CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

20-839/S-038

Trade Name: Plavix 75mg Tablets

Generic Name: clopidogrel bisulfate

Sponsor: Sanofi-aventis U.S., LLC

Approval Date: September 20, 2007

Purpose: A new 300mg loading dose

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

20-839/S-038

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APPLICATION NUMBER:

20-839/S-038

APPROVAL LETTER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 20-839/S-038

Sanofi-aventis U.S., LLC
Attention: Matthew R. Boyd, R.Ph., M.B.A.
Director, US Regulatory Affairs, Marketed Product
55 Corporate Drive
PO Box 5925
Bridgewater, NJ 08807-5925

Dear Mr. Boyd:

Please refer to your supplemental new drug application dated May 21, 2007, received May 22, 2007, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Plavix (clopidogrel bisulfate) 75 mg Tablets.

We also acknowledge your submission dated September 10, 2007.

This supplemental new drug application provides for a new 300 mg loading dose.

We have completed our review of this supplemental new drug application. It is approved, effective on the date of this letter, for use as recommended in the final printed labeling (FPL) submitted on May 21, 2007; however, please note the following:

- Clopidogrel's inactive metabolite (SR26334) was used to demonstrate bioequivalence between the two dosage strengths. The Agency does not usually consider this an acceptable method to test for bioequivalence between the two formulations since prior pharmacokinetic studies conducted assessed the pharmacodynamics and the pharmacokinetics of Plavix due to the metabolite being inactive; however, utilizing the inactive metabolite in this study seems acceptable since:
    - the new strength tablet given is the same strength given previously clinically as the four 75 mg tablets, and
    - the change in rate of absorption will not make a significant difference as this will be administered as a one-time dose for the indication of acute coronary syndrome to be administered with aspirin followed by a daily 75 mg dose of Plavix and aspirin.

- Establishment of bioequivalence between the new dosage strength of 300 mg and four 75 mg tablets of Plavix has been made; however, this method of establishing bioequivalence will not be acceptable under any other setting. In the future, bioequivalence will be based on the parent drug due to analytical methods now being able to measure the parent drug, unlike when Plavix was initially approved when only the inactive metabolite was measurable.

Please note that a two (2) year expiry period is granted for the new 300 mg strength of Plavix (clopidogrel bisulfate) when stored at 25°C (77°F) in the approved container closure system.

In addition, submit three copies of the introductory promotional materials that you propose to use for this product. Submit all proposed materials in draft or mock-up form, not final print. Send one copy to the Division of Cardiovascular and Renal Products and two copies of both the promotional materials and the package insert directly to:

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

If you issue a letter communicating important information about this drug product (i.e., a "Dear Health Care Professional" letter), we request that you submit a copy of the letter to this NDA and a copy to the following address:

MEDWATCH
Food and Drug Administration
5515 Security Lane
HFD-001, Suite 5100
Rockville, MD 20852

We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 314.80 and 314.81.

If you have any questions, please call:

Ms. Meg Pease-Fye, M.S.
Regulatory Project Manager
(301) 796-1130

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

Attached:
Approved package insert

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

/s/

Norman Stockbridge
9/20/2007 04:26:36 PM

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

20-839/S-038

LABELING

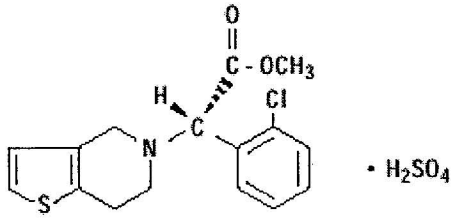
Rx only

PLAVIX®
clopidogrel bisulfate tablets

DESCRIPTION

Plavix (clopidogrel bisulfate) is an inhibitor of ADP-induced platelet aggregation acting by direct inhibition of adenosine diphosphate (ADP) binding to its receptor and of the subsequent ADP-mediated activation of the glycoprotein GPIIb/IIIa complex. Chemically it is methyl (+)-(*S*)-α-(2-chlorophenyl)-6,7-dihydrothieno[3,2-c]pyridine-5(4*H*)-acetate sulfate (1:1). The empirical formula of clopidogrel bisulfate is $C_{16}H_{16}ClNO_2S \cdot H_2SO_4$ 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.

CLINICAL PHARMACOLOGY

Mechanism of Action

Clopidogrel is an inhibitor of platelet aggregation. A variety of drugs that inhibit platelet function have been shown to decrease morbid events in people with established cardiovascular atherosclerotic disease as evidenced by stroke or transient ischemic attacks, myocardial infarction, unstable angina or the need for vascular bypass or angioplasty. This indicates that platelets participate in the initiation and/or evolution of these events and that inhibiting them can reduce the event rate.

Pharmacodynamic Properties

Clopidogrel selectively inhibits the binding of adenosine diphosphate (ADP) to its platelet receptor and the subsequent ADP-mediated activation of the glycoprotein GPIIb/IIIa complex, thereby inhibiting platelet aggregation. Biotransformation of clopidogrel is necessary to produce inhibition of platelet

aggregation, but an active metabolite responsible for the activity of the drug has not been isolated. Clopidogrel also inhibits platelet aggregation induced by agonists other than ADP by blocking the amplification of platelet activation by released ADP. Clopidogrel does not inhibit phosphodiesterase activity.

Clopidogrel acts by irreversibly modifying the platelet ADP receptor. Consequently, platelets exposed to clopidogrel are affected for the remainder of their lifespan.

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.

Pharmacokinetics and Metabolism

After repeated 75-mg oral doses of clopidogrel (base), plasma concentrations of the parent compound, which has no platelet inhibiting effect, are very low and are generally below the quantification limit (0.00025 mg/L) beyond 2 hours after dosing. Clopidogrel is extensively metabolized by the liver. The main circulating metabolite is the carboxylic acid derivative, and it too has no effect on platelet aggregation. It represents about 85% of the circulating drug-related compounds in plasma.

Following an oral dose of ^{14}C-labeled clopidogrel in humans, approximately 50% was excreted in the urine and approximately 46% in the feces in the 5 days after dosing. The elimination half-life of the main circulating metabolite was 8 hours after single and repeated administration. Covalent binding to platelets accounted for 2% of radiolabel with a half-life of 11 days.

Effect of Food: Administration of Plavix (clopidogrel bisulfate) with meals did not significantly modify the bioavailability of clopidogrel as assessed by the pharmacokinetics of the main circulating metabolite.

Absorption and Distribution: Clopidogrel is rapidly absorbed after oral administration of repeated doses of 75 mg clopidogrel (base), with peak plasma levels ($\cong$3 mg/L) of the main circulating metabolite occurring approximately 1 hour after dosing. The pharmacokinetics of the main circulating metabolite are linear (plasma concentrations increased in proportion to dose) in the dose range of 50 to 150 mg of clopidogrel. Absorption is at least 50% based on urinary excretion of clopidogrel-related metabolites.

Clopidogrel and the main circulating metabolite bind reversibly *in vitro* to human plasma proteins (98% and 94%, respectively). The binding is nonsaturable *in vitro* up to a concentration of 100 µg/mL.

Metabolism and Elimination: *In vitro* and *in vivo*, clopidogrel undergoes rapid hydrolysis into its carboxylic acid derivative. In plasma and urine, the glucuronide of the carboxylic acid derivative is also observed.

Special Populations

Geriatric Patients: Plasma concentrations of the main circulating metabolite are significantly higher in elderly ($\geq$75 years) compared to young healthy volunteers but these higher plasma levels were not associated with differences in platelet aggregation and bleeding time. No dosage adjustment is needed for the elderly.

Renally Impaired Patients: After repeated doses of 75 mg Plavix per day, plasma levels of the main circulating metabolite were lower in patients with severe renal impairment (creatinine clearance from 5 to 15 mL/min) compared to subjects with moderate renal impairment (creatinine clearance 30 to 60 mL/min) or healthy subjects. Although inhibition of ADP-induced platelet aggregation was lower (25%) than that observed in healthy volunteers, the prolongation of bleeding time was similar to healthy volunteers receiving 75 mg of Plavix per day.

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

Race: Pharmacokinetic differences due to race have not been studied.

