronary syndromes²³. In general, poor metabolizers (who lack 2C19 activity) demonstrate the lowest active metabolite exposure and antiplatelet effect; intermediate metabolizers have reduced PK and PD effects relative to extensive metabolizers. These effects have been seen consistently across clopidogrel doses and dose regimens.

Several studies have examined the effects of CYP 2C19 genotype on clinical outcome in patients using clopidogrel. In most of the published studies (Collett 2009, Shuldiner 2009, Mega 2009, Sibbing 2009), intermediate and poor metabolizers were pooled and

²¹ Xie HG, et al *Annu Rev Pharmacol Toxicol* 2001; 41: 815.

²² Fontana P et al. *J Thromb Haemost* 2007; 5: 2153.

²³ Shuldiner AR et al. *JAMA* 2009; 302; 849.

generally demonstrated higher rates of cardiovascular death, myocardial infarction, stroke, and stent thrombosis than did EMs. When studies reported outcomes separately for PMs (Simon 2009, Guisti 2009, Bhatt 2009), they tended to have the worst cardiovascular outcomes compared to IMs and EMs. Some information about poor metabolizers and diminished effectiveness was included in a Plavix label modification in May 2009.

The effect of 2C19 genotype on active metabolite levels has been evaluated in a few studies (Brandt 2007, Mega 2009, Umemura 2008) which reveal that both Cmax and AUC are lower in IMs (32% lower Cmax, 26% lower AUC) and PMs (39% Cmax; 43% AUC) compared to extensive metabolizers. To further explore the relationship between 2C19 genotype, clopidogrel dose, and PK and PD effects, the sponsor was required to perform a post market study (PKD 11147) in healthy subjects.

3.2 PKD 11147

A crossover design, pharmacodynamic and pharmacokinetic study of clopidogrel given as 5-day repeated doses of clopidogrel (300 mg loading dose followed by 75 mg/d and 600 mg loading dose followed by 150 mg/d) in 4 different groups of CYP 2C19 genotyped healthy male and female subjects

The pharmacokinetic and pharmacodynamic effects of two different dosing regimens in 4 CYP2C19 genotyped groups are shown below in **Table 1**.

Table 1. Active Metabolite Pharmacokinetics and Antiplatelet Responses by CYP2C19 Metabolizer Status

	Dose	Ultrarapid (n=10)	Extensive (n=10)	Intermediate (n=10)	Poor (n=10)
Cmax (ng/ml)	300 mg (24 h)	24 (10)	32 (21)	23 (11)	11 (4)
	600 mg (24 h)	36 (13)	44 (27)	39 (23)	17 (6)
	75 mg (Day 5)	12 (6)	13 (7)	12 (5)	4 (1)
	150 mg (Day 5)	16 (9)	19 (5)	18 (7)	7 (2)
AUC _{last} (ng.h/ml)	300 mg (24 h)	33 (11)	39 (24)	31 (14)	14 (6)
	600 mg (24 h)	56 (22)	70 (46)	56 (27)	23 (7)
	75 mg (Day 5)	11 (5)	12 (6)	10 (4)	3 (1)
	150 mg (Day 5)	18 (8)	19 (8)	16 (7)	7 (2)
IPA (%)*	300 mg (24 h)	40 (21)	39 (28)	37 (21)	24 (26)
	600 mg (24 h)	51 (28)	49 (23)	56 (22)	32 (25)
	75 mg (Day 5)	56 (13)	58 (19)	60 (18)	37 (23)

	150 mg (Day 5)	68 (18)	73 (9)	74 (14)	61 (14)
VASP-PRI (%) †	300 mg (24 h)	73 (12)	68 (16)	77 (12)	91 (12)
	600 mg (24 h)	51 (20)	48 (20)	56 (26)	85 (14)
	75 mg (Day 5)	40 (9)	39 (14)	50 (16)	83 (13)
	150 mg (Day 5)	20 (10)	24 (10)	29 (11)	61 (18)
Values are mean (SD)					
* Inhibition of platelet aggregation with 5µM ADP					
† Vasodilator-stimulated phosphoprotein – platelet reactivity index; smaller value indicates greater response					

