DEPARTMENT OF HEALTH & HUMA N SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

TRANSMITTED VIA FACSIMILE

Kenneth Palmer, M.S.
Associate Director, Drug Regulatory Affairs
Sanofi-Synthelabo Inc.
90 Park Avenue
New York, New York 10016

RE: NDA #20-839
Plavix (clopidogrel bisulfate) Tablets
MACMIS ID #9466

Dear Mr. Palmer:

As part of its routine monitoring program, the Division of Drug Marketing, Advertising, and Communications (DDMAC) has become aware that Sanofi-Synthelabo Inc. (Sanofi) is promoting its product, Plavix (clopidogrel bisulfate) tablets, in violation of the Federal Food, Drug, and Cosmetic Act (Act) and its implementing regulations. Specifically, we refer to Sanofi's dissemination of a visual aid (69-201499) for Plavix, submitted under cover of Form FDA 2253, that contains promotional claims that are false or misleading. Our specific objections follow.

Overstatement of Efficacy

The clinical evidence for the efficacy of Plavix is derived from the CAPRIE (Clopidogrel versus Aspirin in Patients at Risk of Ischemic Events) trial. The CAPRIE trial demonstrated an overall risk reduction of a combined outcome cluster of events (ischemic stroke (IS), myocardial infarction (MI), and other vascular death).

Your visual aid is misleading because it selectively presents the most favorable relative risk reductions for Plavix versus Aspirin for two of the three individual components (IS and MI) of the combined outcome cluster. Specifically, two full pages of the visual aid (pages 5 & 10) depict a 19.2% relative risk reduction for Plavix versus aspirin for an individual component (MI) of the combined outcome cluster. MI was the individual component of this combined outcome cluster that resulted in the most favorable relative risk reduction for Plavix versus aspirin. Additionally, page 11 of the visual aid includes a similar presentation of the relative risk reduction (5.2%) for IS. However, you limit your presentation of the difference in relative risk reduction for Plavix versus Aspirin for the third component of this combined outcome cluster (other vascular death) to a single statement on the bottom of page 11 of the sales aid (Vascular death not attributed to MI or stroke would not be expected to be reduced by antiplatelet therapy). This component resulted in the least favorable risk reduction for Plavix versus aspirin (no difference). Therefore, the visual aid is misleading because it overstates the efficacy of Plavix by selectively presenting the most favorable relative

risk reduction data for two of the individual components of the combined outcome cluster.

Furthermore, important contextual information that is necessary to interpret these claims, including the actual event rates of these individual outcome events is presented in footnotes at the bottom of the page in a much smaller font size than the relative risk claims. For example, on page 10 of your visual aid, you present the claim "Myocardial Infarction – 19.2% relative risk reduction vs aspirin 325 mg..." along with a very prominent related graphic presentation. However, the absolute risk, as reflected in the actual event rates of patients experiencing an MI (2.9% for Plavix vs 3.47% for aspirin 325 mg), is presented in a footnote at the bottom of the page in a very small font size. Thus, your presentations are misleading because they distort and misrepresent the actual differences between the groups, implying a much larger difference than was actually demonstrated.

In addition, the actual event rates for MI and IS presented in these footnotes are inconsistent with the rates provided in the PI. Specifically, the event rate for MI (3.6%) is not consistent with the rate provided in the PI (3.47%), and the event rates for IS presented in the footnote (4.9% for Plavix and 5.3% for aspirin) are not consistent with the rates provided in the PI (4.56% for Plavix and 4.81% for aspirin).

Unsubstantiated Superiority Claim

On page 4 of the visual aid you present the claim, "Significant overall risk reduction vs. aspirin 325 mg in CAPRIE, a 3 year study of 19,185 patients." This claim is misleading because it suggests that Plavix is superior to aspirin when such has not been demonstrated by substantial evidence. As previously stated in our December 18, 1998, untitled letter, the CAPRIE trial does not provide substantial evidence to support the implication that Plavix has superior efficacy over aspirin. Therefore, claims suggesting that Plavix is significantly better than aspirin are misleading because they are not based on substantial evidence.

Misleading Efficacy Presentation

The mechanisms of action (MOA) for Plavix and aspirin are presented on page 6 under the header "Plavix and Aspirin work differently." This graphic presentation includes the effects of Plavix on the inhibition of platelet aggregation on one side of a single platelet and the effect of aspirin on the inhibition of platelet aggregation on the other side of the same platelet. Directly underneath the graphic depiction of the platelet is an arrow that leads to the concluding text "Inhibition of Platelet Aggregation: Reducing the Risk of MI, Ischemic Stroke, and Vascular Death." This presentation suggests that concurrent use of Plavix and aspirin will produce an additive effect on the inhibition of platelet aggregation. However, the safety and efficacy of taking Plavix in combination with aspirin has not been demonstrated by substantial evidence. Therefore, this MOA presentation is misleading because it suggests that the combined use of Plavix and aspirin is safe and effective when such has not been demonstrated.

Fair Balance

This promotional piece fails to present risk information with a prominence and readability reasonably comparable to the presentation of information on the effectiveness of the drug. Claims promoting the effectiveness and safety of Plavix are presented in large bolded print throughout the visual aid (12 pages). In contrast, the majority of your risk information about Plavix is limited to one page of the visual aid. This risk information is further minimized by use of paragraphing and the absence of a signal to alert readers to its importance. Furthermore, the pages of the visual aid that do not include risk information fail to specify the location of this information in the piece.

In order to address these objections, you should immediately cease distribution of these materials immediately and all other promotional materials for Plavix that contain the same or similar claims or presentations. You should respond in writing by May 23, 2001, with your intent and plans to comply with this request. Your response should include a list of materials discontinued, and the date on which these materials were discontinued.