CLINICAL STUDIES

The clinical evidence for the efficacy of Plavix is derived from four double-blind trials involving 81,090 patients: the CAPRIE study (Clopidogrel vs. Aspirin in Patients at Risk of Ischemic Events), a comparison of Plavix to aspirin, and the CURE (Clopidogrel in Unstable Angina to Prevent Recurrent Ischemic Events), the COMMIT/CCS-2 (Clopidogrel and Metoprolol in Myocardial Infarction Trial / Second Chinese Cardiac Study) studies comparing Plavix to placebo, both given in combination with aspirin and other standard therapy and CLARITY-TIMI 28 (Clopidogrel as Adjunctive Reperfusion Therapy – Thrombolysis in Myocardial Infarction).

Recent Myocardial Infarction (MI), Recent Stroke or Established Peripheral Arterial Disease

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 months) with at least a week of residual neurological signs; or 3) objectively 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 nonvascul causes were all classified as vascular.

Table 1: Outcome Events in the CAPRIE Primary Analysis

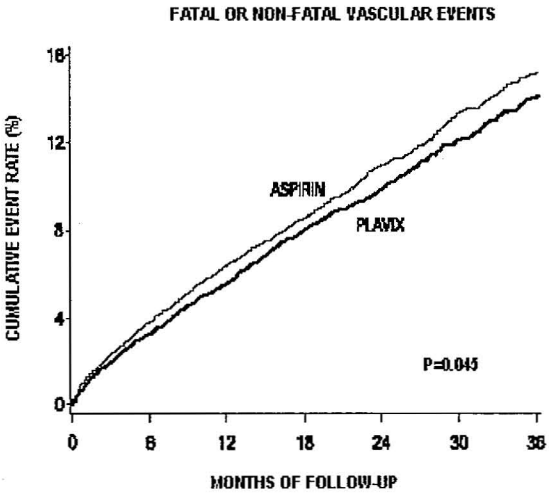
	Plavix	aspirin
Patients	9599	9586
IS (fatal or not)	438 (4.6%)	461 (4.8%)
MI (fatal or not)	275 (2.9%)	333 (3.5%)
Other vascular death	226 (2.4%)	226 (2.4%)
Total	939 (9.8%)	1020 (10.6%)

As shown in the table, Plavix (clopidogrel bisulfate) was associated with a lower incidence of outcome events of every kind. The overall 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 again lower in the Plavix group.

The curves showing the overall event rate are shown in Figure 1. The event curves separated early and continued to diverge over the 3-year follow-up period.

Figure 1: Fatal or Non-Fatal Vascular Events in the CAPRIE Study



Although the statistical significance favoring Plavix over aspirin was marginal (P=0.045), and represents the result of a single trial that has not been replicated, the comparator drug, aspirin, is itself effective (vs. placebo) in reducing cardiovascular events in patients with recent myocardial infarction or stroke. Thus, the difference between Plavix and placebo, although not measured directly, 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.

In the meta-analyses of studies of aspirin vs. placebo in patients similar to those in CAPRIE, aspirin was associated with a reduced incidence of thrombotic events. There was a suggestion of heterogeneity in these studies too, with the effect strongest in patients with a history of myocardial infarction, weaker in patients with a history of stroke, and not discernible in patients with a history of peripheral vascular disease. With respect to the inferred comparison of Plavix to placebo, there is no indication of heterogeneity.

Acute Coronary Syndrome

The CURE study included 12,562 patients with acute coronary syndrome without ST segment elevation (unstable angina or non-Q-wave myocardial infarction) 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 segment 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/day) 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 (9.30%) in the Plavix-treated group and 719 (11.41%) in the placebo-treated group, a 20% relative risk reduction (95% CI of 10%-28%; p=0.00009) for the Plavix-treated group (see Table 2).

At the end of 12 months, the number of patients experiencing the co-primary outcome (CV death, MI, stroke or refractory ischemia) was 1035 (16.54%) in the Plavix-treated group and 1187 (18.83%) in the placebo-treated group, a 14% relative risk reduction (95% CI of 6%-21%, p=0.0005) for the Plavix-treated group (see Table 2).

In the Plavix-treated group, each component of the two primary endpoints (CV death, MI, stroke, refractory ischemia) occurred less frequently than in the placebo-treated group.

Table 2: Outcome Events in the CURE Primary Analysis

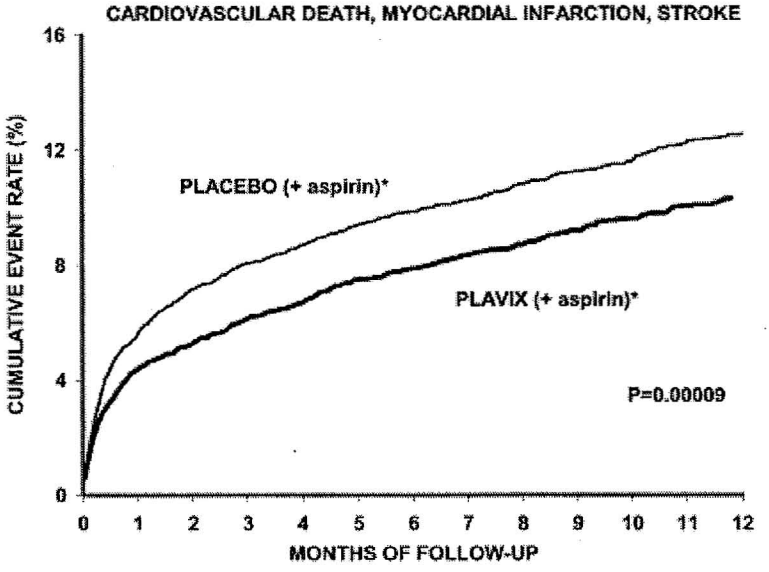
Outcome	Plavix (+ aspirin)* (n=6259)		Placebo (+ aspirin)* (n=6303)	Relative Risk Reduction (%) (95% CI)
Primary outcome (Cardiovascular death, MI, Stroke)	582	(9.3%)	719 (11.4%)	20% (10.3, 27.9) P=0.00009
Co-primary outcome (Cardiovascular death, MI, Stroke, Refractory Ischemia)	1035	(16.5%)	1187 (18.8%)	14% (6.2, 20.6) P=0.00052
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)
Refractory ischemia	544	(8.7%)	587 (9.3%)	7% (-4.0, 18.0)

* 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.

The benefits of Plavix (clopidogrel bisulfate) were maintained throughout the course of the trial (up to 12 months).

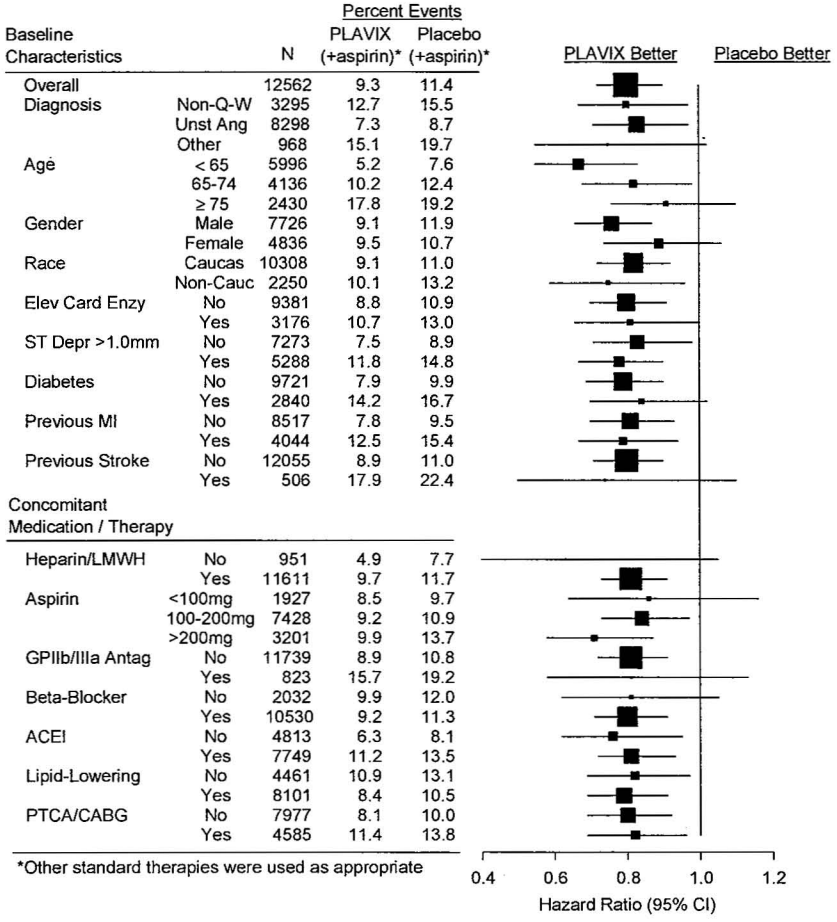
Figure 2: Cardiovascular Death, Myocardial Infarction, and Stroke in the CURE Study



*Other standard therapies were used as appropriate

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 3. The benefits associated with Plavix were independent of the use of other acute and long-term cardiovascular therapies, including heparin/LMWH (low molecular weight heparin), IV 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 3: 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%, P=0.0001), 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%, P=0.003). The use of Plavix in CURE did not impact 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%, P=0.1658).