Decreased exposure (C_{max}) to the active metabolite was most notable in the PM group (compared to UMs, EMs, and IMs). Pharmacodynamic (antiplatelet effects) were reduced in poor metabolizers in both dose regimens tested. However, administering the larger dose regimen (clopidogrel 600 mg load followed by 150 mg/d) did increase the antiplatelet effects of clopidogrel so that the pharmacodynamic effects resembled those seen in intermediate metabolizers receiving conventional doses of clopidogrel (300 mg load followed by 75mg)

3.3 Agency Comments and Recommendations

These studies demonstrate consistently lower drug exposure and anti-platelet effects in patients who are PMs. Major differences in PK and PD response were not seen among UMs, EMs, and IMs. Using a higher dose of clopidogrel in PMs increases anti-platelet response; however, these doses have not been tested in a clinical outcomes trial.

These findings led to the addition of a warning to the Plavix label (label approved 3/12/10). The updated label includes information about diminished effectiveness in poor metabolizers and a recommendation that prescribers consider alternative anti-platelet agents or dosing regimens for Plavix. The new information appears in a boxed warning in the label to highlight this important information for prescribers who use Plavix. The box appears as below:

WARNING: DIMINISHED EFFECTIVENESS IN POOR METABOLIZERS

The effectiveness of Plavix is (b) (4) activation to an active metabolite by the cytochrome P450 (CYP) system, principally CYP2C19. (b) (4)

(b) (4). **Poor metabolizers** (b) (4) treated with Plavix at recommended doses exhibit higher cardiovascular event rates than (b) (4) patients with normal CYP2C19 function. Tests are available to identify a patient's CYP2C19 genotype; these tests can be used as an aid in determining therapeutic strategy. Consider alternative treatment or treatment strategies in patients identified as poor metabolizers of CYP2C19.

A FDA Drug Safety Communication was also issued on 3/12/10 describing the data behind the new boxed warning²⁴.

4.0 PMR fulfillment

The following post-marketing required studies are considered fulfilled: PKM 11806, INT11146, INT11166, PKD11147, MIH0751.

²⁴ Accessed March 15, 2010.

<http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm203888.htm>

Appendix 1: Platelet Assays

Platelet function can be measured by various methods, several of which have been fairly well studied. However, there are no established standards or guidelines for a preferential test, definition of poor response to antiplatelet therapy, or utility in predicting adverse clinical outcomes relating to poor response. In addition, widespread use of these tests is limited because of test complexity, high cost and lengthy turnaround times for results. Three methodologies for measuring platelet function are described below:

Light transmittance aggregometry (LTA) has historically been considered the “gold standard” test as it has been the most widely investigated^{25,26} method to predict clinical outcomes. With this methodology, platelet aggregation is measured after stimulation with various agonists, most frequently, adenosine diphosphate (ADP) at 5 or 20 μ M. Commonly cited cutoffs for poor response²⁷ are Δ **maximal platelet aggregation (MPA)** <10%, **MPA** >50%, and **residual platelet aggregation (RPA)** >14%. Other sources define hyporesponsiveness²⁸ as <20% **inhibition of platelet aggregation (IPA)** with 20 μ M ADP. Disadvantages of this method include variable reproducibility, requirement for large sample volume, and lengthy processing time.

Vasodilator-stimulated phosphoprotein (VASP) specifically measures P2Y₁₂-mediated platelet aggregation (the mechanism by which clopidogrel inhibits aggregation) and thus, may provide more stable results. It has also been evaluated for its ability to predict clinical outcomes. A commonly cited cutoff²⁹ for poor response is a **platelet reactivity index (PRI)** >50%. Disadvantages of VASP methodology include the need for complex testing procedures (flow cytometry).

Point of care assays (e.g., Verify-Now method-Accumetrics) use agonists to stimulate platelet aggregation. The clinical utility of the Verify-Now bedside test is currently being tested in the GRAVITAS³⁰ study.