If you have any further questions, please direct them to me by facsimile at 301-594-6771 or at the Food and Drug Administration, Division of Drug Marketing, Advertising, and Communications, HFD-42, Rm 17B-20, 5600 Fishers Lane, Rockville, MD 20857.

We remind you that only written communications are considered official. In all future correspondence regarding this particular matter please refer to MACMIS ID #9466 in addition to the NDA number.

Sincerely,

{See appended electronic signature page}

Andrew S.T. Haffer, Pharm.D.
Regulatory Review Officer
Division of Drug Marketing,
Advertising, and Communications

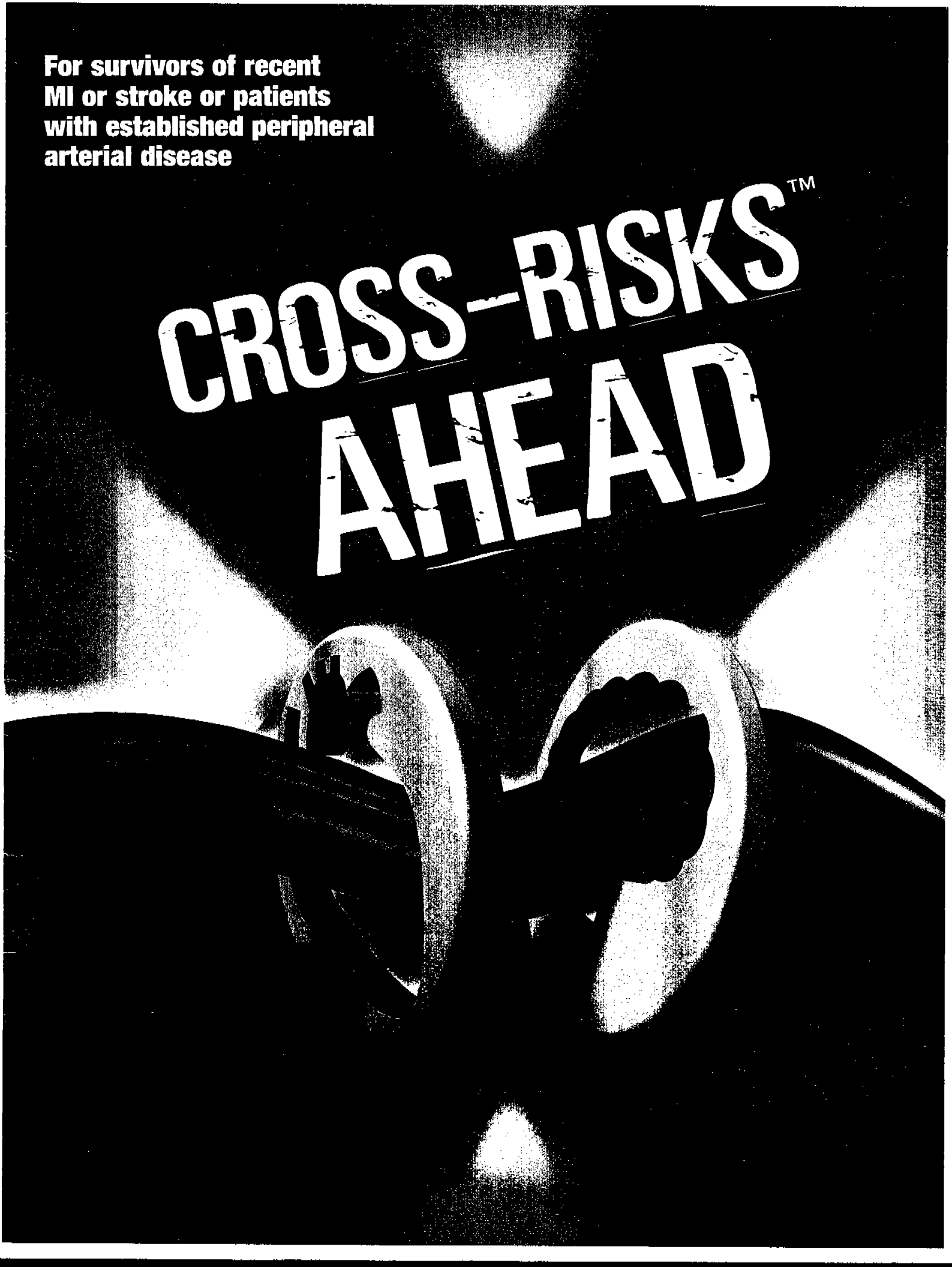
This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

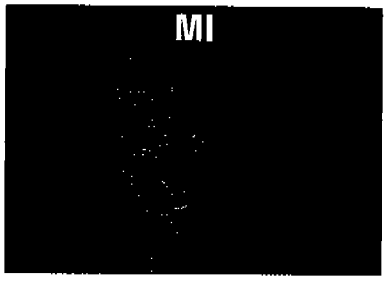
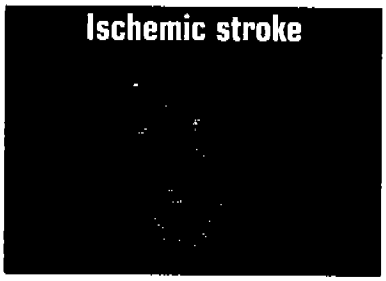
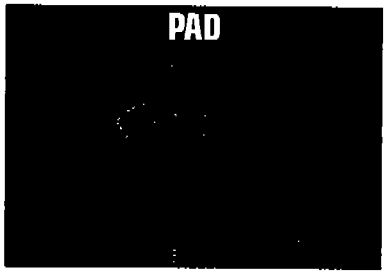
Andrew Haffer
5/9/01 03:44:51 PM

For survivors of recent MI or stroke or patients with established peripheral arterial disease

CROSS-RISKS™ AHEAD



INCREASED CROSS-RISK™* OF MI AND STROKE LASTS A LIFETIME[1,2]

	Increased risk of MI†	Increased risk of stroke†
 MI	**5-7 X greater risk[3]** (includes death)	**3-4 X greater risk[4]** (includes TIA)
 Ischemic stroke	**2-3 X greater risk[4]** (includes angina and sudden death‡)	**9 X greater risk[5]**
 PAD	**4 X greater risk[6]** (includes only fatal MI and other CHD death§)	**2-3 X greater risk[4]** (includes TIA)

CHD=coronary heart disease.