In patients with ST-segment elevation acute myocardial infarction, safety and efficacy of clopidogrel have been evaluated in two randomized, placebo-controlled, double-blind studies, COMMIT- a large outcome study conducted in China - and CLARITY- a supportive study of a surrogate endpoint conducted internationally.

The randomized, double-blind, placebo-controlled, 2x2 factorial design COMMIT trial included 45,852 patients presenting within 24 hours of the onset of the symptoms of suspected 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/day) or placebo, in combination with aspirin (162 mg/day), for 28 days or until hospital discharge whichever came first.

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

The patient population included 28% women, 58% patients ≥60 years (26% patients ≥70 years) and 55% patients who received thrombolytics, 68% received ace-inhibitors, and only 3% had percutaneous coronary intervention (PCI).

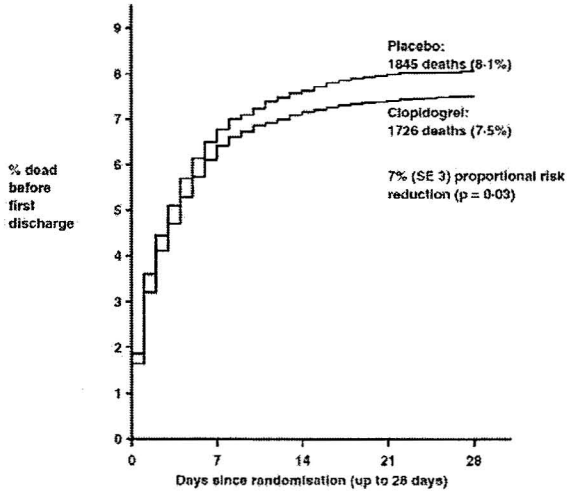
As shown in Table 3 and Figures 4 and 5 below, Plavix significantly reduced the relative risk of death from any cause by 7% (p = 0.029), and the relative risk of the combination of re-infarction, stroke or death by 9% (p = 0.002).

Table 3: 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

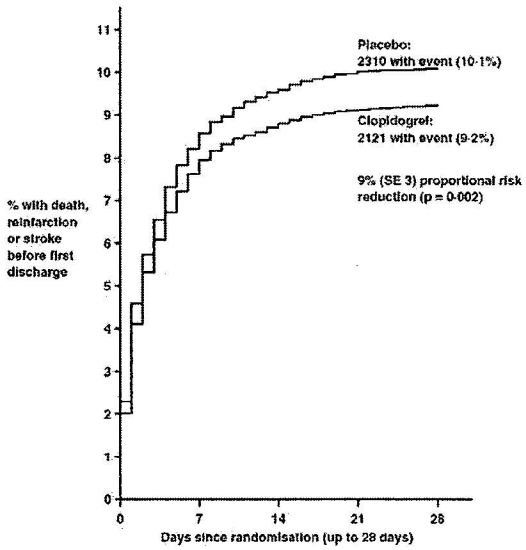
*The difference between the composite endpoint and the sum of death+non-fatal MI+non-fatal stroke indicates that 9 patients (2 clopidogrel and 7 placebo) suffered both a non-fatal stroke and a non-fatal MI.
** Non-fatal MI and non-fatal stroke exclude patients who died (of any cause).

Figure 4: Cumulative Event Rates for Death in the COMMIT Study*



* All treated patients received aspirin.

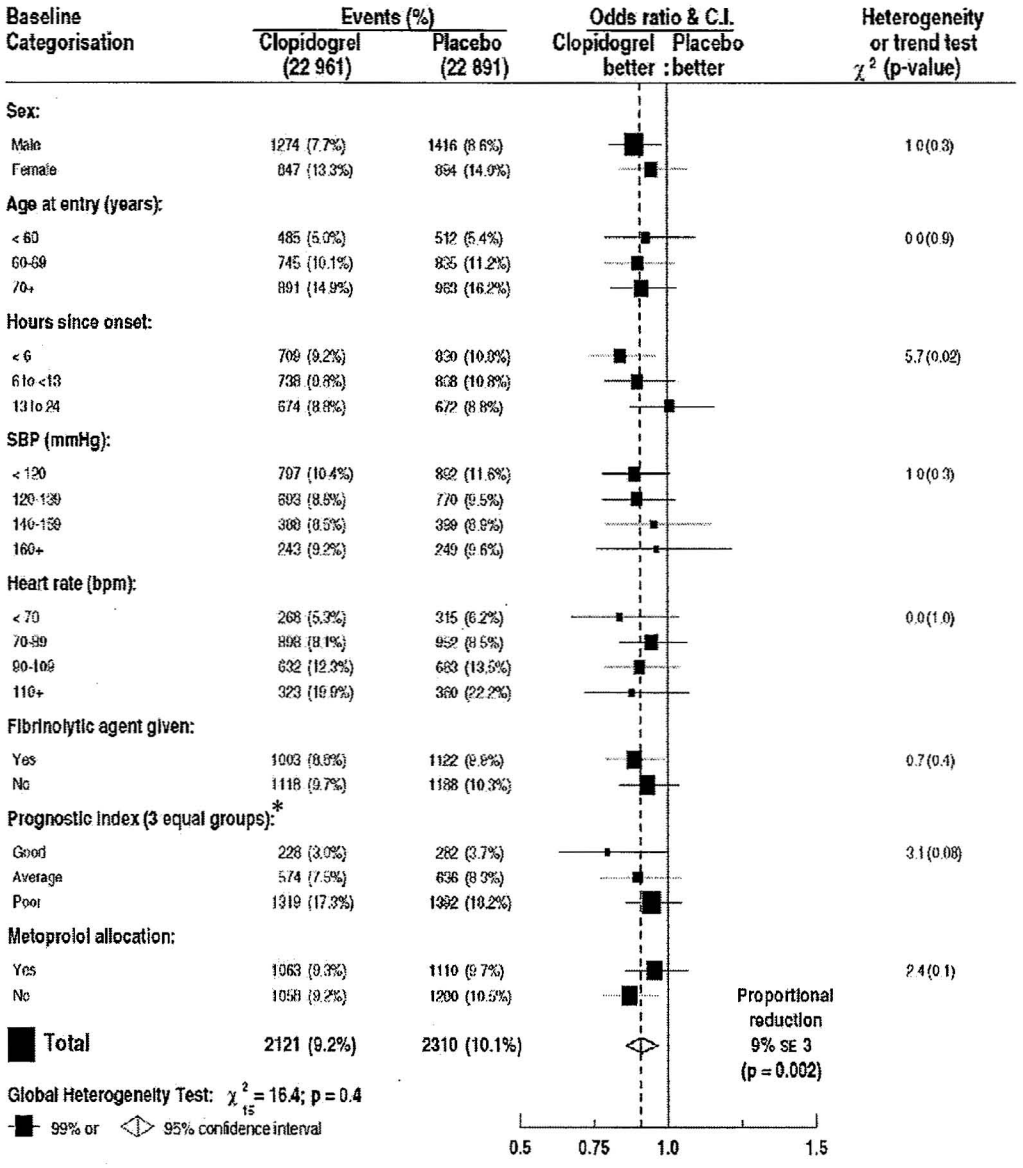
Figure 5: Cumulative Event Rates for the Combined Endpoint Re-Infarction, Stroke or Death in the COMMIT Study *



* All treated patients received aspirin.