²⁵ Gurbel PA et al. J Amer Coll Cardiol 2007; 50: 1822-34.

²⁶ Gum PA et al. Am J Cardiol 2001; 88: 230-5.

²⁷ Erlinge D et al. J Am Coll Cardiol 2008; 52: 1968-77.

²⁸ Brandt JT et al. Am Heart J 2007; 153: 66.

²⁹ Barragan P et al. Catheter Cardiovasc Interv 2003; 59: 295-302.

³⁰ Price MJ et al. Am Heart J 2009; 157: 818-24.

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-20839	SUPPL-42	SANOFI AVENTIS US LLC	PLAVIX
SAFETY-386	ORIG-1	NO FIRM	PLAVIX (CLOPIDOGREL)

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/s/

MARY R SOUTHWORTH
03/17/2010

RHPM Review of Product Draft Labeling

Application: NDA 20-839/S-042 PLR Conversion
Applicant: sanofi aventis US, LLC
Submission Date: 17 June 2009
Receipt Date: 17 June 2009
Product Name: Plavix® (clopidogrel bisulfate) 75 mg Tablets

Background: Sanofi-aventis submitted NDA 20-839/S-042 on 17Jun09. This submission was to update the package insert to the Physician's Labeling Rule (PLR) format. In addition to updating the label to PLR, the Division also updated a number of sections with new information recently submitted to the Agency as part of Post-Marketing Requirements detailed in our 6Mar09 FDAAA letter. Sanofi aventis' last approved USPI was approved on May 5, 2009 (S-040).

Review: Sanofi-aventis submitted package insert labeling with the following revisions:

1. A boxed warning was added to the Full Prescribing Information to read as follows:

WARNING: DIMINISHED EFFECTIVENESS IN POOR METABOLIZERS

The effectiveness of Plavix is (b) (4) its activation to an active metabolite by the cytochrome P450 (CYP) system, principally CYP2C19 (b) (4) (5.1)]. (b) (4)

Poor metabolizers (b) (4)

(b) (4) treated with Plavix at recommended doses exhibit higher cardiovascular event rates than (b) (4) patients with normal CYP2C19 function. Tests are available to identify a patient's CYP2C19 genotype; these tests can be used as an aid in determining therapeutic strategy (b) (4) (12.5)]. Consider alternative treatment or treatment strategies in patients identified as CYP2C19 poor metabolizers (b) (4) (2.3)]. (b) (4)

2. A new subsection, 2.3, **CYP2C19 Poor Metabolizers**, was added to the **DOSAGE AND ADMINISTRATION** section:

“2.3 CYP2C19 Poor Metabolizers

CYP2C19 poor metabolizer status is associated with diminished antiplatelet response to clopidogrel. Although a higher dose regimen (600 mg loading dose followed by 150 mg once daily) in poor metabolizers increases antiplatelet response [see *Clinical Pharmacology (12.5)*], an appropriate dose regimen for this patient population has not been established in clinical outcome trials.”

3. In Section 5, **WARNINGS AND PRECAUTIONS**, the subsection, **Thrombotic thrombocytopenic purpura (TTP)**, was moved to 5.5 and the following subsections were added or amended significantly:

“5.1 Diminished Antiplatelet Activity Due to Impaired CYP2C19 Function

Clopidogrel is a prodrug. Inhibition of platelet aggregation by clopidogrel is entirely due to 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. Avoid concomitant use of Plavix and drugs that inhibit CYP2C19 activity. 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 [see *Drug Interactions (7.1)*].