This chart is based on epidemiologic data and is not intended to provide a direct basis for comparison of risks between event categories. Data for the associated risk increase in events were taken from different sources. The increase in risk of events was based on 10-year follow-up except for risk of stroke following stroke, which measures subsequent risk per year.

*Cross-risk: the risk of both MI and stroke.

- Stroke survivors are twice as likely to die from cardiovascular disease (including MI) as from stroke[7]

†Versus the general population.
‡Sudden death defined as death documented within 1 hour and attributed to CHD.
§Does not include nonfatal MI.
‖Versus patients without the additional ischemic sequelae.
¶Long-term prognosis after initial MI by preexisting cardiovascular condition; age-adjusted relative risks.

PLEASE SEE FULL PRESCRIBING INFORMATION ON FINAL PAGES.

Epidemiologic data show that

CROSS-RISKS™ ARE EVEN GREATER WITH EVIDENCE OF ADDITIONAL ISCHEMIA

Atherosclerotic condition	+	Ischemia	=	Increased risk of:
MI		ST-segment elevation		Stroke: 140%[8‖]
Stroke/TIA		MI		A second MI: Up to 103%[2‖¶]
Intermittent claudication		MI		A second MI: Up to 104%[2‖¶]

PLAVIX protection reduces the long-term risk of MI and stroke in patients with recent MI, recent stroke, or established PAD[9]

ONCE-A-DAY

Plavix®

(clopidogrel bisulfate) 75mg tablets

PROVEN PROTECTION AGAINST BOTH MI AND STROKE

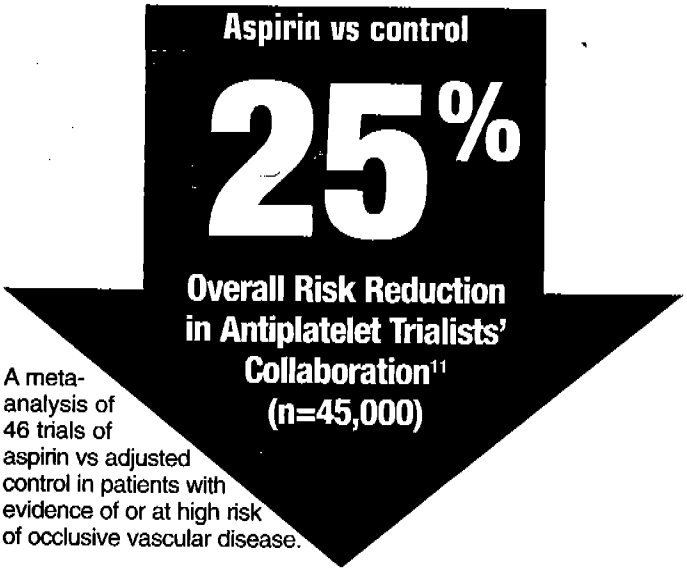
IN PATIENTS WITH ATHEROSCLEROSIS: RECENT MI, RECENT STROKE, OR ESTABLISHED PERIPHERAL ARTERIAL DISEASE

PLAVIX REDUCES THE RISK OF MI, STROKE, AND VASCULAR DEATH*

Significant overall risk reduction† vs aspirin 325 mg daily in CAPRIE, a study of 19,185 patients[9,10]

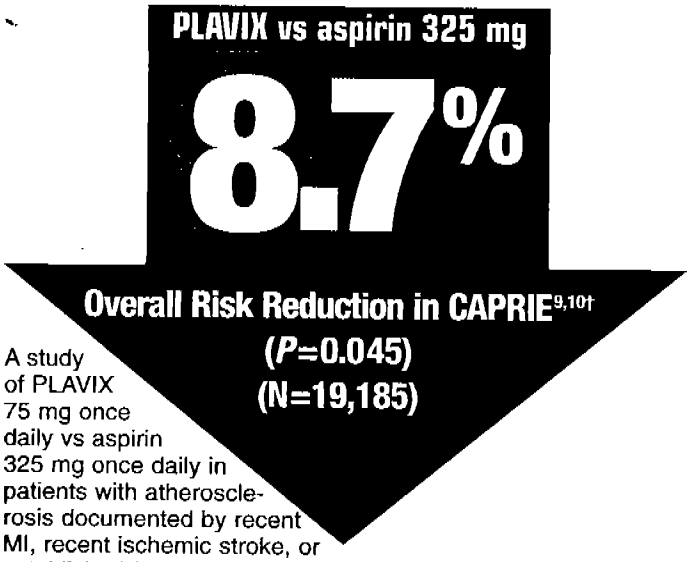
- Benefits seen during the first 6 months (a time of high risk) and continued throughout the 3-year study[9,10]

In an earlier meta-analysis, aspirin vs control reduced the risk of MI, stroke, and vascular death



A meta-analysis of 46 trials of aspirin vs adjusted control in patients with evidence of or at high risk of occlusive vascular disease.

Overall Risk Reduction† in MI, ischemic stroke, and vascular death with PLAVIX vs aspirin 325 mg



A study of PLAVIX 75 mg once daily vs aspirin 325 mg once daily in patients with atherosclerosis documented by recent MI, recent ischemic stroke, or established PAD.