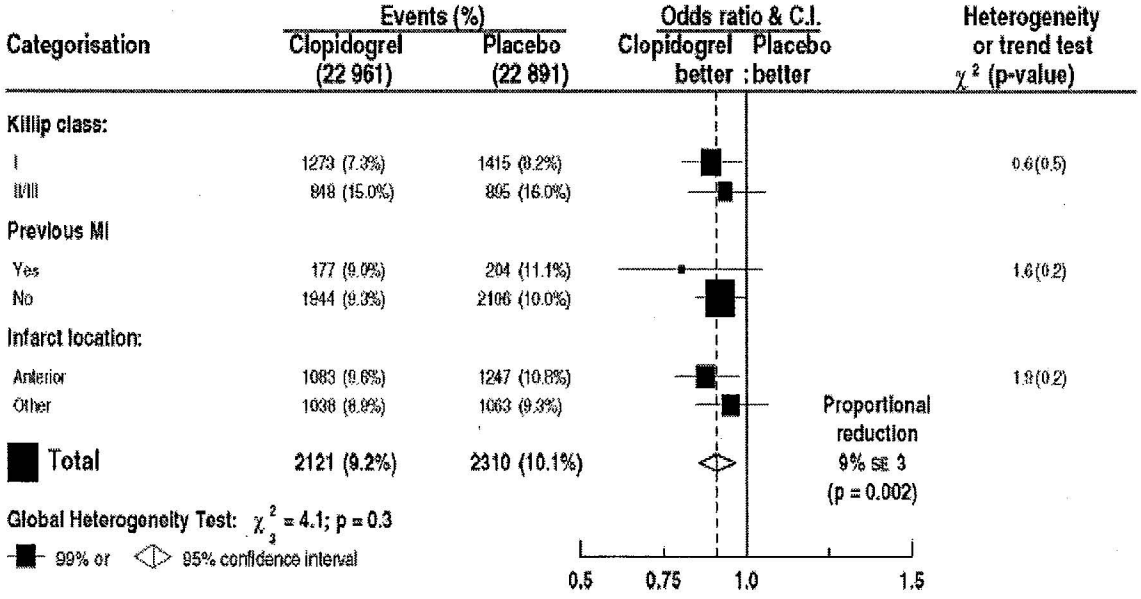
The effect of Plavix did not differ significantly in various pre-specified subgroups as shown in Figure 6. Additionally, the effect was similar in non-prespecified subgroups including those based on infarct location, Killip class or prior MI history (see Figure 7). Such subgroup analyses should be interpreted very cautiously.

Figure 6: 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 7: Effects of Adding Plavix to Aspirin in the Non-Prespecified Subgroups in the COMMIT Study



The randomized, double-blind, placebo-controlled CLARITY trial included 3,491 patients, 5% U.S., presenting within 12 hours of the onset of a ST elevation myocardial infarction and planned for thrombolytic therapy. Patients were randomized to receive Plavix (300-mg loading dose, followed by 75 mg/day) or placebo until angiography, discharge, or Day 8. Patients also received aspirin (150 to 325 mg as a loading dose, followed by 75 to 162 mg/day), a fibrinolytic agent and, when appropriate, heparin for 48 hours. The patients were followed for 30 days.

The primary endpoint was the occurrence of the composite of an occluded infarct-related artery (defined as TIMI Flow Grade 0 or 1) on the predischarge angiogram, or death or recurrent myocardial infarction by the time of the start of coronary angiography.

The patient population was mostly Caucasian (89.5%) and included 19.7% women and 29.2% patients ≥65 years. A total of 99.7% of patients received fibrinolytics (fibrin specific: 68.7%, non-fibrin specific: 31.1%), 89.5% heparin, 78.7% beta-blockers, 54.7% ACE inhibitors and 63% statins.

The number of patients who reached the primary endpoint was 262 (15.0%) in the Plavix-treated group and 377 (21.7%) in the placebo group, but most of the events related to the surrogate endpoint of vessel patency.

Table 4: Event Rates for the Primary Composite Endpoint in the CLARITY Study

	Clopidogrel 1752	Placebo 1739	OR	95% CI
Number (%) of patients reporting the composite endpoint	262 (15.0%)	377 (21.7%)	0.64	0.53, 0.76
Occluded IRA				

N (subjects undergoing angiography)	1640	1634		
n (%) patients reporting endpoint	192 (11.7%)	301 (18.4%)	0.59	0.48, 0.72
Death				
n (%) patients reporting endpoint	45 (2.6%)	38 (2.2%)	1.18	0.76, 1.83
Recurrent MI				
n (%) patients reporting endpoint	44 (2.5%)	62 (3.6%)	0.69	0.47, 1.02

*The total number of patients with a component event (occluded IRA, death, or recurrent MI) is greater than the number of patients with a composite event because some patients had more than a single type of component event.

INDICATIONS AND USAGE

Plavix (clopidogrel bisulfate) is indicated for the reduction of atherothrombotic events as follows:

- **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.

- **Acute Coronary Syndrome**
  For patients with non-ST-segment elevation acute coronary syndrome (unstable angina/non-Q-wave MI) including patients who are to be managed medically and those who are to be managed with percutaneous coronary intervention (with or without stent) or CABG, Plavix has been shown to decrease the rate of a combined endpoint of cardiovascular death, MI, or stroke as well as the rate of a combined endpoint of cardiovascular death, MI, stroke, or refractory ischemia.

  For patients with ST-segment elevation acute myocardial infarction, 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. This benefit is not known to pertain to patients who receive primary angioplasty.

CONTRAINDICATIONS

The use of Plavix is contraindicated in the following conditions:

Hypersensitivity to the drug substance or any component of the product.
Active pathological bleeding such as peptic ulcer or intracranial hemorrhage.

WARNINGS

Thrombotic thrombocytopenic purpura (TTP):
TTP has been reported rarely following use of Plavix, sometimes after a short exposure (<2 weeks). TTP is a serious condition that can be fatal and 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**.)

PRECAUTIONS

General

Plavix prolongs the bleeding time and therefore should be used with caution in patients who may be at risk of increased bleeding from trauma, surgery, or other pathological conditions (particularly

gastrointestinal and intraocular). If a patient is to undergo elective surgery and an antiplatelet effect is not desired, Plavix should be discontinued 5 days prior to surgery.

Due to the risk of bleeding and undesirable hematological effects, blood cell count determination and/or other appropriate testing should be promptly considered, whenever such suspected clinical symptoms arise during the course of treatment (see **ADVERSE REACTIONS**).

In patients with recent TIA or stroke who are at high risk of 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.

GI Bleeding: In CAPRIE, Plavix was associated with a rate of gastrointestinal bleeding of 2.0%, vs. 2.7% on aspirin. In CURE, the incidence of major gastrointestinal bleeding was 1.3% vs. 0.7% (Plavix + aspirin vs. placebo + aspirin, respectively). Plavix should be used with caution in patients who have lesions with a propensity to bleed (such as ulcers). Drugs that might induce such lesions should be used with caution in patients taking Plavix.

Use in Hepatically Impaired Patients: Experience is limited in patients with severe hepatic disease, who may have bleeding diatheses. Plavix should be used with caution in this population.

Use in Renally-impaired Patients: Experience is limited in patients with severe renal impairment. Plavix should be used with caution in this population.

Information for Patients

Patients should be told that it may take them longer than usual to stop bleeding, that they may bruise and/or bleed more easily when they take Plavix or Plavix combined with aspirin, and that they should report any unusual bleeding to their physician. Patients should inform physicians and dentists that they are taking Plavix and/or any other product known to affect bleeding before any surgery is scheduled and before any new drug is taken.

Drug Interactions

Study of specific drug interactions yielded the following results:
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.

Nonsteroidal Anti-Inflammatory Drugs (NSAIDs): In healthy volunteers receiving naproxen, concomitant administration of Plavix was associated with increased occult gastrointestinal blood loss. NSAIDs and Plavix should be coadministered with caution.

Warfarin: Because of the increased risk of bleeding, the concomitant administration of warfarin with Plavix should be undertaken with caution. (See **PRECAUTIONS–General**.)

Other Concomitant Therapy: No clinically significant pharmacodynamic interactions were observed when Plavix was coadministered with **atenolol, nifedipine,** or both atenolol and nifedipine. The pharmacodynamic activity of Plavix was also not significantly influenced by the coadministration of **phenobarbital, cimetidine** or **estrogen**.

The pharmacokinetics of **digoxin** or **theophylline** were not modified by the coadministration of Plavix (clopidogrel bisulfate).