5.2 GENERAL RISK OF BLEEDING

THIENOPYRIDINES, INCLUDING PLAVIX, INCREASE THE RISK OF BLEEDING. IF A PATIENT IS TO UNDERGO SURGERY AND AN ANTIPLATELET EFFECT IS NOT DESIRED, DISCONTINUE PLAVIX 5 DAYS PRIOR TO SURGERY. IN PATIENTS WHO STOPPED THERAPY MORE THAN FIVE DAYS PRIOR TO CABG THE RATES OF MAJOR BLEEDING WERE SIMILAR (EVENT RATE 4.4% PLAVIX + ASPIRIN; 5.3% PLACEBO + ASPIRIN). IN PATIENTS WHO REMAINED ON THERAPY WITHIN FIVE DAYS OF CABG, THE MAJOR BLEEDING RATE WAS 9.6% FOR PLAVIX + ASPIRIN, AND 6.3% FOR PLACEBO + ASPIRIN.

THIENOPYRIDINES INHIBIT PLATELET AGGREGATION FOR THE LIFETIME OF THE PLATELET (7-10 DAYS), SO WITHHOLDING A DOSE WILL NOT BE USEFUL IN MANAGING A BLEEDING EVENT OR THE RISK OF BLEEDING ASSOCIATED WITH AN INVASIVE PROCEDURE. BECAUSE THE HALF-LIFE OF CLOPIDOGREL'S ACTIVE METABOLITE IS SHORT, IT MAY BE POSSIBLE TO RESTORE HEMOSTASIS BY ADMINISTERING EXOGENOUS PLATELETS; HOWEVER, PLATELET TRANSFUSIONS WITHIN 4 HOURS OF THE LOADING DOSE OR 2 HOURS OF THE MAINTENANCE DOSE MAY BE LESS EFFECTIVE.

5.3 Discontinuation of Plavix

Avoid lapses in therapy, and if Plavix must be temporarily discontinued, restart as soon as possible. Premature discontinuation of Plavix may increase the risk of cardiovascular events.”

4. New information was added to Section 7, **DRUG INTERACTIONS**, under the subsection 7.1, **CYP2C19 Inhibitors**:

“Omeprazole

In a crossover clinical study, 72 healthy subjects were administered Plavix (300 mg loading dose followed by 75 mg per 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 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 and Precautions (5.1)*].”

5. Due to a lack of useful information for the prescriber, the following subsections were deleted from Section 7, **DRUG INTERACTIONS**:

“Aspirin: Aspirin did not modify the clopidogrel-mediated inhibition of ADP-induced platelet aggregation. Concomitant administration of 500 mg of aspirin twice a day for 1 day did not significantly increase the prolongation of bleeding time induced by PLAVIX. PLAVIX potentiated the effect of aspirin on collagen-induced platelet aggregation. PLAVIX and aspirin have been administered together for up to one year.

Heparin: In a study in healthy volunteers, PLAVIX did not necessitate modification of the heparin dose or alter the effect of heparin on coagulation. Coadministration of heparin had no effect on inhibition of platelet aggregation induced by PLAVIX.”

6. The following subsection, **7.3 Warfarin (CYP2C9 Substrates)**, was updated to read:

“Although the administration of clopidogrel 75 mg per day did not modify the pharmacokinetics of S-warfarin (a CYP2C9 substrate) or INR in patients receiving long-term warfarin therapy, coadministration of Plavix with warfarin increases the risk of bleeding because of independent effects on hemostasis.”

7. Information regarding moderate renal impairment (creatinine clearance from 30 to 60 mL/min) was added to section 8.6, **Renal Impairment**, and 12.2, **Pharmacodynamics**.

8. In Section 12, **CLINICAL PHARMACOLOGY**, subsection 12.3, **Pharmacokinetics**, information regarding unmetabolized clopidogrel was removed from this subsection and the following information was added:

“Effect of Food

Plavix can be administered with or without food. In a study in healthy male subjects when Plavix 75 mg per day was given with a standard breakfast, mean inhibition of ADP-induced

platelet aggregation was reduced by less than 9%. The active metabolite AUC₀₋₂₄ was unchanged in the presence of food, while there was a 57% decrease in active metabolite C_{max}. Similar results were observed when a Plavix 300 mg loading dose was administered with a high-fat breakfast.”