Although the statistical significance favoring PLAVIX over aspirin was marginal (P=0.045, based on overall incidence of primary outcome events: 9.78% for PLAVIX vs 10.64% for aspirin), 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.

*In patients with atherosclerosis documented by recent MI, recent ischemic stroke, or established PAD.
†Overall risk reduction in the primary analysis in CAPRIE for MI, ischemic stroke, and vascular death was calculated based on first events following study enrollment (intent-to-treat analysis).

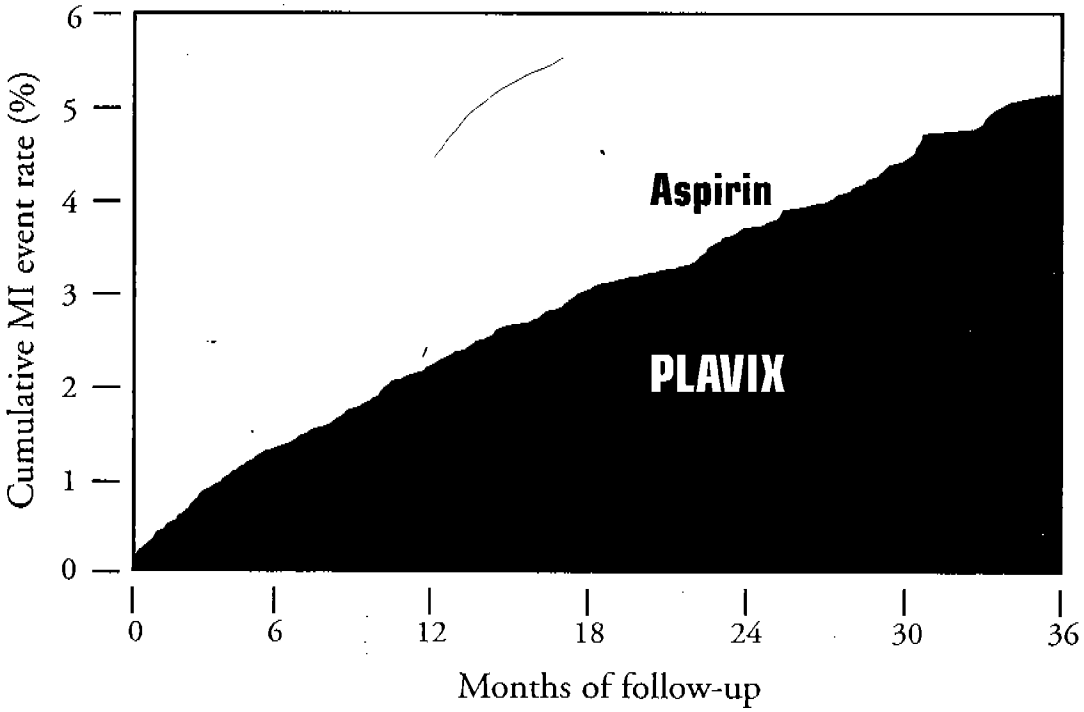
PLEASE SEE FULL PRESCRIBING INFORMATION ON FINAL PAGES.

PLAVIX REDUCES THE RISK OF FATAL OR NONFATAL MI*

–as demonstrated in an additional CAPRIE analysis[10,12‡]

Significant reduction in risk seen over 3-year study period (P=0.008) vs aspirin 325 mg daily[10,12]

Cumulative risk of first MI following PLAVIX or aspirin 325 mg



PLAVIX vs aspirin 325 mg

19.2%

Relative risk reduction[10,12‡]
(P=0.008)
(N=19,185)

Based on first MIs occurring over the 3 years of the CAPRIE study in all three patient subgroups (recent MI, recent ischemic stroke, or established PAD)[10,12]

Event curves separated early and continued to widen over the 3-year follow-up period[10]

‡The relative risk of experiencing an MI (fatal or nonfatal) is based on a post hoc analysis of individual outcome events, based on the percentage of patients experiencing an MI (2.9% for PLAVIX vs 3.6% for aspirin 325 mg). While not planned in the protocol, the analysis provides additional insight into the overall efficacy results.