At high concentrations *in vitro*, clopidogrel inhibits P_{450} (2C9). Accordingly, Plavix may interfere with the metabolism of **phenytoin, tamoxifen, tolbutamide, warfarin, torsemide, fluvastatin,** and many **non-steroidal anti-inflammatory agents,** but there are no data with which to predict the magnitude of these interactions. Caution should be used when any of these drugs is coadministered with Plavix.

In addition to the above specific interaction studies, patients entered into clinical trials with Plavix received a variety of concomitant medications including **diuretics, beta-blocking agents, angiotensin converting enzyme inhibitors, calcium antagonists, cholesterol lowering agents, coronary vasodilators, antidiabetic agents** (including **insulin**), **thrombolytics, heparins** (unfractionated and LMWH), **GPIIb/IIIa antagonists, antiepileptic agents** and **hormone replacement therapy** without evidence of clinically significant adverse interactions.

There are no data on the concomitant use of oral anticoagulants, non study oral anti-platelet drugs and chronic NSAIDs with clopidogrel.

Drug/Laboratory Test Interactions

None known.

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/m^2 basis).

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 on a mg/m^2 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.

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, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the nursing woman.

Pediatric Use

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

Geriatric Use

Of the total number of subjects in the CAPRIE, CURE and CLARITY 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 3 and 6 for the CURE and COMMIT trials, respectively (see **CLINICAL STUDIES**). The observed risk of bleeding events with clopidogrel plus aspirin versus placebo plus aspirin by age category is provided in Tables 5 and 6 for the CURE and COMMIT trials, respectively (see **ADVERSE REACTIONS**).

ADVERSE REACTIONS

Plavix has been evaluated for safety in more than 42,000 patients, including over 9,000 patients treated for 1 year or more. The clinically important adverse events observed in CAPRIE, CURE, CLARITY and COMMIT are discussed below.

The overall tolerability of Plavix in CAPRIE was similar to that of aspirin regardless of age, gender and race, with an approximately equal incidence (13%) of patients withdrawing from treatment because of adverse reactions.

Hemorrhagic: In CAPRIE patients receiving Plavix, gastrointestinal hemorrhage occurred at a rate of 2.0%, and required hospitalization in 0.7%. In patients receiving aspirin, the corresponding rates were 2.7% and 1.1%, respectively. The incidence of intracranial hemorrhage was 0.4% for Plavix compared to 0.5% for aspirin.

In CURE, Plavix use with aspirin was associated with an increase in bleeding compared to placebo with aspirin (see Table 5). There was an excess in major bleeding in patients receiving Plavix plus aspirin compared with placebo plus aspirin, primarily gastrointestinal and at puncture sites. The incidence of intracranial hemorrhage (0.1%), and fatal bleeding (0.2%), were the same in both groups.

The overall incidence of bleeding is described in Table 5 for patients receiving both Plavix and aspirin in CURE.

Table 5: 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/LMWH, and the rate of bleeding in these patients was similar to the overall results.

There was no excess in major bleeds within seven days after coronary bypass graft surgery in patients who stopped therapy more than five days prior to surgery (event rate 4.4% Plavix + aspirin; 5.3% placebo + aspirin). In patients who remained on therapy within five days of bypass graft surgery, the event rate was 9.6% for Plavix + aspirin, and 6.3% for placebo + aspirin.

In CLARITY, the incidence of major bleeding (defined as intracranial bleeding or bleeding associated with a fall in hemoglobin > 5 g/dL) was similar between groups (1.3% versus 1.1% in the Plavix + aspirin and in the placebo + aspirin groups, respectively). This was consistent across subgroups of patients defined by baseline characteristics, and type of fibrinolytics or heparin therapy. The incidence of fatal bleeding (0.8% versus 0.6% in the Plavix + aspirin and in the placebo + aspirin groups, respectively) and intracranial hemorrhage (0.5% versus 0.7%, respectively) was low and similar in both groups.

The overall rate of noncerebral major bleeding or cerebral bleeding in COMMIT was low and similar in both groups as shown in Table 6 below.

Table 6: Number (%) of Patients with Bleeding Events in COMMIT

Type of bleeding	Plavix (+ aspirin) (N=22961)	Placebo (+ aspirin) (N=22891)	P-value
Major* noncerebral or cerebral bleeding**	134 (0.6%)	125 (0.5%)	0.59
Major noncerebral	82 (0.4%)	73 (0.3%)	0.48
Fatal	36 (0.2%)	37 (0.2%)	0.90
Hemorrhagic stroke	55 (0.2%)	56 (0.2%)	0.91
Fatal	39 (0.2%)	41 (0.2%)	0.81
Other noncerebral bleeding (non-major)	831 (3.6%)	721 (3.1%)	0.005
Any noncerebral bleeding	896 (3.9%)	777 (3.4%)	0.004

* Major bleeds are 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%.

Adverse events occurring in ≥2.5% of patients on Plavix in the CAPRIE controlled clinical trial are shown below regardless of relationship to Plavix. The median duration of therapy was 20 months, with a maximum of 3 years.

Table 7: Adverse Events Occurring in ≥2.5% of Plavix Patients in CAPRIE

	% Incidence (% Discontinuation)	
Body System **Event**	**Plavix [n=9599]**	**Aspirin [n=9586]**
Body as a Whole – general disorders		
Chest Pain	8.3 (0.2)	8.3 (0.3)
Accidental/Inflicted Injury	7.9 (0.1)	7.3 (0.1)
Influenza-like symptoms	7.5 (<0.1)	7.0 (<0.1)
Pain	6.4 (0.1)	6.3 (0.1)
Fatigue	3.3 (0.1)	3.4 (0.1)
Cardiovascular disorders, general		
Edema	4.1 (<0.1)	4.5 (<0.1)
Hypertension	4.3 (<0.1)	5.1 (<0.1)
Central & peripheral nervous system disorders		
Headache	7.6 (0.3)	7.2 (0.2)
Dizziness	6.2 (0.2)	6.7 (0.3)
Gastrointestinal system disorders		
Any event	27.1(3.2)	29.8 (4.0)
Abdominal pain	5.6 (0.7)	7.1 (1.0)
Dyspepsia	5.2 (0.6)	6.1 (0.7)
Diarrhea	4.5 (0.4)	3.4 (0.3)
Nausea	3.4 (0.5)	3.8 (0.4)
Metabolic & nutritional disorders		
Hypercholesterolemia	4.0 (0)	4.4 (<0.1)
Musculo-skeletal system disorders		
Arthralgia	6.3 (0.1)	6.2 (0.1)
Back Pain	5.8 (0.1)	5.3 (<0.1)

Platelet, bleeding, & clotting disorders		
Purpura/Bruise	5.3 (0.3)	3.7 (0.1)
Epistaxis	2.9 (0.2)	2.5 (0.1)
Psychiatric disorders		
Depression	3.6 (0.1)	3.9 (0.2)
Respiratory system disorders		
Upper resp tract infection	8.7 (<0.1)	8.3 (<0.1)
Dyspnea	4.5 (0.1)	4.7 (0.1)
Rhinitis	4.2 (0.1)	4.2 (<0.1)
Bronchitis	3.7 (0.1)	3.7 (0)
Coughing	3.1 (<0.1)	2.7(<0.1)
Skin & appendage disorders		
Any event	15.8 (1.5)	13.1 (0.8)
Rash	4.2 (0.5)	3.5 (0.2)
Pruritus	3.3 (0.3)	1.6 (0.1)
Urinary system disorders		
Urinary tract infection	3.1 (0)	3.5 (0.1)

No additional clinically relevant events to those observed in CAPRIE with a frequency ≥2.5%, have been reported during the CURE and CLARITY controlled studies. COMMIT collected only limited safety data.

Other adverse experiences of potential importance occurring in 1% to 2.5% of patients receiving Plavix (clopidogrel bisulfate) in the controlled clinical trials are listed below regardless of relationship to Plavix. In general, the incidence of these events was similar to that in patients receiving aspirin (in CAPRIE) or placebo + aspirin (in the other clinical trials).