- The previous text in the subsection, Metabolism, was amended and the following new information was added:

“The C_{max} of the active metabolite is twice as high following a single 300 mg clopidogrel loading dose as it is after four days of 75 mg maintenance dose. C_{max} occurs approximately 30 to 60 minutes after dosing. In the 75 to 300 mg dose range, the pharmacokinetics of the active metabolite deviates from dose proportionality: increasing the dose by a factor of four results in 2.0- and 2.7-fold increases in C_{max} and AUC, respectively.”

9. Subsection 12.5, **Pharmacogenomics**, was altered extensively. The following table and paragraph were deleted. Instead, the information included in the below table was included in narrative format in the second paragraph of this subsection:

(b) (4) **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 600 mg loading doses and 75 mg 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%.”

- Upon receipt of new information, the following study information was added to the **Pharmacogenomics** subsection:

“Table 3: Active Metabolite Pharmacokinetics and Antiplatelet Responses by CYP2C19 Metabolizer Status

	Dose	Ultrarapid (n=10)	Extensive (n=10)	Intermediate (n=10)	Poor (n=10)
Cmax (ng/mL)	300 mg (24 h)	24 (10)	32 (21)	23 (11)	11 (4)
	600 mg (24 h)	36 (13)	44 (27)	39 (23)	17 (6)
	75 mg (Day 5)	12 (6)	13 (7)	12 (5)	4 (1)
	150 mg (Day 5)	16 (9)	19 (5)	18 (7)	7 (2)
IPA (%)*	300 mg (24 h)	40 (21)	39 (28)	37 (21)	24 (26)
	600 mg (24 h)	51 (28)	49 (23)	56 (22)	32 (25)
	75 mg (Day 5)	56 (13)	58 (19)	60 (18)	37 (23)
	150 mg (Day 5)	68 (18)	73 (9)	74 (14)	61 (14)
VASP-PRI (%) †	300 mg (24 h)	73 (12)	68 (16)	77 (12)	91 (12)
	600 mg (24 h)	51 (20)	48 (20)	56 (26)	85 (14)
	75 mg (Day 5)	40 (9)	39 (14)	50 (16)	83 (13)
	150 mg (Day 5)	20 (10)	24 (10)	29 (11)	61 (18)
Values are mean (SD)					
* Inhibition of platelet aggregation with 5µM ADP; larger value indicates greater platelet inhibition					
† Vasodilator-stimulated phosphoprotein – platelet reactivity index; smaller value indicates greater platelet inhibition					

A crossover study in 40 healthy subjects, 10 each in the four CYP2C19 metabolizer groups, evaluated pharmacokinetic and antiplatelet responses using 300 mg followed by 75 mg per day and 600 mg followed by 150 mg per day, each for a total of 5 days. Decreased active metabolite exposure and diminished inhibition of platelet aggregation were observed in the poor metabolizers as compared to the other groups. When poor metabolizers received the 600 mg/150 mg regimen, active metabolite exposure and antiplatelet response were greater than with the 300/75 mg regimen (see Table 3). An appropriate dose regimen for this patient population has not been established in clinical outcome trials.”

10. Information regarding (b) (4) was deleted from various sections in the label. The most notable sections were **ADVERSE REACTIONS** (Section 6.1, **Clinical Studies Experience**), **USE IN SPECIFIC POPULATIONS** (Section 8.5, **Geriatric Use**), **CLINICAL PHARMACOLOGY** (Section 12.3, **Pharmacokinetics**), and **CLINICAL STUDIES** (Section 14.1, **Acute Coronary Syndrome**).
11. In Section 14, **CLINICAL STUDIES**, under Table 4, “**Outcome Events in the CURE Primary Analysis**”, information regarding the (b) (4), was removed.