ONCE-A-DAY

Plavix®

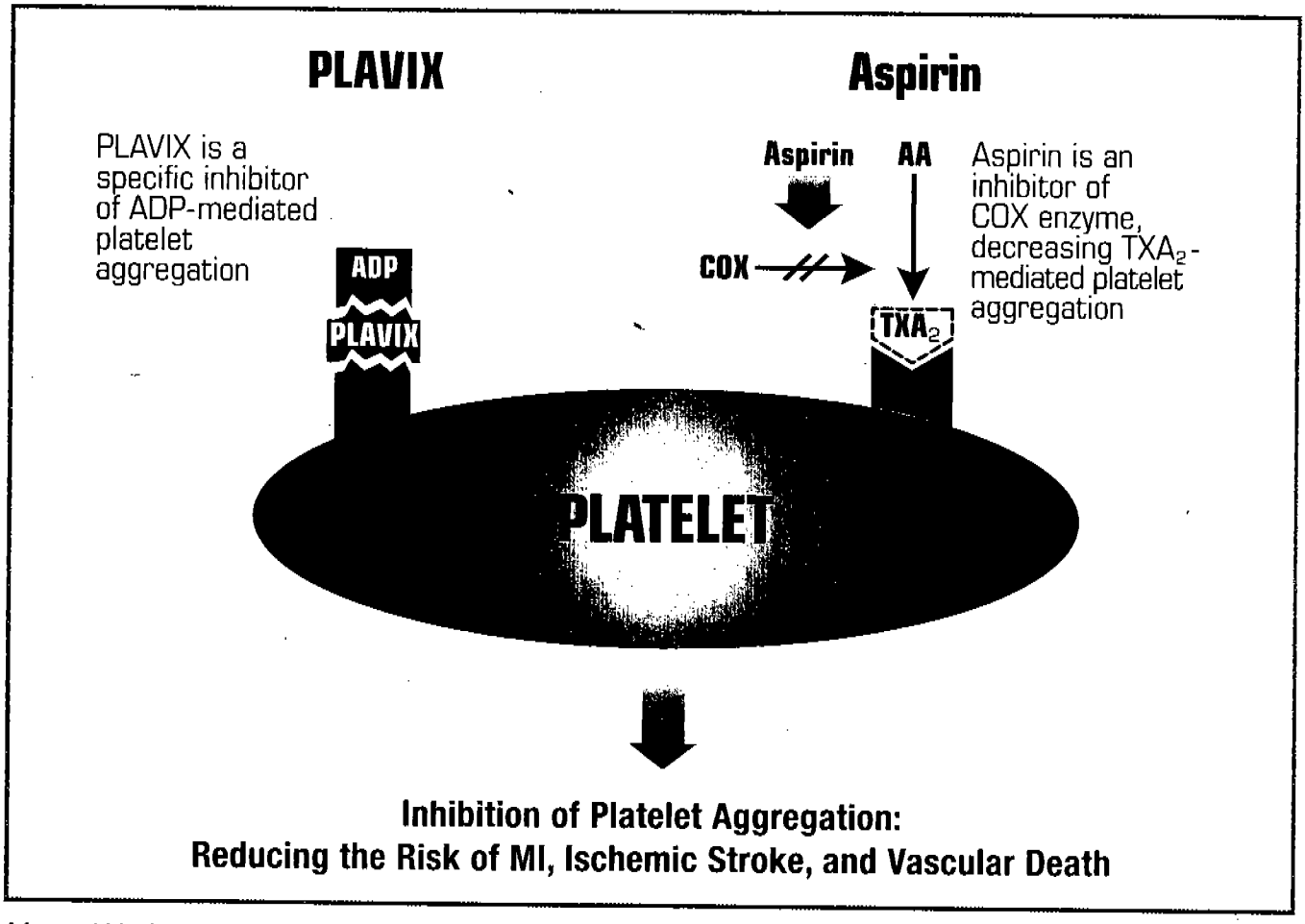
(clopidogrel bisulfate) 75 mg tablets

PROVEN PROTECTION AGAINST BOTH MI AND STROKE

IN PATIENTS WITH ATHEROSCLEROSIS: RECENT MI, RECENT STROKE, OR ESTABLISHED PERIPHERAL ARTERIAL DISEASE

PLAVIX AND ASPIRIN WORK DIFFERENTLY

PLAVIX is a potent and specific inhibitor of ADP-mediated platelet aggregation



AA=arachidonic acid
ADP=adenosine diphosphate
TXA_2=thromboxane A_2
COX=cyclooxygenase

As seen in the 3-year, 19,185-patient CAPRIE study

PLAVIX HAS A PROVEN SAFETY AND TOLERABILITY PROFILE

	Incidence	
SAFETY	PLAVIX 75 mg (n=9599)	Aspirin 325 mg (n=9586)
GI hemorrhage	2.0%	2.7%
Hospitalization due to GI hemorrhage	0.7%	1.1%
GI ulcers	0.7%	1.2%
Intracranial hemorrhage	0.4%	0.5%
Severe neutropenia	0.04%	0.02%
TOLERABILITY		
Abdominal pain	5.6%	7.1%
Purpura	5.3%	3.7%
Dyspepsia	5.2%	6.1%
Diarrhea	4.5%	3.4%
Rash	4.2%	3.5%
Pruritus	3.3%	1.6%
Discontinuance due to adverse GI events	3.2%	4.0%
Gastritis[10]	0.8%	1.3%

PLAVIX is contraindicated in patients with active pathologic bleeding such as peptic ulcer or intracranial hemorrhage. As with other antiplatelet agents, PLAVIX should be used with caution in patients who may be at risk of increased bleeding from trauma, surgery, or other drug therapy.

As part of the worldwide postmarketing experience with PLAVIX, suspected cases of thrombotic thrombocytopenic purpura (TTP) have been reported at a rate of about 4 cases per million patients exposed. See WARNINGS.

ONCE-A-DAY

Plavix®

(clopidogrel bisulfate) 75mg tablets

PROVEN PROTECTION AGAINST BOTH MI AND STROKE

IN PATIENTS WITH ATHEROSCLEROSIS: RECENT MI, RECENT STROKE, OR ESTABLISHED PERIPHERAL ARTERIAL DISEASE

PLAVIX PROTECTION IS EASY TO INITIATE AND CONTINUE

- Convenient once-daily dosing--one 75-mg tablet, with or without food
- No dosage adjustment necessary for elderly or renally impaired patients
- Shown to be equally effective in men and women
- PLAVIX does not require routine hematological monitoring[10]

  Although the risk of myelotoxicity appears to be quite low, this possibility should be considered when a patient receiving PLAVIX demonstrates fever or other signs of infection.

- No clinically significant adverse interactions seen with the following in CAPRIE:
  - ACE inhibitors
  - Antidiabetic agents
  - Beta blockers
  - Calcium channel blockers
  - Cholesterol-lowering agents
  - Coronary vasodilators
  - Diuretics
- PLAVIX is on formulary at over 90% of hospitals and managed care plans[13]
- More than 3 million patients have been treated with PLAVIX since its introduction[10]

PLEASE SEE FULL PRESCRIBING INFORMATION ON FINAL PAGES.