Autonomic Nervous System Disorders: Syncope, Palpitation. *Body as a Whole-general disorders:* Asthenia, Fever, Hernia. *Cardiovascular disorders:* Cardiac failure. *Central and peripheral nervous system disorders:* Cramps legs, Hypoaesthesia, Neuralgia, Paraesthesia, Vertigo. *Gastrointestinal system disorders:* Constipation, Vomiting. *Heart rate and rhythm disorders:* Fibrillation atrial. *Liver and biliary system disorders:* Hepatic enzymes increased. *Metabolic and nutritional disorders:* Gout, hyperuricemia, non-protein nitrogen (NPN) increased. *Musculo-skeletal system disorders:* Arthritis, Arthrosis. *Platelet, bleeding & clotting disorders:* GI hemorrhage, hematoma, platelets decreased. *Psychiatric disorders:* Anxiety, Insomnia. *Red blood cell disorders:* Anemia. *Respiratory system disorders:* Pneumonia, Sinusitis. *Skin and appendage disorders:* Eczema, Skin ulceration. *Urinary system disorders:* Cystitis. *Vision disorders:* Cataract, Conjunctivitis.

Other potentially serious adverse events which may be of clinical interest but were rarely reported (<1%) in patients who received Plavix in the controlled clinical trials are listed below regardless of relationship to Plavix. In general, the incidence of these events was similar to that in patients receiving aspirin (in CAPRIE) or placebo + aspirin (in the other clinical trials).

Body as a whole: Allergic reaction, necrosis ischemic. *Cardiovascular disorders:* Edema generalized. *Gastrointestinal system disorders:* Peptic, gastric or duodenal ulcer, gastritis, gastric ulcer perforated, gastritis hemorrhagic, upper GI ulcer hemorrhagic. *Liver and Biliary system disorders:* Bilirubinemia, hepatitis infectious, liver fatty. *Platelet, bleeding and clotting disorders:* hemarthrosis, hematuria, hemoptysis, hemorrhage intracranial, hemorrhage retroperitoneal, hemorrhage of operative wound, ocular hemorrhage, pulmonary hemorrhage, purpura allergic, thrombocytopenia. *Red blood cell disorders:* Anemia aplastic, anemia hypochromic. *Reproductive disorders, female:* Menorrhagia. *Respiratory*

system disorders: Hemothorax. *Skin and appendage disorders:* Bullous eruption, rash erythematous, rash maculopapular, urticaria. *Urinary system disorders*: Abnormal renal function, acute renal failure. *White cell and reticuloendothelial system disorders:* Agranulocytosis, granulocytopenia, leukemia, leukopenia, neutropenia.

Postmarketing Experience

The following events have been reported spontaneously from worldwide postmarketing experience:

- *Body as a whole:*
  - hypersensitivity reactions, anaphylactoid reactions, serum sickness
- *Central and Peripheral Nervous System disorders:*
  - confusion, hallucinations, taste disorders
- *Hepato-biliary disorders:*
  - abnormal liver function test, hepatitis (non-infectious), acute liver failure
- *Platelet, Bleeding and Clotting disorders:*
  - cases of bleeding with fatal outcome (especially intracranial, gastrointestinal and retroperitoneal hemorrhage)
  - thrombotic thrombocytopenic purpura (TTP) – some cases with fatal outcome – (see **WARNINGS**)
  - agranulocytosis, aplastic anemia/pancytopenia
  - conjunctival, ocular and retinal bleeding
- *Respiratory, thoracic and mediastinal disorders:*
  - bronchospasm, interstitial pneumonitis
- *Skin and subcutaneous tissue disorders:*
  - angioedema, erythema multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis, lichen planus
- *Renal and urinary disorders:*
  - glomerulopathy, increased creatinine levels
- *Vascular disorders:*
  - vasculitis, hypotension
- *Gastrointestinal disorders:*
  - colitis (including ulcerative or lymphocytic colitis), pancreatitis, stomatitis
- *Musculoskeletal, connective tissue and bone disorders:*
  - myalgia

OVERDOSAGE

Overdose following clopidogrel administration may lead to prolonged bleeding time and subsequent 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 (in baboons), prostration, difficult breathing, and gastrointestinal hemorrhage in all species.

Recommendations About Specific Treatment:

Based on biological plausibility, platelet transfusion may be appropriate to reverse the pharmacological effects of Plavix if quick reversal is required.

DOSAGE AND ADMINISTRATION

Recent MI, Recent Stroke, or Established Peripheral Arterial Disease

The recommended daily dose of Plavix is 75 mg once daily.

Acute Coronary Syndrome

For patients with non-ST-segment elevation acute coronary syndrome (unstable angina/non-Q-wave MI), Plavix should be initiated with a single 300-mg loading dose and then continued at 75 mg once daily. Aspirin (75 mg-325 mg once daily) should be initiated and continued in combination with Plavix. In CURE, most patients with Acute Coronary Syndrome also received heparin acutely (see **CLINICAL STUDIES**).

For patients with ST-segment elevation acute myocardial infarction, the recommended dose of Plavix is 75 mg once daily, administered in combination with aspirin, with or without thrombolytics. Plavix may be initiated with or without a loading dose (300 mg was used in CLARITY; see **CLINICAL STUDIES**).

Plavix can be administered with or without food.

No dosage adjustment is necessary for elderly patients or patients with renal disease. (See **Clinical Pharmacology: Special Populations.**)

HOW SUPPLIED

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 63653-1332-1 unit-dose packages of 4
NDC 63653-1332-2 unit-dose packages of 30
NDC 63653-1332-3 unit-dose packages of 100

Storage

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

Distributed by:
Bristol-Myers Squibb/Sanofi Pharmaceuticals Partnership
Bridgewater, NJ 08807

sanofi aventis

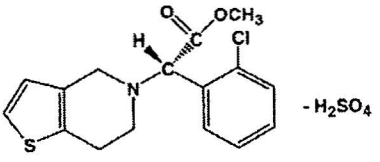
Bristol-Myers Squibb Company

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

20-839/S-038

CHEMISTRY REVIEW(S)

CHEMIST'S REVIEW	1. ORGANIZATION: PME	2. NDA Number 20-839
3. Name and Address of Applicant (City & State) Sanofi-Aventis U.S. LLC 55 Corporate Drive Bridgewater, NJ 08807		4. Supplement(s) Number(s) Date(s) SE2-038 5/21/07
5. Drug Name Plavix®	6. Nonproprietary Name Clopidogrel bisulfate	7. Amendments - Dates SE2-038 (BC) 9/10/07
Supplement Provides For: the use of new 300 mg strength of Plavix® (clopidogrel bisulfate) tablets as an additional dosage strength to replace the intake of four 75 mg tablets as a loading dose.		
9. Pharmacological Category Prevention of Vascular Ischemia	10. How Dispensed Rx	11. Related NDAs DMF (b) (4) and (b) (4)
12. Dosage Form(s) Tablet	13. Potencies EQ 75 mg base	
Chemical Name and Structure: Methyl (+)-(*S*)- α-(2-chlorophenyl)-6,7-dihydrothieno[3,2-c] pyridine-5(4*H*)acetate sulfate (1:1)  Molecular Formula: $C_{16}H_{16}ClNO_2S.\ H_2SO_4$ Molecular Weight: 419.9 (bisulfate) and 321.8 (base)		15. Records/Reports Current Yes X No Reviewed Yes No X
Comments: This PA supplement is an EDR submission. This supplement is subject of DMF (b) (4) review. This supplement, SE2-038, provides for the use of a new 300 mg strength of Plavix tablets as an additional dosage strength to replace the intake of four 75 mg tablets as a loading dose. The applicant has provided a Letter of Authorization from the DMF holders to incorporate by reference DMF (b) (4) and DMF (b) (4) into any IND and NDA applications submitted by Sanofi-Aventis U.S. LLC. The DMFs (b) (4) and (b) (4) have been reviewed by this reviewer, Kris Raman, Ph.D., dated 2/8/07 and 9/19/07, respectively, and found adequate to support the **NDA 20-839**. Clopidogrel bisulfate (b) (4) manufactured according to DMF (b) (4)/ (b) (4) is acceptable to be as drug substance and as active component in Plavix® tablets.		
17. Conclusions and Recommendations: The Office of Compliance has given an overall acceptable recommendation for the facilities (please see attachment on page 18 – 20). This application is recommended '**Approval**' from CMC perspective.		
18. Reviewer:		
Name Kris Raman, Ph.D.	**Signature**	**Date Completed** 9/18/07, revised 9/19/07

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

/s/

Kris Raman
9/19/2007 03:25:24 PM
CHEMIST

Hasmukh Patel
9/19/2007 03:40:53 PM
CHEMIST
Signed for Dr. James Vidra.