12. Under Section 14, **CLINICAL STUDIES**, a new subsection, **Lack of Established Benefit of Plavix plus Aspirin in Patients with Multiple Risk Factors or Established Vascular Disease**, was added to include information regarding the clinical trial “CHARISMA”:

“CHARISMA

The CHARISMA trial was a 15,603 subject, randomized, double-blind, parallel group study comparing Plavix (75 mg daily) to placebo for prevention of ischemic events in patients with vascular disease or multiple risk factors for atherosclerosis. All subjects were treated with aspirin 75-162 mg daily. The mean duration of treatment was 23 months. The study failed to demonstrate a reduction in the occurrence of the primary endpoint, a composite of CV death, MI, or stroke. A total of 534 (6.9%) patients in the Plavix group versus 573 (7.4%) patients in the placebo group experienced a primary outcome event (p=0.22). Bleeding of all severities was more common in the subjects randomized to Plavix.”

13. As part of the PLR conversion, the following information under Section 17, **PATIENT COUNSELING INFORMATION**, was included:

“17.1 Benefits and Risks

- Summarize the effectiveness features and potential side effects of Plavix.
- Tell patients to take Plavix exactly as prescribed.
- Remind patients not to discontinue Plavix without first discussing it with the physician who prescribed Plavix.

17.2 Bleeding

Inform patients that they:

- will bruise and bleed more easily.
- will take longer than usual to stop bleeding.
- should report any unanticipated, prolonged, or excessive bleeding, or blood in their stool or urine.

17.3 Other Signs and Symptoms Requiring Medical Attention

- Inform patients that TTP is a rare but serious condition that has been reported with Plavix and other drugs in this class of drugs.
- Instruct patients to get prompt medical attention if they experience any of the following symptoms that cannot otherwise be explained: fever, weakness, extreme skin paleness, purple skin patches, yellowing of the skin or eyes, or neurological changes.

17.4 Invasive Procedures

Instruct patients to:

- inform physicians and dentists that they are taking Plavix before any invasive procedure is scheduled.
- tell the doctor performing the invasive procedure to talk to the prescribing health care professional before stopping Plavix.

17.5 Concomitant Medications

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 omeprazole, so the physician knows about other treatments that may affect how Plavix works (e.g., warfarin and NSAIDs) [see Warnings and Precautions (5)].”

14. Lastly, there were a number of grammatical and editorial changes made throughout the label.

Comments:

- The sponsor was active in the negotiation of this new label and submitted a number of revisions along with responses to various information requests. These submissions were dated September 15, October 6, 22, 30, November 19, December 14, 2009, and January 11, 13, 25, February 1, 12, and March 8, 10, 2010. The final version of the label, incorporating all of the agreed upon changes, was submitted on 10 March 2010.
- DDMAC was consulted on this review. Emily Baker completed the consult and logged her review in DARRTS, dated 26 February 2010.
- Dr. Southworth, Safety Deputy Division Director, also conducted a review which included the Division's collective reasoning behind a majority of these labeling changes. Her review is dated 16 March 2010.
- An approval letter for Dr. Stockbridge's signature was drafted, detailing all of major changes to the label, and signed on 12 March 2010.

Alison Blaus
Regulatory Health Project Manager
dr: ab/1Mar10
f: ab/16Mar10

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-20839	SUPPL-42	SANOFI AVENTIS US LLC	PLAVIX

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/s/

ALISON L BLAUS
03/16/2010

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Drug Marketing, Advertising, and Communications

****PRE-DECISIONAL AGENCY MEMO****

Date: February 26, 2009

To: Alison Blaus – Regulatory Project Manager
Division of Cardiovascular and Renal Products (DCRP)

From: Emily Baker – Regulatory Review Officer
Division of Drug Marketing, Advertising, and Communications (DDMAC)

Through: Mike Sauers – Group Leader
Division of Drug Marketing, Advertising, and Communications (DDMAC)

Subject: **DDMAC draft labeling comments**
NDA 20-839 Plavix (clopidogrel bisulfate) Tablets

DDMAC has reviewed the proposed product labeling (PI) for Plavix (clopidogrel bisulfate) Tablets (Plavix), submitted for consult on January 19, 2010.

The following comments are provided using the updated proposed PI as of February 24, 2010. If you have any questions about DDMAC's comments, please do not hesitate to contact me.