References: **1.** Kannel WB. Epidemiologic relationship of disease among the different vascular territories. In: Fuster V, Ross R, Topol EJ, eds. *Atherosclerosis and Coronary Artery Disease*. Philadelphia, Pa: Lippincott-Raven; 1996;II:1591-1599. **2.** Cupples LA, Gagnon DR, Wong ND, et al. Preexisting cardiovascular conditions and long-term prognosis after initial myocardial infarction: The Framingham Study. *Am Heart J*. 1993;125:863-872. **3.** Adult Treatment Panel II. National Cholesterol Education Program: Second Report of the Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults. *Circulation*. 1994;89:1333-1363. **4.** Kannel WB. Risk factors for atherosclerotic cardiovascular outcomes in different arterial territories. *J Cardiovasc Risk*. 1994;1:333-339. **5.** Wilterdink JL, Easton JD. Vascular event rates in patients with atherosclerotic cerebrovascular disease. *Arch Neurol*. 1992;49:857-863. **6.** Criqui MH, Langer RD, Fronek A, et al. Mortality over a period of 10 years in patients with peripheral arterial disease. *N Engl J Med*. 1992;326:381-386. **7.** Sacco RL, Shi T, Zamanillo MC, Kargman DE. Predictors of mortality and recurrence after hospitalized cerebral infarction in an urban community: The Northern Manhattan Stroke Study. *Neurology*. 1994;44:626-634. **8.** Mooe T, Eriksson P, Stegmayr B. Ischemic stroke after acute myocardial infarction — a population-based study. *Stroke*. 1997;28:762-767. **9.** CAPRIE Steering Committee. A randomised, blinded, trial of clopidogrel versus aspirin in patients at risk of ischaemic events (CAPRIE). *Lancet*. 1996;348:1329-1339. **10.** Data on file, Sanofi-Synthelabo Inc. **11.** Antiplatelet Trialists' Collaboration. Collaborative overview of randomised trials of antiplatelet therapy—I: prevention of death, myocardial infarction, and stroke by prolonged antiplatelet therapy in various categories of patients. *BMJ*. 1994;308:81-106. **12.** Gent M. Benefit of clopidogrel in patients with coronary disease. *Circulation*. 1997;96(suppl):I-467. Abstract 2608. **13.** HRA Managed Care Formulary Report (March 2000). **14.** Rupprecht HJ. Consistency of the benefit of clopidogrel across a range of vascular-related endpoints: results from CAPRIE. *Eur Heart J*. 1998;19:Abstract P484.

ONCE-A-DAY

Plavix®

(clopidogrel bisulfate) 75mg tablets

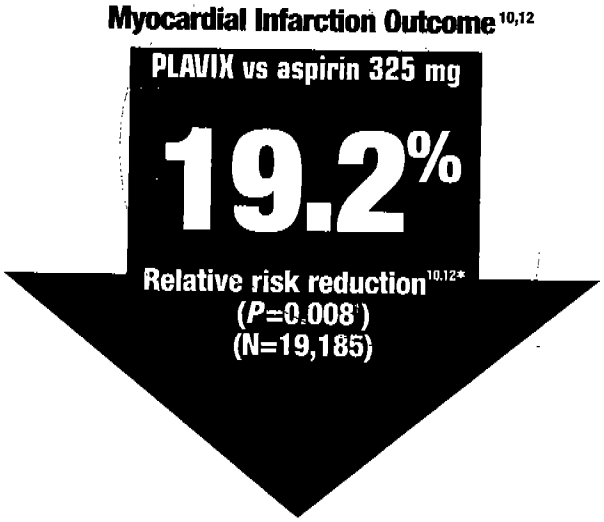
PROVEN PROTECTION AGAINST BOTH MI AND STROKE

IN PATIENTS WITH ATHEROSCLEROSIS: RECENT MI, RECENT STROKE, OR ESTABLISHED PERIPHERAL ARTERIAL DISEASE

PLAVIX demonstrated a relative risk reduction in fatal or nonfatal MI vs aspirin 325 mg daily

–as demonstrated in an additional CAPRIE analysis[10,12*]

- Myocardial infarction–19.2% relative risk reduction vs aspirin 325 mg in first MIs seen across the entire CAPRIE population[10,12*]



In patients with recent MI, recent ischemic stroke, or established PAD

*The relative risk of experiencing an MI (fatal or nonfatal) is based on a post hoc analysis of individual outcome events, based on the percentage of patients experiencing an MI (2.9% for PLAVIX vs 3.6% for aspirin 325 mg). While not planned in the protocol, the analysis provides additional insight into the overall efficacy results.

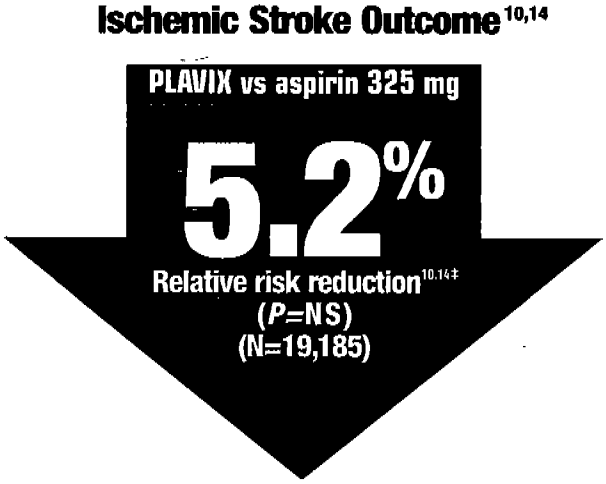
†Although the relative risk reduction in MI favoring PLAVIX vs aspirin 325 mg was statistically significant, this finding represents the result of a single trial that has not been replicated.

PLEASE SEE FULL PRESCRIBING INFORMATION ON FINAL PAGES.