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

20-839/S-038

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW
DIVISION OF PHARMACEUTICAL EVALUATION I

NDA 20-839/SLR038 **SUBMISSION DATE:** May 21, 2007
E-mail September 3, 2007

TYPE:	New 300mg Strength
BRAND NAME:	Plavix®
GENERIC NAME:	Clopidogrel Bisulfate
DOSAGE STRENGTH:	300 mg oral immediate release tablet
INDICATION:	Acute coronary syndrome
SPONSOR:	Sanofi-Synthelabo, Inc. Malverne, PA
PRIMARY REVIEWER:	Lydia Velazquez, Pharm.D.
TEAM LEADER:	Patrick Marroum, Ph.D.

SUBMISSION

Sanofi-Synthelabo, Inc. has submitted a new dosage strength supplement pursuant to Section 505(b) in Title 21 of the CFR.

In the indication of acute coronary syndrome, clopidogrel is to be taken with aspirin with a starting loading dose of 300 mg. This supplement application provides for the use of a new 300 mg strength Plavix® tablet as an additional dosage strength to replace the administered four 75 mg tablets as the loading dose.

The purpose of this review is to determine if the submitted bioequivalence study report is acceptable and does establish bioequivalence between four 75 mg tablets and the new 300 mg dosage strength of Plavix®.

RECOMMENDATION

The Office of Clinical Pharmacology and Biopharmaceutics has reviewed NDA 20-839 submitted on May 21, 2007 for Plavix® and has the following comments:

REVIEWER'S COMMENTS:

1. An approval of the new 300 mg strength has been granted.

2. Clopidogrel's inactive metabolite (SR26334) was used to demonstrate bioequivalence between the two dosage strengths. Traditionally within the Agency, this would be an unacceptable way to test for bioequivalence between the two formulations since prior pharmacokinetic studies conducted assessed the pharmacodynamics and the pharmacokinetics of Plavix® due to the metabolite being inactive. However, since i) the new strength tablet given is the same strength given previously clinically as four 75 mg tablets, ii) change in rate of absorption won't make much difference since it is being given

as a one-time dose for the indication of acute coronary syndrome to be administered with aspirin followed by daily 75 mg dose of Plavix® and aspirin, utilizing the inactive metabolite in this study seems acceptable.

3. Establishment of bioequivalence between the new dosage strength of 300 mg and four 75 mg tablets of Plavix® has been made. However, this method of establishing bioequivalence will not be acceptable under any other setting. In the future bioequivalence will be based on the parent drug due to analytical methods now being able to measure the parent drug. Unlike when Plavix® was approved and we were only able to measure the inactive metabolite.

Please forward the above comment to the sponsor.

Lydia Velazquez, Pharm.D.
Division of Pharmaceutical Evaluation I
Primary Reviewer

FT Initialed by Patrick Marroum, Ph.D. _____
CC list: HFD-110: NDA 20-839; HFD-860: (VelazquezL, MarroumP, MehtaM, UppoorR); CDER Central Document Room

STUDY BEQ6629 – A SINGLE DOSE BIOEQUIVALENCE STUDY COMPARING THE NEW-IR TABLET OF SR25990C DOSED AT 300 MG WITH FOUR TABLETS OF SR25990C DOSE AT 75 MG (REFERENCE), IN HEALTHY MALE AND FEMALE SUBJECTS.

STUDY INVESTIGATOR AND SITE: ANNE KERVELLA, MD
ZA des Greffières, Rue Auguste Perret
17140 Lagord, France

REPORT # BEQ6629
STUDY DATES: August 23rd, 2006 to November 6th, 2006

Objectives:	***Primary:*** To evaluate, after single oral dose administration, the bioequivalence between a 300 mg IR (immediate release) tablet (new formulation) and four 75 mg tablets of clopidogrel (SR25990C). ***Secondary:*** To assess the clinical and laboratory safety of clopidogrel after each administration.

FORMULATIONS:

Investigational product:	Clopidogrel 300 mg tablet formulation (Test)
Dose:	300 mg single dose in fasted conditions
Administration:	Oral with 240 mL of non-carbonated water
Batch number:	CL-010489
Reference therapy:	Clopidogrel 75 mg tablet formulation (Ref)
Dose:	4 x 75 mg single dose in fasted conditions
Administration:	Oral, 4 tablets taken one by one with water at each intake, for a total of 240 mL of non-carbonated water.
Batch number:	AR054699

Note: Batch number CL-010489 was derived from batch 3655 found in the CMC section of the submission; which was a batch size of (b) (4) tablets.

Methodology:	Single center, randomized, open-label, single oral dose, two-treatment by two-sequence crossover study		
Number of subjects evaluated:	Planned: 56	Randomized: 56	Treated: 56
	Pharmacodynamics: NA	Safety: 56	Pharmacokinetics: 56
Diagnosis and criteria for inclusion:	Healthy male and female subjects, aged between 18 and 45 years (at least 30% of one gender)		

Duration of treatment: 1 day for Period 1 and 1 day for Period 2	**Duration of observation:** Screening: 2 to 21 days Treatment phase: 2 single doses separated by a washout of 10 to 14 days Follow-up period: 10 to 14 days after dosing Total duration: 4 to 7 weeks

The use of concomitant medication was not allowed during the study, with the exception of hormonal contraceptives as specified in the inclusion criteria.

Specifically, any treatment known to interact with coagulation or hemostasis were to be prohibited until the end of the study (see Section 6.3.2):

- Any antiplatelet agent including aspirin, ticlopidine, clopidogrel, dipyridamole, GPIIb/IIIa antagonists or any drugs containing salicylates,
- Any steroidal or nonsteroidal anti-inflammatory drugs,
- Any anticoagulants.

Exceptional use of acetaminophen was permitted under prescription of the responsible physician. However, if a specific treatment was required for any reason, an accurate record was to be kept on the appropriate record form, including the name of the medication (international nonproprietary name), daily dosage, duration and indication for such use. The Sponsor was to be informed within 48 hours.

Subjects were refrained from drinking alcohol, tea, coffee, citrus and cola beverages and eating citrus fruit during the study.

ANALYTICAL METHODS:

All PK assays were conducted under the responsibility of the Global Metabolism and Pharmacokinetics Department of sanofi-aventis Recherche et Développement (part of sanofi-aventis group) in Bridgewater (USA).

The plasma concentrations of SR26334 were determined by a validated liquid chromatography-tandem mass spectrometry (LC-MS/MS) method (DOH0588), with a limit of quantification (LOQ) of 50 ng/mL.

Linearity

The plasma calibrations were linear for concentrations ranging from 50 to 10000 ng/mL. The coefficient of determination was 0.9967 or better. This was calculated from the slopes of the calibration lines (n=3).

Lower Limit of Quantitation (LLOQ)

The LLOQ was 50.0 ng/mL.

Accuracy and Precision

The accuracy ranged from 0.361 to 3.51 of nominal values and the total precision ranged from 4.90 to 6.81%.

PK SAMPLE COLLECTION AND CALCULATIONS:

Plasma samples for SR26334 assays were collected prior to dosing and 0.25, 0.5, 0.75, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 12, 16, 24, 30, 36 and 48 hours after dosing.

Clopidogrel carboxylic acid metabolite SR26334 C_{max} (maximum plasma concentration observed), t_{max} (first time to reach C_{max}), AUC_{last} [area under the plasma concentration versus time curve calculated using trapezoidal method from time zero to real time t_{last} (corresponding to the last concentration above the limit of quantification)], AUC (area under the plasma concentration versus time curve extrapolated to infinity), $t_{1/2z}$ (terminal half-life).

For log-transformed C_{max}, AUC and AUC_{last}, estimates with 90% confidence intervals (CI) for the ratios of formulation means (combination tablet Test/separate tablets Ref) were computed within the linear model framework (with fixed term for formulation, gender, period, and sequence, and random term for subject within sequence-by-gender), and converting to ratios by antilog transformation.

For $t_{1/2z}$, difference between formulations was tested for significance with p-value computed within the above linear mixed effects model framework on log-transformed $t_{1/2z}$.

Safety:	Clinical, biological tolerability including adverse events (AEs), clinical laboratory parameters (clinical chemistry, hematology, urinalysis and coagulation tests), vital signs, including heart rate (HR), systolic and diastolic blood pressure (SBP and DBP), 12-lead electrocardiogram (ECG).