24 Pages have been Withheld in Full as Draft Labeling immediately following this page.

Application
Type/Number

Submission
Type/Number

Submitter Name

Product Name

NDA-20839

SUPPL-42

SANOFI AVENTIS
US LLC

PLAVIX

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/s/

EMILY K BAKER
02/26/2010

MEMORANDUM

To: Alison Blaus
Division of Cardiovascular and Renal Products

From: Iris Masucci, PharmD, BCPS
Division of Drug Marketing, Advertising, and Communications
for the Study Endpoints and Label Development (SEALD) Team, OND

Date: January 14, 2010

Re: Comments on draft labeling for Plavix (clopidogrel bisulfate) tablets
NDA 20-839/S042

We have reviewed the proposed label for Plavix (FDA versions dated 11/20/09 and 1/13/10) and offer the following comments. These comments are based on Title 21 of the Code of Federal Regulations (201.56 and 201.57), the preamble to the Final Rule, labeling Guidances, and FDA recommendations to provide for labeling quality and consistency across review divisions. We recognize that final labeling decisions rest with the review division after a full review of the submitted data.

Please see attached label for recommended changes.

22 Pages have been Withheld in Full as Draft Labeling immediately following this page.

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-20839	SUPPL-42	SANOFI AVENTIS US LLC	PLAVIX

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/s/

IRIS P MASUCCI
01/15/2010

LAURIE B BURKE
01/19/2010

REQUEST FOR DDMAC LABELING REVIEW CONSULTATION

****Please send immediately following the Filing/Planning meeting****

TO: CDER-DDMAC-RPM	FROM: (Name/Title, Office/Division/Phone number of requestor) Alison Blaus, Regulatory Health Project Manager, DCaRP, (301) 796-1138
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REQUEST DATE	IND NO. 34,663	NDA/BLA NO 20-839	TYPE OF DOCUMENTS (PLEASE CHECK OFF BELOW)
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NAME OF DRUG Plavix (clopidogrel bisulfate)	PRIORITY CONSIDERATION	CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE (Generally 1 week before the wrap-up meeting)
-------------------------------------------------------	------------------------	------------------------	--------------------------------------------------------------------------

NAME OF FIRM: sanofi aventis	PDUFA Date: December 2009
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TYPE OF LABEL TO REVIEW

TYPE OF LABELING: (Check all that apply) <input checked="" type="checkbox"/> PACKAGE INSERT (PI) <input type="checkbox"/> PATIENT PACKAGE INSERT (PPI) <input type="checkbox"/> CARTON/CONTAINER LABELING <input type="checkbox"/> MEDICATION GUIDE <input type="checkbox"/> INSTRUCTIONS FOR USE(IFU)	TYPE OF APPLICATION/SUBMISSION <input type="checkbox"/> ORIGINAL NDA/BLA <input type="checkbox"/> IND <input type="checkbox"/> EFFICACY SUPPLEMENT <input type="checkbox"/> SAFETY SUPPLEMENT <input type="checkbox"/> LABELING SUPPLEMENT <input type="checkbox"/> PLR CONVERSION	REASON FOR LABELING CONSULT <input type="checkbox"/> INITIAL PROPOSED LABELING <input type="checkbox"/> LABELING REVISION
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EDR link to submission:

EDR Location: <\\CDSESUB1\EVSPROD\NDA020839\0012>

Above is a link to the original submission. The label has changed significantly since this point.

Please Note: There is no need to send labeling at this time. DDMAC reviews substantially complete labeling, which has already been marked up by the CDER Review Team. The DDMAC reviewer will contact you at a later date to obtain the substantially complete labeling for review.

COMMENTS/SPECIAL INSTRUCTIONS:

A labeling supplement to convert Plavix to PLR format was received in June 2008. In addition to the conversion, we are including new information relevant to the new pharmacology/pharmacogenomics data. This will include a boxed warning regarding genetic testing and to avoid use in those patients who are poor metabolizers. Upon approval of the label, I will include the appropriate language in the Approval Letter. Please let me know if you need anything.