PLAVIX demonstrated a relative risk reduction in fatal or nonfatal ischemic stroke vs aspirin 325 mg daily

–as demonstrated in an additional CAPRIE analysis[10,14‡]

- Ischemic stroke–5.2% relative risk reduction vs aspirin 325 mg in first ischemic strokes seen across the entire CAPRIE population[10,14‡]



In patients with recent MI, recent ischemic stroke, or established PAD

Vascular death not attributed to MI or stroke would not be expected to be reduced by antiplatelet therapy

‡The relative risk of experiencing an ischemic stroke (fatal or nonfatal) is based on a post hoc analysis of individual outcome events, based on the percentage of patients experiencing an ischemic stroke (4.9% for PLAVIX vs 5.3% for aspirin 325 mg). While not planned in the protocol, the analysis provides additional insight into the overall efficacy results.

ONCE-A-DAY

Plavix®

(clopidogrel bisulfate) 75 mg tablets

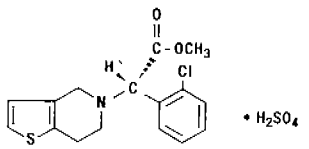
PROVEN PROTECTION AGAINST BOTH MI AND STROKE

IN PATIENTS WITH ATHEROSCLEROSIS: RECENT MI, RECENT STROKE, OR ESTABLISHED PERIPHERAL ARTERIAL DISEASE

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 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.

Each tablet contains anhydrous lactose, hydrogenated castor oil, microcrystalline cellulose, polyethylene glycol 6000 and pregelatinized starch as inactive ingredients. The pink film coating contains ferric oxide (red), hydroxypropyl methylcellulose 2910, polyethylene glycol 6000 and titanium dioxide. 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 atherosclerotic cardiovascular disease as evidenced by stroke or transient ischemic attacks, myocardial infarction, or need for 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 (≅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 (≥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. No dosage adjustment is needed in renally impaired patients.

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 the CAPRIE (Clopidogrel vs. Aspirin in Patients at Risk of Ischemic Events) trial. This 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) objectively established peripheral arterial disease. Patients received randomized treatment for an average of 1.6 years (maximum of 3 years).

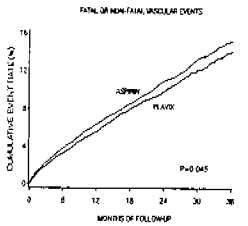
The trial's primary outcome was the time to first occurrence of new ischemic stroke (fatal or not), new myocardial infarction (fatal or not), or other vascular death. Deaths not easily attributable to nonvascular causes were all classified as vascular.

Outcome Events of the Primary Analysis

Patients	PLAVIX 9599	aspirin 9586
IS (fatal or not)	438 (4.56%)	461 (4.81%)
MI (fatal or not)	275 (2.86%)	333 (3.47%)
Other vascular death	226 (2.35%)	226 (2.36%)
Total	939 (9.78%)	1020 (10.64%)

As shown in the table, PLAVIX (clopidogrel bisulfate) was associated with a lower incidence of outcome events of every kind. The overall risk reduction (9.78% vs. 10.64%) 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 the figure. The event curves separated early and continued to diverge over the 3-year follow-up period.



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 atherothrombotic 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.

INDICATIONS AND USAGE
PLAVIX (clopidogrel bisulfate) is indicated for the reduction of atherosclerotic events (myocardial infarction, stroke, and vascular death) in patients with atherosclerosis documented by recent stroke, recent myocardial infarction, or established peripheral arterial disease.

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 (<2weeks). TTP is a serious condition requiring prompt treatment. It is characterized by thrombocytopenia, microangiopathic hemolytic anemia (schistocytes [fragmented RBCs] seen on peripheral smear), neurological findings, renal dysfunction, and fever. TTP was not seen during clopidogrel's clinical trials, which included over 11,300 clopidogrel-treated patients. In world-wide postmarketing experience, however, TTP has been reported at a rate of about four cases per million patients exposed, or about 11 cases per million patient-years. The background rate is thought to be about four cases per million person-years.

PRECAUTIONS
General
As with other anti-platelet agents, PLAVIX should be used with caution in patients who may be at risk of increased bleeding from trauma, surgery, or other pathological conditions. If a patient is to undergo elective surgery and an antiplatelet effect is not desired, PLAVIX should be discontinued 7 days prior to surgery.

GI Bleeding: PLAVIX prolongs the bleeding time. In CAPRIE, PLAVIX was associated with a rate of gastrointestinal bleeding of 2.0% vs. 2.7% on aspirin. 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 (such as aspirin and other nonsteroidal anti-inflammatory drugs [NSAIDs]) 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.

Information for Patients
Patients should be told that it may take them longer than usual to stop bleeding when they take PLAVIX, and that they should report any unusual bleeding to their physician. Patients should inform physicians and dentists that they are taking PLAVIX 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. The safety of chronic concomitant administration of aspirin and PLAVIX has not been established.

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. The safety of this combination has not been established, however, and concomitant use should be undertaken with caution.

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: The safety of the coadministration of PLAVIX (clopidogrel bisulfate) with warfarin has not been established. Consequently, concomitant administration of these two agents 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 CAPRIE received a variety of concomitant medications **including diuretics, beta-blocking agents, angiotensin converting enzyme inhibitors, calcium antagonists, cholesterol lowering agents, coronary vasodilators, antidiabetic agents, antiepileptic agents** and **hormone replacement therapy** without evidence of clinically significant adverse interactions.

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.

ADVERSE REACTIONS

PLAVIX has been evaluated for safety in more than 11,300 patients, including over 7,000 patients treated for 1 year or more. The overall tolerability of PLAVIX 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. The clinically important adverse events observed in CAPRIE are discussed below.

Hemorrhagic: In patients receiving PLAVIX in CAPRIE, 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.