RESULTS:

Pharmacokinetic results

Descriptive statistics on SR26334 plasma pharmacokinetic (PK) parameters, after a single oral administration of clopidogrel 4x75 mg tablets or 300 mg tablet, in fasting conditions are presented in the table below.

SR26334 PK parameters	Clopidogrel 4x75mg (n=55*)	Clopidogrel 300mg (n=55*)
C_{max} (ng/mL)	10600 (30)	11200 (26)
t_{max} (h)	1.50 [0.75 ; 4.00]	1.50 [0.50 ; 2.50]
AUC_{last} (h.ng/mL)	42500 (26)	43000 (26)
AUC (h.ng/mL)	43800 (26)	44300 (27)
$t_{1/2z}$ (h)	10.8 (27)	10.5 (29)

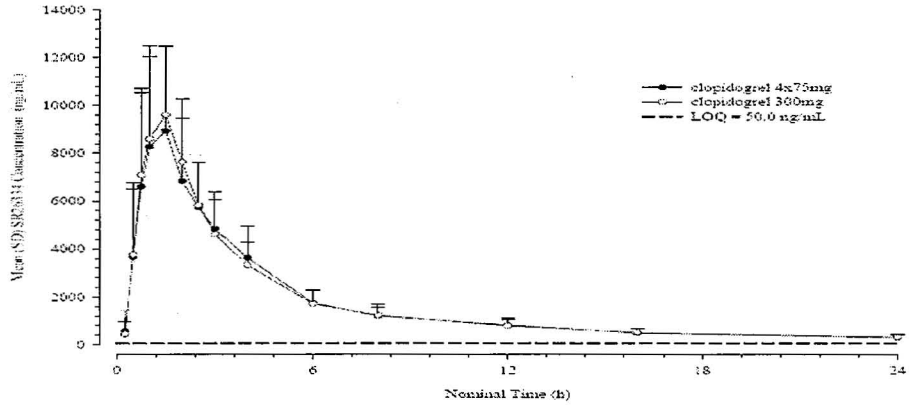
Tabulated values are arithmetic mean (CV%) except for t_{max} where values are Median (Min-Max)
* 1 subject discontinued after Period 1 in each treatment group

The formulation ratio (300 mg tablet/4x75 mg tablets) for the PK parameters of SR26334, together with 90% CI are presented in the following table, (n=56).

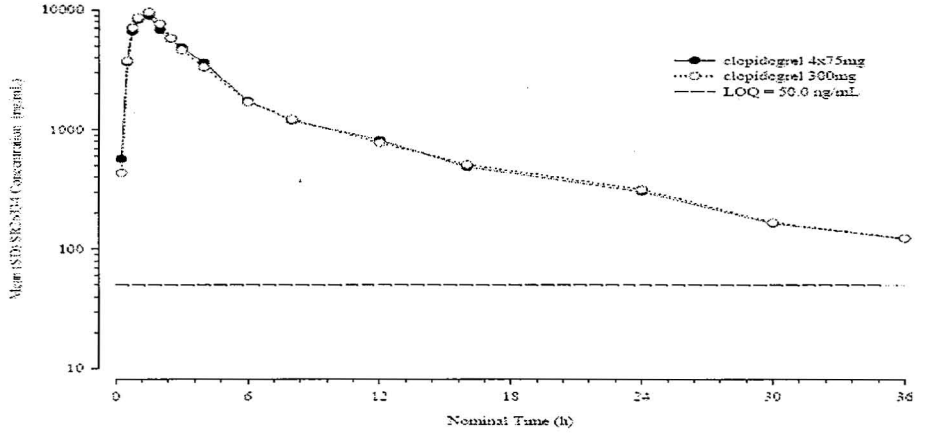
Parameters	Estimated ratio	90% Confidence Interval
C_{max}	1.08	[1.01 – 1.14]
AUC_{last}	1.02	[0.99 – 1.05]
AUC	1.01	[0.99 – 1.04]

Both formulations were bioequivalent: whatever the parameters, 90% CIs were contained in the [0.80-1.25] bioequivalence interval. In addition, there was no statistically significant formulation effect on SR26334 $t_{1/2z}$.

Linear plot of mean plasma concentration versus time curve of SR26334



Semi-logarithmic plot of mean plasma concentration versus time curve of SR26334



Safety results:	There were no deaths or serious adverse events (SAEs) reported during the study and none of the subjects discontinued due to AEs. One subject on clopidogrel 4x75 mg (Ref) experienced 1 treatment emergent adverse event (TEAE) and 5 subjects on clopidogrel 300 mg (Test) experienced 5 TEAE. There were no clinically relevant changes in laboratory test results, vital signs or ECG parameters.

Conclusions:	The aim of this study was to demonstrate that the two clopidogrel tablets strength are bioequivalent, based on the rate and extent of the main circulating metabolite of clopidogrel, SR26334, after a single administration of the same dose in fasted conditions. Results show that the clopidogrel 300 mg tablet (Test) is bioequivalent to 4x75 mg tablets (Ref), both in term of SR26334 Cmax and AUCs, with 90% CIs contained in the [0.80 –1.25] bioequivalence interval. In addition, there is no statistically significant formulation effect on SR26334 t1/2z. In the conditions of this study, clopidogrel 300 mg tablet (Test) and 4x75 mg tablets (Ref) are well tolerated.

REVIEWER'S COMMENTS:

Clopidogrel's inactive metabolite (SR26334) was used to demonstrate bioequivalence between the two dosage strengths. Traditionally within the Agency, this would be an unacceptable way to test for bioequivalence between the two formulations since prior pharmacokinetic studies conducted assessed the pharmacodynamics and the pharmacokinetics of Plavix® due to the metabolite assayed being inactive. However, since i) the new strength tablet given is the strength given previously clinically as four 75 mg tablets and ii) change in rate of absorption won't make much difference since it is being given as a one-time dose for the indication of acute coronary syndrome to be administered with aspirin, utilizing the inactive metabolite in this study seems acceptable.

STUDY FLOW CHART

Phase	Screening	Period 1			Wash out	Period 2				End-of-study
Day	D-21 to D-2	D-1	D1	D2	D3	10 to 14 days	D-1	D1	D2	D3	D15
Informed consent	X										
Inclusion /exclusion criteria	X	X					X				
Previous Medical/Surgical History	X	X									
Prior / concomitant medications	←----------										----------→
Inclusion			X								
Admission		X					X				
Discharge					X					X	
IP administration											
clopidogrel			X					X			
Pharmacokinetics											
SR26334 PK samples			X	X	X			X	X	X	
Safety											
Physical examination (BMI)	X	X					X				X
Vital signs, ECG	X	X			X		X			X	X
Serology	X										
Archival blood sample			X								
Hematology, biochemistry, urinalysis	X	X					X				X
Coagulation tests	X	X					X				X
Urine Drug Screen, alcohol test	X	X					X				
β-HCG plasma test (if female)	X	X					X				X
Adverse event collection	←----------										----------→

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/s/

Lydia Velazquez
9/14/2007 10:18:39 AM
BIOPHARMACEUTICS

Patrick Marroum
9/17/2007 10:55:53 AM
BIOPHARMACEUTICS

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

20-839/S-038

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 20-839/S-038

PRIOR APPROVAL SUPPLEMENT

Sanofi-aventis U.S., LLC
Attention: Matthew R. Boyd, R.Ph., M.B.A.
Director
US Regulatory Affairs, Marketed Product
55 Corporate Drive
PO Box 5925
Bridgewater, NJ 08807-5925

Dear Dr. Boyd:

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

Name of Drug Product: Plavix® (clopidogrel bisulfate) Tablets

NDA Number: 20-839

Supplement number: S-038

Date of supplement: May 21, 2007

Date of receipt: May 22, 2007

This supplemental application proposes to add a new strength to replace the intake of four 75 mg tablets as a loading dose.

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 July 21, 2007 in accordance with 21 CFR 314.101(a). If the application is filed, the user fee goal date will be September 21, 2007.

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 any question, please contact:

Meg Pease-Fye, M.S.
Regulatory Project Manager
(301) 796-1130

Sincerely,

(See appended electronic signature page)

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

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

/s/

Edward Fromm
6/29/2007 11:10:44 AM