Mid-Cycle Meeting: N/A
Labeling Meetings: N/A
Wrap-Up Meeting: N/A

SIGNATURE OF REQUESTER: Alison Blaus	
SIGNATURE OF RECEIVER	METHOD OF DELIVERY (Check one) <input checked="" type="checkbox"/> eMAIL <input type="checkbox"/> HAND

Application
Type/Number

Submission
Type/Number

Submitter Name

Product Name

NDA-20839

SUPPL-42

SANOFI AVENTIS
US LLC

PLAVIX

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/s/

ALISON L BLAUS

01/19/2010

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

20839Orig1s042

**ADMINISTRATIVE and CORRESPONDENCE
DOCUMENTS**



NDA 20-839

GENERAL ADVICE

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 New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Plavix (clopidogrel bisulfate) 75 mg Tablets.

We also refer to your July 31, 2009 submission, containing two drug interaction studies (INT11146, INT11166) with omeprazole 80 mg administered concomitantly and separated by 12 hours with the standard clopidogrel dose regimen of a 300 mg loading dose followed by a 75 mg maintenance dose.

We have reviewed the above referenced material and have the following request. We respectfully ask that you submit a response to the following within 10 business days. This response should be submitted to the NDA as an amendment to the labeling supplement (S-042) dated June 17, 2009.

Please incorporate the following changes to the label:

- Information regarding the drug interaction with omeprazole should be included in the Warnings and Precautions section of labeling (Section 5) and Highlights.
- Specific information about these two studies (INT11146, INT11166) should be added to the Drug Interactions section of the labeling (Section 7) in order to help the prescriber make an informed decision about the risk and benefit of taking omeprazole with clopidogrel. This should include:
 - A description of the effects of co-administration on active metabolite exposure
 - A description of the effects of lower active metabolite exposure on platelet aggregation
 - A statement that separating administration of the drugs by 12 hours is not useful
 - A statement that concomitant use of the omeprazole and clopidogrel is not recommended
 - A recommendation about how to handle other 2C19 inhibitors

To address the last point, you should consider the similarities and differences between omeprazole and other 2C19 inhibitors and how they might influence that recommendation. Moreover, a hypothesis on the mechanism of the interaction (given the results of study INT11166), should be included in the labeling proposal.

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

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-20839	PMR/PMC-1	SANOFI AVENTIS US LLC	PLAVIX
NDA-20839	SUPPL-42	SANOFI AVENTIS US LLC	PLAVIX

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/s/

ALISON L BLAUS
09/14/2009

NORMAN L STOCKBRIDGE
09/14/2009



DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 20-839/S-042

PRIOR APPROVAL SUPPLEMENT

Sanofi-adventis US LLC
Attention: Colleen M. Davenport, Ph.D.
Director, Regulatory Development
Corporate Regulatory Affairs
9 Great Valley Parkway
P.O. Box 3026
Malvern, PA 19355

Dear Dr. Davenport:

We have received your supplemental new drug application submitted under section 505(b)(1) of the Federal Food, Drug, and Cosmetic Act for the following:

Name of Drug Product: Plavix[®] (SR25990C)

NDA Number: 20-839

Supplement number: S-042

Date of supplement: June 17, 2009

Date of receipt: June 17, 2009

This supplemental application proposes revisions to the Prescribing Information in accordance with the New Content and Format of Labeling requirements.

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on August 16, 2009 in accordance with 21 CFR 314.101(a).

Please cite the application number listed above at the top of the first page of all submissions to this application. Send all submissions, electronic or paper, including those sent by overnight mail or courier, to the following address:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Cardiovascular and Renal Products
5901-B Ammendale Road
Beltsville, MD 20705-1266

If you have questions, please contact:

Ms. Alison Blaus
Regulatory Health Project Manager
(301) 796-1138

Sincerely,

{See appended electronic signature page}

Edward Fromm, RPh., RAC
Chief, Project Management Staff
Division of Cardiovascular and Renal Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

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/s/

EDWARD J FROMM

08/06/2009

see revision