Neutropenia/agranulocytosis: Ticlopidine, a drug chemically similar to PLAVIX, is associated with a 0.8% rate of severe neutropenia (less than 450 neutrophils/μL). Patients in CAPRIE (see **Clinical Trials**) were intensively monitored for neutropenia. Severe neutropenia was observed in six patients, four on PLAVIX and two on aspirin. Two of the 9599 patients who received PLAVIX (clopidogrel bisulfate) and none of the 9586 patients who received aspirin had neutrophil counts of zero.

One of the four PLAVIX patients was receiving cytotoxic chemotherapy, and another recovered and returned to the trial after only temporarily interrupting treatment with PLAVIX.

Although the risk of myelotoxicity with PLAVIX thus appears to be quite low, this possibility should be considered when a patient receiving PLAVIX demonstrates fever or other sign of infection.

Gastrointestinal: Overall, the incidence of gastrointestinal events (e.g. abdominal pain, dyspepsia, gastritis and constipation) in patients receiving PLAVIX (clopidogrel bisulfate) was 27.1%, compared to 29.8% in those receiving aspirin.

The incidence of peptic, gastric or duodenal ulcers was 0.7% for PLAVIX and 1.2% for aspirin.

Cases of diarrhea were reported in 4.5% of patients in the PLAVIX group compared to 3.4% in the aspirin group. However, these were rarely severe (PLAVIX=0.2% and aspirin=0.1%).

The incidence of patients withdrawing from treatment because of gastrointestinal adverse reactions was 3.2% for PLAVIX and 4.0% for aspirin.

Rash and Other Skin Disorders: The incidence of skin and appendage disorders in patients receiving PLAVIX was 15.8% (0.7% serious); the corresponding rate in aspirin patients was 13.1% (0.5% serious).

The overall incidence of patients withdrawing from treatment because of skin and appendage disorders adverse reactions was 1.5% for PLAVIX and 0.8% for aspirin.

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.

Adverse Events Occurring in ≥2.5% of PLAVIX Patients

	% 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 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		
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)
Continued		
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	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		
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)

Incidence of discontinuation, regardless of relationship to therapy, is shown in parentheses.

Other adverse experiences of potential importance occurring in 1% to 2.5% of patients receiving PLAVIX (clopidogrel bisulfate) in the CAPRIE controlled clinical trial are listed below regardless of relationship to PLAVIX. In general, the incidence of these events was similar in the aspirin-treated group.

Autonomic Nervous System Disorders: Syncope, Palpitation. *Body as a Whole - general disorders:* Asthenia, Hernia. *Cardiovascular disorders:* Cardiac failure. *Central and peripheral nervous system disorders:* Cramps legs, Hypoaesthesia, Neuralgia, Paresthesia, 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 are listed below regardless of relationship to PLAVIX. In general, the incidence of these events was similar in the aspirin group.

Body as a whole: Allergic reaction, necrosis ischemic. *Cardiovascular disorders:* Edema generalized. *Gastrointestinal system disorders:* 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. *White cell and reticuloendothelial system disorders:* Agranulocytosis, granulocytopenia, leukemia, leukopenia, neutrophils decreased.

Postmarketing Experience
The following events have been reported spontaneously from worldwide postmarketing experience: very rare cases of hypersensitivity reactions including angioedema, bronchospasms, and anaphylactoid reactions. Suspected thrombotic thrombocytopenic purpura (TTP) has been reported as part of the world-wide postmarketing experience, see **WARNINGS**.

OVERDOSAGE

One case of deliberate overdosage with PLAVIX (clopidogrel bisulfate) was reported in the large, controlled clinical study. A 34-year-old woman took a single 1,050-mg dose of PLAVIX (equivalent to 14 standard 75-mg tablets). There were no associated adverse events. No special therapy was instituted, and she recovered without sequelae.

No adverse events were reported after single oral administration of 600 mg (equivalent to 8 standard 75-mg tablets) of PLAVIX in healthy volunteers. The bleeding time was prolonged by a factor of 1.7, which is similar to that typically observed with the therapeutic dose of 75 mg of PLAVIX per day.

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

The recommended dose of PLAVIX is 75 mg once daily 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) is available as a pink, round, biconvex, film-coated tablet 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

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

Manufactured by:
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New York, NY 10016
Distributed by:
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New York, NY 10016

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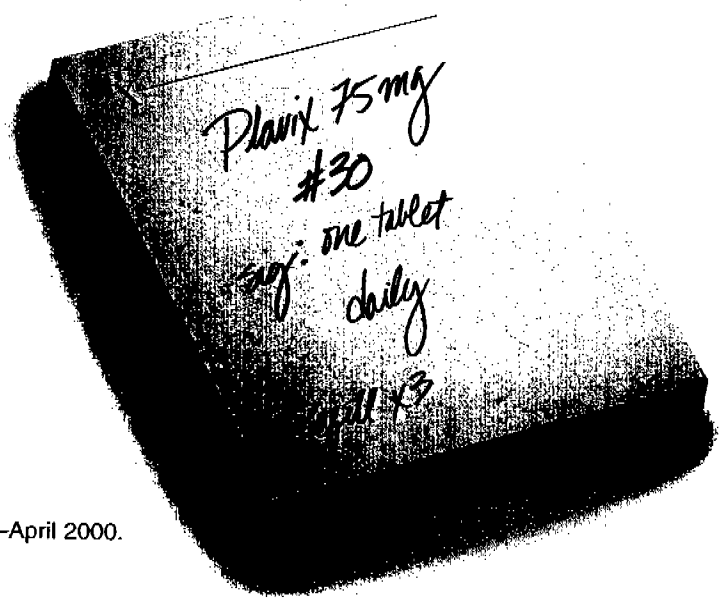

*Audited IMS data, March 1998–April 2000.

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